ORIGINAL ARTICLE

Lung Cancer Screening Using Low Dose CT Scanning in Germany

Extrapolation of Results From the National Lung Screening Trial

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SUMMARY

Background: It is now debated whether the screening of heavy smokers for lung cancer with low dose computed tomography (low dose CT) might lower their mortality due to lung cancer. We use data from the National Lung Screening Trial (NLST) in the USA to predict the likely effects of such screening in Germany.

Methods: The number of heavy smokers aged 55–74 in Germany was extrapolated from survey data obtained by the Robert Koch Institute. Published data from the NLST were then used to estimate the likely effects of low dose CT screening of heavy smokers in Germany.

Results: If low dose CT screening were performed on 50% of the heavy smokers in Germany aged 55–74, an estimated 1 329 506 persons would undergo such screening. If the screening were repeated annually, then, over three years, 916 918 screening CTs would reveal suspect lesions, and the diagnosis of lung cancer would be confirmed thereafter in 32 826 persons. At least one positive test result in three years would be obtained in 39.1% of the participants (519 837 persons). 4155 deaths from lung cancer would be prevented over 6.5 years, and the number of persons aged 55–74 who die of lung cancer in Germany would fall by 2.6%. 12 449 persons would have at least one complication, and 1074 persons would die in the 60 days following screening.

Conclusion: The screening of heavy smokers for lung cancer can lower their risk of dying of lung cancer by 20% in relative terms, corresponding to an absolute risk reduction of 0.3 percentage points. These figures can provide the background for a critical discussion of the putative utility of this type of screening in Germany.

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The National Lung Screening Trial (NLST), completed in 2011, provided a new evidential basis for the use of low dose computed tomography (low dose CT) to screen for lung cancer (1). Altogether, this randomized study included 53 454 heavy smokers in the age group 55 to 74 years. The participants underwent either conventional radiographic examination or low dose thoracic CT (average effective dose 1.4 mSv; estimated organ dose for the lungs 4.5 mGy [2]) annually for a period of 3 years. The median observation period thereafter was 6.5 years.

Lung cancer mortality was 1.3% in the low dose CT group and 1.6% in the conventional radiography group. The number needed to screen (NNS) in order for low dose CT to prevent one additional lung cancer death among persons who had already undergone at least one screening was 320. Overall mortality was also lower for low dose CT (7.0%) than for conventional radiography (7.5%).

A Cochrane Review of screening for lung cancer revealed that yearly low dose CT screening is associated with reduced lung cancer mortality in high-risk smokers. The authors remarked, however, that further data on cost effectiveness and the relationship between benefit and harm in various risk groups and settings are required (3).

The authors of the NLST drew attention to the following limitations of the study:

- Healthier smokers may have been particularly attracted to participate.
- CT scanning technology has advanced since the end of the study period (August 2002 to September 2007).
- The study was carried out in specialized lung cancer centers.
- The effect of screening for longer than 3 years could not be estimated.
- Together with a high rate of false-positive findings, the rate of overdiagnosis could not be estimated.
- The risk of radiation-induced cancer remains to be analyzed.

The last two points have since been addressed with the aid of statistical models. Other authors have also raised a number of questions that need to be answered before a position can be elaborated with regard to population-related low dose CT screening (4, 5).

Even with these limitations/problems, and although a meta-analysis of European studies is being planned (6), public debate of the benefits and risks of screening for lung cancer is inevitable. The discussion has recently been fueled by the decision of the US Centers for Medicare and Medicaid Services to cover the cost of low dose CT screening for those insured by Medicare (7).

Elaboration of a position for low dose CT screening in Germany requires consideration of issues with a bearing on the willingness of the population to undergo screening: the examination should be brief, universally available, minimally invasive, and free of charge for the participant and should involve low levels of pain and risk. The screening should be of high quality, and suspect findings should have clear consequences (8).

Our aim in writing this article is to extrapolate the results of low dose CT screening in the NLST to a population-wide lung cancer screening program in Germany and thus to provide a basis for critical discussion of such screening for lung cancer in this country. It is expressly not the aim of this article to criticize, express opinions, or take a position with regard to low dose CT screening.

Material and methods

The number of heavy smokers in the age group 55 to 74 years (reflecting the NLST participants) in the German population was estimated with the aid of data from the Robert Koch Institute *(eBox 1)*. The key data of the NLST were extracted from the original publication (1). The low dose CT imaging findings were divided into positive, i.e., suspicious of lung cancer (non-calcified nodes at least 4 mm in diameter), other lesions (e.g., adenopathy or similar), and slight or no changes. The NLST definitions of minor, intermediate, and major complications are shown in *eBox 2*. The authors of the original NLST publication did not present a number needed to harm (NNH), so this was calculated from the published data *(eBox 3)*.

The relative frequencies of events and adverse effects in the NLST were applied to the portion of the German population that fulfilled the smoking history criteria of the original publication (1). It was assumed that only 50% of these persons would take part in low dose CT screening.

The influence of the NNS and willingness to participate on the number of avoidable lung cancer deaths (N_p) was investigated in a sensitivity analysis. N_p is calculated from the number of eligible persons N_e, the willingness to participate R, and the NNS: $N_p = N_e \times R/NNS$.

The estimated rate of overdiagnosis was taken from the work of Patz et al. (9). All existing official pronouncements by organizations and professional bodies were identified by a systematic survey of the published literature (search term: "lung cancer screening" [title], N = 643 publications; 10 May 2015) *(eTable 1)*.

Results

Table 1 summarizes the results of the NLST. The rate of positive findings, i.e., suspicion of tumor, was much higher in the low dose CT group, although the proportion of false-positive results was almost identical between the two groups. Thirty-nine percent of those in the low dose CT group and 16% in the conventional radiography group had at least one positive screening result. While the incidence of lung cancer was higher in the low dose CT group (645 per 100 000 person-years) than in the radiography group (572 per 100 000 person-years; relative effect size 1.13, 95% confidence interval [95% CI] 1.03 to 1.23), lung cancer mortality and overall mortality were lower for the low dose CT group than for the radiography group (lung cancer mortality: 247 versus 309 per 100 000 person-years; overall mortality: 1877 versus 2000, rate not reported). The absolute reduction in risk of lung cancer mortality (median duration of follow-up 6.5 years) was 0.3 percentage points (from 1.6 to 1.3%), corresponding to a relative risk reduction of 20% (mortality ratio 0.80; 95% CI 0.73 to 0.93).

Applying the inclusion criteria of the NLST, 2 659 012 persons in Germany would be eligible for low dose CT screening. This group comprises 13.6% of all 55 to 74-year-olds in the country *(eTable 2)*. If 50% were willing to participate, 1 329 506 persons would be screened. Application of the NLST parameters to this population would necessitate 3 796 404 low dose CT investigations over a 3-year period, 916 918 of which would arouse suspicion of a tumor. Alongside clinical examination, clarification would involve 530 712 diagnostic imaging procedures (including thoracic CT in 456 167 cases). Invasive procedures such as bronchoscopy or exploratory surgery would take place in 71 703 cases. The suspicion of lung cancer would be confirmed in 32 826 persons *(Table 2)*. The rate of true-positive screening results is therefore 6.3% in relation to all 519 837 persons with at least one positive screening result and 3.6% for all 916 918 of screenings arousing suspicion of a tumor.

According to Patz et al., 6073 (18.5%) of the 32 826 lung cancer diagnoses would represent overdiagnosis (9). Over the 3 years of screening there would be at least one positive screening result in 519 837 participants (39.1%), in 487 011 of whom further investigation would reveal no lung cancer. For the 1 329 506 persons screened, an NNS of 320 would mean prevention of 4155 lung cancer deaths (without "death certificate only" [DCO] cases) in the 6.5 years of follow-up. The sensitivity analyses show that the number of preventable lung cancer deaths is strongly dependent both on the readiness of heavy smokers to participate and on the NNS. For example, with a participation rate of only 30% and a higher NNS (e.g., 360) the number of preventable lung cancer deaths would be 2216 *(Figure)*.

TABLE 1

Results of the National Lung Screening Trial (1)

	Low dose CT		Conventional chest radiography		Relative effect size	95% CI
	N	%	N	%		
Participants	26 722		26 732			
Compliance		95.0		93.0		
Screening examinations	75 126		73 470			
Positive results	18 146	24.2	5043	6.9		
– False positive	17 497	96.4	4764	94.5		
– True positive	649	3.6	279	5.5		
Conspicuous result without suspicion of malignancy	5622	7.5	1575	2.1		
At least one positive result (proportion of participants)		39.1		16.0		
Lung cancer diagnosed	**1060**		**941**			
– After positive result	649		279			
– After negative result	44		137			
– After end of study or no screening performed*[1]	367		525			
Program sensitivity*[2]		94.1		67.9		
Incidence of lung cancer (per 100 000 person years)	645		572		1.13	1.03–1.23
Deaths (from any cause)	**1877**		**2000**			
Relative reduction in overall mortality (%)					6.7	1.2–13.6
Unknown cause of death	12		9			
Known cause of death	1865		1991			
– Lung cancer, incl. DCO	427	22.9	503	25.3		
– Other neoplasms	416	22.3	442	22.2		
– Cardiovascular diseases	486	26.1	470	23.6		
– Diseases of the respiratory tract	175	9.4	226	11.4		
– Treatment complications	12	0.6	7	0.4		
– Others	349	18.7	343	17.2		
Lung cancer deaths, without DCO	356		443			
Lung cancer mortality (per 100 000), without DCO	247		309		0.80	0.73–0.93
Relative risk reduction (%)					20.0	6.8–26.7
Participants with at least one screening	26 455		26 232			
– Lung cancer deaths (without DCO)	346	1.3	425	1.6		
Number needed to screen	320					
Number needed to harm *[3]						
– Major complication	307–453					
– Intermediate complication	192–281					
– Minor complication	1406–2671					
– At least one complication	109–163					
– Death within 60 days of highly invasive procedure	1272–3815					

*[1] Altogether there were 3875 death certificates, 1877 in the low dose CT group and 1998 in the conventional radiography group; the cause of death was unknown in 12 and 7 persons respectively; the denominators for the percentages of causes of death relate to all deaths for which the cause was known, i.e., 1865 and 1991 deaths respectively; overall (low dose CT and conventional radiography) lung cancer was diagnosed 892 times, n = 35 in participants who were not screened at all, n = 802 in screened participants but after the end of the screening phase, and n = 55 in persons who were scheduled for but had not yet undergone screening .

*[2] The program sensitivity for the first 3 years was calculated from the data of Patz et al. (9).

*[3] See *eBox 3*

CT, computed tomography; N, number; 95% CI, 95% confidence interval; DCO, death certificate only (deaths for which the death certificate is the only source of information); for definitions of major, intermediate, and minor complications, see *eBox 2*

TABLE 2

Hypothetical calculation of key data on diagnostic follow-up of screening participants in Germany who had one positive result (i.e., tumor suspected) in three rounds of low dose CT screening

Variable	Number of persons n	Proportion of positive results	Number of positive results
Positive result (tumor suspected)			
T0 (100%)	1 329 506	0.2733	363 354
T1 (93.94%)	1 248 938	0.2792	348 703
T2 (91.61%)	1 217 960	0.1682	204 861
Total positive results			**916 918**
Lung cancer confirmed		0.0358	32 826
Lung cancer not confirmed		0.9642	884 092
Full information on diagnostic follow-up*			916 918
At least one diagnostic follow-up examination		0.7207	660 823
Clinical examination		0.5892	540 248
Imaging procedures		0.5788	530 712
– Chest radiography		0.1439	131 945
– Thoracic CT		0.4975	456 167
– FDG PET or FDG PET-CT		0.0831	76 196
Percutaneous cytology		0.0182	16 688
– Transthoracic		0.0143	13 112
– Extrathoracic		0.0045	4126
Bronchoscopy		0.0379	34 751
– Without cytology or biopsy		0.0181	16 596
– With cytology or biopsy		0.0221	20 264
Operation		0.0403	36 952
– Mediastinoscopy/otomy		0.0066	6052
– Thoracoscopy		0.0132	12 103
– Thoracotomy		0.0288	26 407
Other procedures		0.0185	16 963

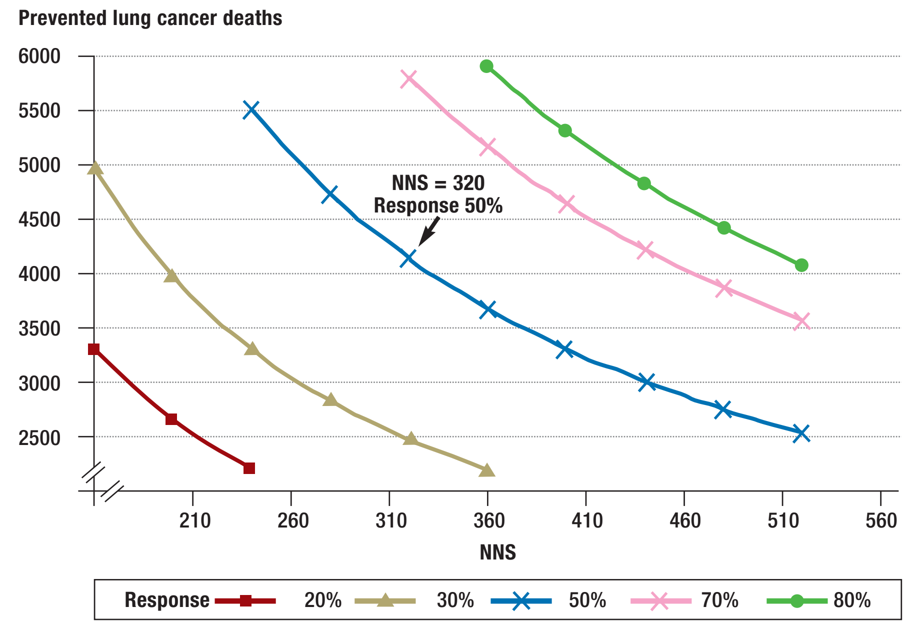
T0, T1, T2: first, second, and third annual screening; participation of 50% of the 2 659 014 heavy smokers in Germany who fulfilled the study criteria in the first screening was assumed. The relative decrease in cohort size from T0 to T1 and T2 is identical with the relative decrease in size of the low dose CT arm of the National Lung Screening Trial (NLST). In the NLST information on diagnostic follow-up in 2.4% of the persons with a positive result was missing. For our calculation we assumed that no data were missing.
* In contrast to the NLST, we assume availability of complete diagnostic work-up on all participants with a positive screening result.
CT, computed tomography; n, number; FDG PET, fluorodeoxyglucose positron emission tomography

A 3-year screening program in Germany would be associated with at least one complication in the course of further investigation in 12 449 persons. According to the definition of the NLST there would be 4363 major complications, including death, and 1074 deaths (505 with and 569 without confirmation of lung cancer) would occur within 60 days of screening following highly invasive interventions. These deaths include mortality associated with confirmatory procedures and all other causes. Of the 884 092 participants with a positive screening result in whom lung cancer was suspected but not verified, 569 (0.06%) would suffer a major complication.

Discussion

Extrapolation from the NLST data reveals that 13.6% of all 55 to 74-year-olds in Germany—i.e., 2.7 million people—would be eligible for low dose CT lung cancer screening, should it be introduced. In heavy smokers, the anticipated reduction in relative and absolute risk, respectively, of death from lung cancer after three rounds of screening and a median observation time of 6.5 years would be 20% (relative risk reduction [RRR]) and 0.3 percentage points (absolute risk reduction [ARR]). An overview of the current recommendations issued by organizations and professional bodies can be found in *eTable 1*.

FIGURE



Prevented deaths from lung cancer in Germany by participation rate and number needed to screen (NNS)

The extrapolation of prevented lung cancer deaths from the National Lung Screening Trial (NLST) data relates to the number of 2 659 012 heavy smokers in the age group 55 to 74 years. The principal analysis (arrow) was based on the assumption that 50% of persons in this age bracket would be willing to participate in a screening program, with an NNS of 320 (as in the NLST). In this scenario, 4155 lung cancer deaths would be prevented in Germany in the 6.5 years of follow-up. The individual curves show the impact of participation rate (20–80%) and NNS on the number of lung cancer deaths prevented

It can be calculated that low dose CT screening of heavy smokers in the age bracket 55 to 74 years would prevent 4155 deaths from lung cancer nationwide within 6.5 years. In 2013, 24 361 members of this age group died of lung cancer in Germany (www.gbe-bund.de, accessed on 5 January 2015). Assuming constant mortality over a 6.5-year period, a total of 158 347 persons aged 55 to 74 years would die of lung cancer. Screening of heavy smokers with a participation rate of 50% would prevent 2.6% of lung cancer deaths (4155/158 347) in this age group in the general population.

Implementation of a low dose CT screening program in Germany

In contrast to organized screening programs in which invitations are sent to all members of the population in the target group, use of residential registry data to invite all 55 to 74-year-olds to take part in low dose CT screening for lung cancer seems impractical, given that only 13.6% of those in this age bracket are current or previous heavy smokers. Planning is hampered by the lack of an organized system for invitation.

In the NLST, screened persons with suspected cancer were often investigated and, when necessary, treated at specialized lung centers. However, no standardized procedure for confirmatory investigation was defined. The NLST authors report that surgical resection in their study was associated with mortality of 1% (1). In a representative population study from the USA the mortality was 4% and the survival rate was related to the number of operations performed (10). Assuming that this connection between surgeon's experience and patient survival also applies to Germany, if screening were introduced it would have to be decided to which institutions participants with suspected tumor should be referred. Germany currently has 43 lung centers certified by the German Cancer Society (DKG) (www.oncomap.de/index.php, accessed on 25 February 2015).

Cumulative effective radiation dose and damage

The expected number of radiation-related lung cancer deaths was calculated taking account of not only the low dose CT screening but also the follow-up CT examinations to clarify the nature of suspect lesions (11). Statistical models calibrated to the individual data from the NLST were used to this end. The extrapolations were made on the basis of a simulated cohort of 100 000 persons followed up from 45 to 90 years of age. In such a cohort, annual low dose CT screening of 55 to 74-year-old heavy smokers would prevent 459 deaths from lung cancer. However, 24 of those screened would die of lung cancer caused by the radiation received.

In contrast to the NLST, in which annual low dose CT screening was limited to 3 years, we simulated 20 low dose CT examinations plus the potential follow-up CT. This simulation in a group of 100 000 participants revealed that 141 lung cancers would be overdiagnosed (2.7% of all lung cancers and 8.7% of lung cancers detected by screening) (11). A further extrapolation—assuming yearly low dose CT screening (2 mSv) from 55 to 74 years of age and the necessary confirmatory investigations (follow-up CT; 8 mSv)—yielded a cumulative effective radiation dose (lungs) of up to 280 mSv (12).

The effective radiation dose from low dose CT scanners can be expected to fall further in future, resulting in fewer radiation-induced deaths from lung cancer. The existing sensitivity analyses suggest that, with the current models, the impact on prevented lung cancer deaths of a decreased radiation dose from modern CT scanners would be much lower than that of, for example, a change of 10% in either the participation rate or the NNS.

Possible measures to reduce false-positive results

In the NLST 64% of confirmatory examinations revealed nodes of no more than 7 mm in diameter. Repeated volumetric measurements of lesions, as practiced in the NELSON Trial (13) and the UK Lung Screen Pilot Trial (14), could further reduce the rate of false-positive results. Predictably, raising the minimum diameter of nodes to be referred for clarification lowers the rate of false positives. A minimum diameter of 8 mm (instead of 4 mm) in the NLST would have avoided 66% of the false-positive results and 10.5% of the lung cancers found on screening would have been diagnosed later or remained undetected (15).

In a follow-up publication the NLST collective was divided on the basis of various factors estimated from multivariate regression models into quintiles (Q) of 5-year lung cancer mortality risk (Q1: 0.15–0.55%; Q2: 0.56–0.84%; Q3: 0.85–1.23%; Q4: 1.24–2.00%; Q5: >2%) *(eBox 4)*. From Q1 to Q5 the NNS went down from 5276 to 161. If screening were restricted to quintiles Q3 to Q5 (i.e., from an estimated 5-year lung cancer mortality risk of 0.85%), the NNS would be 208. The proportion of false positives would fall from 97% (Q1) to 88% (Q5). The ratio of the number of persons with false-positive results to the number of prevented lung cancer deaths would fall sharply from 1648 (Q1) to 65 (Q5). Eighty-eight percent of all lung cancer deaths preventable by screening would fall among the 60% of the total collective contained in the three highest quintiles (risk ≥ 0.85%) (16).

Consequences for mental health

If around 520 000 persons in Germany have at least one screening result arousing suspicion of tumor over a 3-year period but cancer is confirmed in "only" approximately 33 000 persons in the following 6.5 years, that means some 487 000 men and women have a false-positive result with ensuing investigations and psychic stress. The NLST does not report the psychic consequences of false-positive findings. The NELSON Trial showed that after a second screening, anxiety and stress in persons whose first screening aroused suspicion of tumor or indicated another, non-oncological lesion decrease to the initial levels (17). In participants whose first screening revealed no abnormal findings, anxiety and stress sank to levels lower than before screening (18). A false-positive result was associated with a higher likelihood of giving up smoking. In the context of the NELSON Trial, it was observed that the rate of giving up smoking in the CT group was higher than the expected rate in the general population (14.5% versus 3–7%) (18). However, repeated negative screening could lead some participants to start smoking again.

Cost effectiveness of low dose CT screening

A detailed cost effectiveness analysis of the NLST data showed additional costs of US$ 1631 per screened person, associated with a gain of 0.0316 years of life and 0.0201 quality-adjusted life years (QALYs). The corresponding incremental cost–effectiveness ratio (ICER) was US$ 52 000 per extra year of life and US$ 81 000 per additional QALY *(eBox 5)*. However, the results of this analysis were heavily dependent on the assumptions made (19).

Summary

The data presented here for lung cancer screening by low dose CT provide a basis for critical discussion of the potential value of such screening in the German population. The extrapolations for Germany were made under the assumption that the results of the NLST are both internally valid and transferable to the population of this country.

Conflict of interest statement

Prof. Schuler has received payments for consulting (advisory board) from AstraZeneca, Boehringer Ingelheim, Novartis, and Celgene. He has received honoraria for expert advice in legal proceedings. He has received reimbursement of conference fees from Boehringer Ingelheim and Lilly. He has received financial support for studies (third-party funding) from AstraZeneca, Boehringer Ingelheim, BMS, Lilly, and Novartis. He is a member of the scientific advisory board of the Institute for Quality and Efficiency in Health Care (IQWIG).

The remaining authors declare that no conflict of interest exist.

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REFERENCES

1. Aberle DR, Adams AM, Berg CD, et al.: Reduced lung-cancer mortality with low-dose computed tomographic screening. N Engl J Med 2011; 365: 395–409.
2. Larke FJ, Kruger RL, Cagnon CH, et al.: Estimated radiation dose associated with low-dose chest CT of average-size participants in the National Lung Screening Trial. Am J Roentgenol 2011; 197: 1165–9.
3. Manser R, Lethaby A, Irving LB, et al.: Screening for lung cancer. Cochrane Database Syst Rev 2013; 6: CD001991.
4. Bach PB, Mirkin JN, Oliver TK, et al.: Benefits and harms of CT screening for lung cancer: a systematic review. JAMA 2012; 307: 2418–29.
5. Prokop M: Lung cancer screening: the radiologist's perspective. Semin Respir Crit Care Med 2014; 35: 91–8.
6. Field JK, van KR, Pedersen JH, et al: European randomized lung cancer screening trials: Post NLST J Surg Oncol 2013; 108: 280–6.
7. Schmidt C: Lung cancer screening poised to expand. J Natl Cancer Inst 2015; 107: 6–7.
8. Giersiepen K, Hense HW, Klug SJ, Antes G, Zeeb H: [Planning, implementation and evaluation of cancer screening programs]. Z Arztl Fortbild Qualitatssich 2007; 101: 43–9.

TABLE 3

Hypothetical calculation of complications following the most invasive procedures for clarification of a positive result (tumor suspected) among participants in low dose CT screening in Germany

	Thoracotomy, thoracoscopy, or mediastinoscopy		Bronchoscopy		Needle biopsy		Non-invasive procedure		Total	
	N	Proportion	N	Proportion	N	Proportion	N	Proportion	N	Proportion
Lung cancer confirmed	25 745		3844		1668		1569		32 826	
No complications	17 398	0.6758	3490	0.9079	1314	0.7879	1316	0.8387	23 519	0.7165
At least one complication	8347	0.3242	354	0.0921	354	0.2121	253	0.1613	9307	0.2835
– major	3591	0.1395	101	0.0263	0	0	101	0.0645	3794	0.1156
– intermediate	4096	0.1591	253	0.0658	354	0.2121	101	0.0645	4804	0.1463
– minor	656	0.0255	0	0	0	0	51	0.0323	707	0.0215
Death within 60 days of the most invasive procedure	252	0.0098	202	0.0526	51	0.0303	0	0	505	0.0154
Lung cancer not confirmed	8487		11 758		3448		860 398		884 092	
No complications	7142	0.8415	11 188	0.9515	3082	0.8939	859 538	0.9990	880 949	0.9964
At least one complication	1345	0,1585	570	0.0485	366	0.1061	860	0.0010	3 142	0.0036
– major	466	0.0549	103	0.0088	0	0.0000	0	0.0000	569	0.0006
– intermediate	673	0.0793	466	0.0396	313	0.0909	860	0.0010	2 312	0.0026
– minor	207	0.0244	0	0.0000	52	0.0152	0	0.0000	259	0.0003
Death within 60 days of the most invasive procedure	104	0.0122	207	0.0176	0	0.0000	258	0.0003	569	0.0006
All procedures for clarification of a positive result	34 232		15 602		5116		861 967		916 918	
No complications	24 540	0,7169	14 678	0,9408	4396	0.8593	860 854	0.9987	904 468	0.9864
At least one complication	9692	0.2831	924	0.0592	720	0.1407	1113	0.0013	12 449	0.0136
– major	4057	0.1185	205	0.0131	0	0.0000	101	0.0001	4363	0.0048
– intermediate	4769	0.1393	719	0.0461	667	0.1304	962	0.0011	7116	0.0078
– minor	864	0.0252	0	0.0000	52	0.0102	51	0.0001	967	0.0011
Death within 60 days of the most invasive procedure	356	0.0104	409	0.0262	51	0.0099	258	0.0003	1074	0.0012

If a given diagnostic procedure was repeated in the same patient, the first procedure was counted; complications arising before the most invasive procedure were not included in analysis; each participant could have up to three positive screening results and thus be counted up to three times in each row of figures. Proportions were calculated for each column

KEY MESSAGES

- With a participation rate of 50%, annual screening of heavy smokers in the age group 55 to 74 years in Germany for a period of 3 years would result in detection of a suspected tumor in 916 918 examinations and confirmation of lung cancer in 32 826 persons.
- There would be at least one positive screening result in 519 837 persons over the 3 years of screening, 487 011 of whom would be found not to have lung cancer on further investigation.
- A total of 4155 deaths from lung cancer would be prevented over a period of 6.5 years, and the number of lung cancer deaths in the age group 55 to 74 years would decrease by 2.6%.
- A total of 12 449 persons would suffer at least one complication, and 1074 persons would die within 60 days after the most invasive procedures.

9. Patz EF, Jr., Pinsky P, Gatsonis C, et al.: Overdiagnosis in low-dose computed tomography screening for lung cancer. JAMA Intern Med 2014; 174: 269–74.
10. Bach PB, Cramer LD, Schrag D, Downey RJ, Gelfand SE, Begg CB: The influence of hospital volume on survival after resection for lung cancer. N Engl J Med 2001; 345: 181–8.
11. de Koning HJ, Meza R, Plevritis SK, 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.
12. McCunney RJ, Li J: Radiation risks in lung cancer screening programs: a comparison with nuclear industry workers and atomic bomb survivors. Chest 2014; 145: 618–24.
13. van Klaveren RJ, Oudkerk M, Prokop M, et al.: Management of lung nodules detected by volume CT scanning. N Engl J Med 2009; 361: 2221–9.
14. Baldwin DR, Duffy SW, Wald NJ, Page R, Hansell DM, Field JK: UK Lung Screen (UKLS) nodule management protocol: modelling of a single screen randomised controlled trial of low-dose CT screening for lung cancer. Thorax 2011; 66: 308–13.
15. Gierada DS, Pinsky P, Nath H, Chiles C, Duan F, Aberle DR: Projected outcomes using different nodule sizes to define a positive CT lung cancer screening examination. J Natl Cancer Inst 2014; 106.
16. Kovalchik SA, Tammemagi M, Berg CD, et al.: Targeting of low-dose CT screening according to the risk of lung-cancer death. N Engl J Med 2013; 369: 245–54.
17. van den Bergh KA, Essink-Bot ML, Borsboom GJ, Scholten ET, van Klaveren RJ, de Koning HJ: Long-term effects of lung cancer computed tomography screening on health-related quality of life: the NELSON trial. Eur Respir J 2011; 38: 154–61.
18. van der Aalst CM, van den Bergh KA, Willemsen MC, de Koning HJ, van Klaveren RJ: Lung cancer screening and smoking abstinence: 2 year follow-up data from the Dutch-Belgian randomised controlled lung cancer screening trial. Thorax 2010; 65: 600–5.
19. Black WC, Gareen IF, Soneji SS, et al.: Cost-effectiveness of CT screening in the National Lung Screening Trial. N Engl J Med 2014; 371: 1793–802.

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@ Supplementary material
For eReferences please refer to:
www.aerzteblatt-international.de/ref3815

eBoxes, eTables:
www.aerzteblatt-international.de/15m0637

Supplementary material to:

Lung Cancer Screening Using Low Dose CT Scanning in Germany

Extrapolation of Results From the National Lung Screening Trial

by Andreas Stang, Martin Schuler, Bernd Kowall, Kaid Darwiche, Hilmar Kühl, and Karl-Heinz Jöckel

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eREFERENCES

e1. Aberle DR, Adams AM, Berg CD, et al.: Reduced lung-cancer mortality with low-dose computed tomographic screening. N Engl J Med 2011; 365: 395–409.

e2. Gößwald A, Lange M, Dölle R, Hölling H: [The first wave of the German Health Interview and Examination Survey for Adults (DEGS1): participant recruitment, fieldwork, and quality management]. Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz 2013; 56: 611–9.

e3. Robert Koch-Institut: Verbreitung von Krebserkrankungen in Deutschland. Entwicklungen der Prävalenzen zwischen 1990 und 2010. Berlin: 2010.

e4. Kamtsiuris P, Lange M, Hoffmann R, et al.: [The first wave of the German Health Interview and Examination Survey for Adults (DEGS1): sample design, response, weighting and representativeness]. Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz 2013; 56: 620–30.

e5. Manser R, Lethaby A, Irving LB, et al.: Screening for lung cancer. Cochrane Database Syst Rev 2013; 6: CD001991.

e6. Jaklitsch MT, Jacobson FL, Austin JH, et al.: The American Association for Thoracic Surgery guidelines for lung cancer screening using low-dose computed tomography scans for lung cancer survivors and other high-risk groups. J Thorac Cardiovasc Surg 2012; 144: 33–8.

e7. Couraud S, Cortot AB, Greillier L, et al.: From randomized trials to the clinic: is it time to implement individual lung-cancer screening in clinical practice? A multidisciplinary statement from French experts on behalf of the French intergroup (IFCT) and the groupe d'Oncologie de langue francaise (GOLF). Ann Oncol 2013; 24: 586–97.

e8. Prosch H, Studnicka M, Eisenhuber E, et al.: [Opinion of the Austrian Society of Radiology and the Austrian Society of Pneumology]. Wien Klin Wochenschr 2013; 125: 339–45.

e9. Wender R, Fontham ET, Barrera E Jr., et al.: American Cancer Society lung cancer screening guidelines. CA Cancer J Clin 2013; 63: 107–17.

e10. Field JK, Aberle DR, Altorki N, et al.: The International Association Study Lung Cancer (IASLC) Strategic Screening Advisory Committee (SSAC) response to the USPSTF recommendations. J Thorac Oncol 2014; 9: 141–3.

e11. Frauenfelder T, Puhan MA, Lazor R, et al.: Early detection of lung cancer: a statement from an expert panel of the Swiss university hospitals on lung cancer screening. Respiration 2014; 87: 254–64.

e12. Gould MK: Clinical practice. Lung-cancer screening with low-dose computed tomography. N Engl J Med 2014; 371: 1813–20.

e13. Herth FJ, Hoffmann H, Heussel CP, Biederer J, Groschel A: [Lung cancer screening-update 2014]. Pneumologie 2014; 68: 781–3.

e14. Blackmon SH, Feinglass SR: The United States preventive services task force recommendations for lung cancer screening. Thorac Surg Clin 2015; 25: 199–203.

e15. Kauczor HU, Bonomo L, Gaga M, et al.: ESR/ERS white paper on lung cancer screening. Eur Respir J 2015; 46: 28–39.

e16. Kazerooni EA, Armstrong MR, Amorosa JK, et al.: ACR CT accreditation program and the lung cancer screening program designation. J Am Coll Radiol 2015; 12: 38–42.

e17. Mazzone P, Powell CA, Arenberg D, et al.: Components necessary for high-quality lung cancer screening: American College of Chest Physicians and American Thoracic Society Policy Statement. Chest 2015; 147: 295–303.

e18. Wood DE, Kazerooni E, Baum SL, et al.: Lung cancer screening, version 1.2015: featured updates to the NCCN guidelines. J Natl Compr Canc Netw 2015; 13: 23–34.

eBOX 1

Calculation of the number of heavy smokers in Germany, based on the data of the German Health Interview and Examination Survey for Adults

Eligible for the National Lung Screening Trial (NLST) were persons in the age group 55–74 years with a smoking history of at least 30 pack-years (e1). Ex-smokers were eligible if they had stopped smoking no more than 15 years before inclusion in the study. To estimate how many men and women in Germany would fulfill the NLST criteria for participation in a low dose CT screening program, we used data from the German Health Interview and Examination Survey for Adults (DEGS) (e2). Out of the total of 7115 probands, 428 (6.0%) were excluded from estimation of the prevalence of heavy smoking owing to the absence of data on smoking status, time since giving up smoking, or number of pack-years.

The NLST excluded probands with a history of lung cancer. The estimated 10-year prevalence of lung cancer for men/women in the age groups 50–59, 60–69, and 70–79 years in Germany was, respectively, 0.17%/0.09%, 0.40%/0.14%, and 0.63%/0.16% (e3). The number of persons in Germany eligible for lung cancer screening according to the NLST inclusion criteria was corrected on the basis of these figures.

Further, study-related reasons for exclusion such as thoracic CT in the 18 months immediately preceding recruitment (e1), hemoptysis (e2), or unexplained weight loss exceeding 6.8 kg in the previous 12 months (e3) were not considered, because there are no population-based prevalence data for these factors in heavy smokers. The prevalences calculated per 5-year age band for men and women in Germany who fulfilled the inclusion criteria were statistically weighted by a factor calculated according to the disproportionate sampling design (e4).

eBOX 2

Definition of complications in the National Lung Screening Trial

- **Major complications:**
  Acute respiratory failure, anaphylaxia, bronchopulmonary fistula, cardiac arrest, cerebrovascular event (cerebral insult), heart failure, death, hemothorax requiring drainage, myocardial infarction, respiratory arrest, wound dehiscence, bronchial stump insufficiency requiring thoracostomy or drainage for more than 4 days, empyema, injury of vital organs or vessels, mechanical ventilation for more than 48 h after operation, thromboembolic events requiring intervention, chylus fistula, brachial plexopathy, collapsed lung, infarction of the sigmoid colon

- **Intermediate complications:**
  Blood loss requiring transfusion, cardiac arrhythmia requiring treatment, fever requiring administration of antibiotics, hospitalization after procedure, pain requiring referral to a pain specialist, pneumothorax requiring drainage, rib fracture(s), vocal cord immobility or paresis, infection requiring administration of antibiotics, cardiac ischemia (ST-segment elevation), bronchitis, pneumonia, pleural effusion, sepsis, respiratory distress, splenomegaly with splenic infarcts, mucous plug requiring bronchoscopy, steroid-induced diabetes

- **Minor complications:**
  Allergic reaction, bronchospasm, vasovagal reaction/hypotonia, subcutaneous emphysema, atelectases, pneumothorax not requiring treatment by drainage, ileus, seroma, paresthesias/hyperesthesias, others

eBOX 3

Derivation of the number needed to harm (NNH)

The authors of the National Lung Screening Trial (NLST) (1) reported the number needed to screen (NNS), but did not discuss NNH. According to a recent Cochrane Review, screening using chest radiography yields no benefit for the patient (e5); this means that the NNS for the NLST can be applied to Germany although no systematic screening by means of chest radiography has yet taken place in this country.

With regard to the NNH for Germany, however, it is unclear whether the situation here is better described by the difference in risk from the chest radiography group or from no chest radiography screening. Therefore we report a range of NNH with a lower limit of 0% relative frequency and an upper limit defined by the observed relative frequency of complications in the chest radiography group of the NLST. The denominator of relative frequency of complications was 26 722 persons in the low dose CT group and 26 732 in the chest radiography group.

TABLE - eBOX 3

Derivation of the number needed to harm (NNH)

	Complications								
	Low dose CT		Chest radiography		Persons		Risk		NNH
Lung cancer	Confirmed	Not confirmed	Confirmed	Not confirmed	CT	Chest radiography	CT	Chest radiography	
NNH derivation with chest radiography screening									
Major	75	12	24	4	26 722	26 732	0.00325574	0.00104743	453
Intermediate	95	44	35	9	26 722	26 732	0.00520171	0.00164597	281
Minor	14	5	6	3	26 722	26 732	0.00071102	0.00033668	2671
At least one complication	184	61	65	16	26 722	26 732	0.00916848	0.00303008	163
Death	10	11	11	3	26 722	26 732	0.00078587	0.00052372	3815
NNH derivation without chest radiography screening									
Major	75	12	24	4	26 722	26 732	0.00325574	0	307
Intermediate	95	44	35	9	26 722	26 732	0.00520171	0	192
Minor	14	5	6	3	26 722	26 732	0.00071102	0	1406
At least one complication	184	61	65	16	26 722	26 732	0.00916848	0	109
Death	10	11	11	3	26 722	26 732	0.00078587	0	1272

CT, computed tomography

eBOX 4

Determination of quintiles of 5-year lung cancer mortality risk

The participants' absolute risk of dying from lung cancer and their life expectancy were estimated using Cox proportional hazards regressions, taking account of competing risks. Individual characteristics (age, sex, ethnicity, body mass index, cigarette consumption in pack-years, years since end of smoking, emphysema, and lung cancer in first-degree relatives) were also considered. The risk model was validated using data from the radiography arm of the PCLO Trial (16).

eBOX 5

Cost effectiveness of low dose computed tomography screening

The incremental cost–effectiveness ratio (ICER) sums up the cost effectiveness of an action. The ICER is calculated by dividing the difference between the costs of two possible courses of action by the difference between their effects. Thus, it expresses the average additional cost per unit of difference. Black et al. (19) determined the incremental costs per year of life gained. An ICER of $ 52 000 per life year therefore means that $ 52 000 must be invested in low dose screening to gain one year of life.

For calculation of quality-adjusted life years (QALYs), the prolongation of life achieved by an action is multiplied by an estimation of life quality (utility value) that varies between 0 (worst conceivable quality of life) and 1 (best conceivable quality of life). If the low dose CT screening achieved on average 0.0316 additional years of life per person screened and the utility value were 0.636, the gain in QALY would be 0.0316 × 0.636 = 0.0201. According to the data of the NLST, therefore, one QALY is associated with costs of $ 81 000.

eTABLE 1

Recommendations of organizations and professional bodies on the topic of lung cancer screening, in chronological order

Organization	Year	Reference	Tendency*	Statement
American Association for Thoracic Surgery (AATS)	2012	(e6)	+	Screening according to the NLST criteria recommended – Also for patients aged 50 years or more with at least 20 pack-years
French multidisciplinary expert panel; *Groupe d'Oncologie de Langue Francaise* (GOLF)	2013	(e7)	(+)	Individual screening based on the NLST criteria recommended
Austrian Society of Radiology and Austrian Society of Pneumology	2013	(e8)	+	Screening based on the NLST criteria recommended; detailed patient information and standardized investigation of positive findings required
American Cancer Society	2013	(e9)	+	Screening analogous to the NLST criteria recommended
International Association for the Study of Lung Cancer (IASLC) and Strategic Screening Advisory Committee (SSAC)	2014	(e10)	(+)	Screening analogous to the NLST criteria recommended, but only at specialized centers – Volumetry – Use of better risk prediction models than recommended in the NLST, to reduce false-positive results
Multidisciplinary expert panel of the Swiss university hospitals	2014	(e11)	–	Screening exclusively in the context of a national observational study recommended
American Lung Association	2014	(e12)	+	Screening analogous to the NLST criteria recommended, but only at specialized centers
American Academy of Family Physicians	2014	(e12)	–	Screening cannot be recommended on the basis of a single study
German Respiratory Society, German Thoracic Surgery Society, and German Röntgen Society	2014	(e13)	–	Lung cancer screening currently not recommended
United States Preventive Services Task Force	2015	(e14)	+	Screening analogous to the NLST criteria recommended – Upper age limit extended to 80 years
European Society of Radiology (ESR) and European Respiratory Society (ERS)	2015	(e15)	(+)	Lung cancer screening recommended in clinical studies or at certified multidisciplinary centers
American College of Radiology	2015	(e16)	+	Screening analogous to the NLST criteria recommended, but only at specialized centers
American College of Chest Physicians and American Thoracic Society	2015	(e17)	+	Screening recommended
National Comprehensive Cancer Network (NCCN)	2015	(e18)	+	Screening analogous to the NLST criteria recommended

*This rating sums up the respective authors' current recommendation regarding introduction of lung cancer screening: + = in favor of screening; (+) = tendency towards endorsement of screening under certain conditions; – = rejection of screening at the current time.
NLST, National Lung Screening Trial

eTABLE 2

Estimated number of persons in the age group 55 to 74 years in Germany in 2010 fulfilling the criteria of the National Lung Screening Trial (NLST) for low dose CT screening

Age (years)	Population*2 (n)	Lung cancer prevalence	Adjusted population (n)	History of at least 30 pack-years*1		Eligible persons (n)		
				Current smokers (%)	Previous smokers (%)	Current smokers	Previous smokers	Total
Men								
55–59	2 812 652	0.0017	2 807 870	11.67	8.75	327 678	245 689	573 367
60–64	2 478 851	0.0040	2 468 936	8.98	11.34	221 710	279 977	501 687
65–69	1 922 351	0.0040	1 914 662	4.93	13.30	94 393	254 650	349 043
70–74	2 269 990	0.0063	2 255 689	3.68	5.45	83 009	122 935	205 944
Total	9 483 844		9 447 157			726 790	903 251	1 630 041
Women								
55–59	2 835 731	0.0009	2 833 179	10.64	5.51	301 450	156 108	457 558
60–64	2 581 663	0.0014	2 578 049	8.01	4.56	206 502	117 559	324 061
65–69	2 070 891	0.0014	2 067 992	4.78	2.18	98 850	45 082	143 932
70–74	2 609 224	0.0016	2 605 049	1.45	2.52	37 773	65 647	103 420
Total	10 097 509		10 084 269			644 575	384 396	1 028 971
Men and women together								**2 659 012**

*1 Estimates from the German Health Interview and Examination Survey for Adults (DEGS). No correction was made for the higher prevalence of lung cancer in heavy smokers than in the general population.
*2 German population on 31 December 2012, minus the proportion of persons with known lung cancer; weighted prevalences of current and past smokers (cessation of smoking at least 15 years previously) with at least 30 pack-years from the DEGS.
CT, computed tomography