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# Lung cancer mortality reduction by LDCT screening—Results from the randomized German LUSI trial

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**In 2011, the U.S. National Lung Cancer Screening Trial (NLST) reported a 20% reduction of lung cancer mortality after regular screening by low-dose computed tomography (LDCT), as compared to X-ray screening. The introduction of lung cancer screening programs in Europe awaits confirmation of these first findings from European trials that started in parallel with the NLST. The German Lung cancer Screening Intervention (LUSI) is a randomized trial among 4,052 long-term smokers, 50–69 years of age, recruited from the general population, comparing five annual rounds of LDCT screening (screening arm; $n$ = 2,029 participants) with a control arm ($n$ = 2,023) followed by annual postal questionnaire inquiries. Data on lung cancer incidence and mortality and vital status were collected from hospitals or office-based physicians, cancer registries, population registers and health offices. Over an average observation time of 8.8 years after randomization, the hazard ratio for lung cancer mortality was 0.74 (95% CI: 0.46–1.19; $p$ = 0.21) among men and women combined. Modeling by sex, however showed a statistically significant reduction in lung cancer mortality among women (HR = 0.31 [95% CI: 0.10–0.96], $p$ = 0.04), but not among men (HR = 0.94 [95% CI: 0.54–1.61], $p$ = 0.81) screened by LDCT ($p_{heterogeneity}$ = 0.09). Findings from LUSI are in line with those from other trials, including NLST, that suggest a stronger reduction of lung cancer mortality after LDCT screening among women as compared to men. This heterogeneity could be the result of different relative counts of lung tumor subtypes occurring in men and women.**

## Introduction

Low-dose computed tomography (LDCT) has been, or is being investigated in several randomized trials in the USA and Europe as a tool for early lung cancer detection and screening.[1] In 2011, the American National Lung Screening Trial (NLST) first reported a statistically significant reduction of mortality from lung cancer of about 20%[2] compared to chest X-ray screening. While the NLST findings led professional organizations in the USA to recommend routine screening in high risk populations,[3,4] in Europe the introduction of organized LDCT screening programs

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**What's new?**

**Low-dose computed tomography (LDCT) is an emerging tool for early lung cancer detection. Here, as part of the German Lung Cancer Screening Intervention trial, the benefits of annual LDCT screening were examined in long-term smokers ages 50 to 69. In men and women combined, no statistically significant reduction in lung cancer mortality was observed after five annual rounds of LDCT screening compared to controls. Separate analyses by sex, however, revealed significant reductions in lung cancer mortality among the women who underwent LDCT. The findings support the systematic use of LDCT in lung cancer screening, though critical optimization strategies await investigation.**



has been awaiting confirmation of reduced lung cancer mortality from the Dutch–Belgian NELSON trial,[5] including a total of 15,882 participants, and from a series of five smaller trials in Denmark (DLCST, $n$ = 4,104[6]), Italy (DANTE, $n$ = 2,450;[7] ITALUNG, $n$ = 3,206;[8] MILD, $n$ = 4,099[9]) and Germany (LUSI[10,11]), which were all initiated parallel to the NLST. More recently (2012), a further study (the UK Lung Cancer Screening Trial;[12,13] $n$ = 4,055) was initiated as a pilot for a large multicenter trial in the United Kingdom.

Findings on the effect of LDCT screening on lung cancer mortality have been published recently for trials in Denmark and Italy and were heterogeneous in size or direction.[6–9,14] At the 2018 IASLC lung cancer conference,[15] NELSON presented preliminary findings indicating significant reductions in lung cancer mortality among men and women at 10 years of study follow-up, although a detailed publication on these findings remains pending. We here report results on lung cancer mortality in the German Lung Cancer Screening Intervention study (LUSI)[10,11]—a randomized trial among 4,052 long-term smokers, 50–69 years of age, recruited from the general population—comparing five annual rounds of LDCT screening (screening arm; $n$ = 2,029 participants) to a control arm without screening intervention ($n$ = 2,023), over an average observation time of 8.8 years postrandomization.

## Materials and Methods

LUSI is a clinical research study, registered under ISRCTN registry http://www.isrctn.com/ISRCTN30604390. Detailed baseline descriptions of study design have been given previously in Refs. 10,11. This trial was approved by the local ethical review board of Heidelberg University (073/2001) and by the radiation protection authority (BfS, 22462/2, 2006-045). All study participants provided informed consent.

### Recruitment

Recruitment of study participants was based on a random sample of 50–69 years old men and women from population registers of the area around Heidelberg. Subjects were asked by mailed questionnaire about their past and current smoking habits and, if eligible, invited to the German Cancer Research Center (DKFZ) to participate. Eligibility was defined by at least 25 years smoking of at least 15 cigarettes per day, or at least 30 years smoking of at least 10 cigarettes per day, including ex-smokers who had stopped smoking not more than 10 years before invitation to screening.[16] Recruitment started October 23, 2007, and ended on April 11, 2011 (for further details see Ref. 11).

### Randomization and screening

About 4,052 eligible participants were randomized at first visit into 2,029 to receive a first, and then annually further four LDCT screens, and 2,023 controls without screening ("usual care"). At time of randomization, smoking cessation counseling was offered to all (including ex-smokers); for details, see Ref. 17. Nodules first-time detected by LDCT, in any screening round, were classified by size (largest diameter) in four categories: (*i*) no nodules or less than 5 mm, (*ii*) 5–7 mm, (*iii*) 8–10 mm and (*iv*) 10 mm or larger. Accordingly, after a two-step image evaluation and decision procedure by a trained radiologist and a senior radiologist, screening participants were (*i*) returned to regular annual screening, invited for earlier follow-up LDCT after (*ii*) 6 months or (*iii*) 3 months or (*iv*) recommended immediate diagnostic work-up. In screening rounds 2–5 ("incidence" screens), work-up of the nodules already observed in earlier screens was based exclusively on nodule growth, and classified in three categories: (*i*) no growth or volume doubling time (VDT) more than 600 days (returned to regular annual screening), (*ii*) doubling time within 400–600 days (invited for LDCT after 6 months) or (*iii*) doubling time 400 days or less (recommended immediate workup; see also schematic presentation in Supporting Information Table S1). For immediate work-up, participants were referred to a cooperating pulmonologist, who then decided about further diagnostic procedures or treatments (X-ray, full-dose CT, PET, bronchoscopy, video-assisted thoracoscopic surgery [VATS], biopsy, antibiotic treatment and short-term follow-up) at his or her discretion.

### Prospective collection of questionnaire data

In both arms, starting at baseline recruitment (time point $T_0$), all trial participants filled out a short annual questionnaire inquiring about (recent changes in smoking) habits, use of radiologic (X-ray, CT, MRI) or other (e.g., endoscopic) examinations of the lungs independently of annual LDCT screening, thoracic surgical interventions and the occurrence of cancer (lung or other organs) or cardiovascular diseases (myocardial infarction, stroke and pulmonary embolism). Follow-up questionnaires were filled out either on the occasion of annual screening visits (LDCT arm) or sent by mail to control arm participants. LDCT arm participants not complying with a scheduled screening visit also received the annual questionnaire

by mail. After completing all five screening rounds, annual follow-up questionnaires continued to be sent to participants in both study arms for at least 5 further years. In case of nonresponse to mailed questionnaires, study participants were contacted by telephone and questionnaire data recorded through a short interview. Up to April 2018, depending on the calendar dates at which study participants had been initially recruited and randomized, from time $T_0$ onwards a total of 9–11 questionnaires had been administered to study participants, and their cumulative response rates over time are shown in Supporting Information Figure S1 (up to April 30, 2018).

### Ascertainment of lung cancer incidence and deaths

Although ideally, the cancer registry should be the basic source of information for prospective ascertainment of cancer occurrences, during the first years of the LUSI study the regional registry covering the area around Heidelberg was new and in an early phase of development, and thus incomplete. Therefore, prospective ascertainment of incident lung cancer was determined in two complementary ways, namely, (*i*) active follow-up through annual personal contacts at screening visits (outcome of the LDCT screening and information from attending doctors) and self-reports to annual questionnaires, as described above, plus (*ii*) record linkages with the local cancer registry. A total of 12 incident cases were identified exclusively through death certificates. Supporting Information Table S2 provides full details on the prospective identification of incident cancer cases until April 30, 2018, by study arm, year of follow up and source of notification.

The prospective ascertainment of mortality was principally based on record linkage with municipal population registers, to which we have electronic access and which provide information on vital status and date of death with almost daily actuality, and death certificates were retrieved from registers of the local health authorities. The latest linkage to these population registers was performed in May 2018. For 39 participants, linkage to the registers failed as they had claimed their right to deny data access, and in these instances, we used latest available information on vital status by personal contact.

### Verification of information about incident lung cancers and causes of death

For all reported cases of incident lung cancer, irrespective of the mode of initial identification, detailed information from medical records (pathology reports, medical letters from responsible physicians on diagnosis and treatment and radiology reports) was obtained by contacting the treating clinics. Likewise, for participants who had deceased, the physicians who had certified death were contacted for details, particularly on a possible diagnosis of lung cancer. If lung cancer was mentioned in any way ($n = 84$), an end point committee composed of a chest surgeon (GF), two radiologists (MP, SD) and a pathologist (PAS) classified the cases using methods identical to those in NELSON,[16] with full blinding with regard to the allocation of patients to either the screening or control arm.

### Time window of the present evaluation

For the present evaluation, we fixed the end of follow-up for lung cancer mortality on April 30, 2018, the date of our most recent linkage to mortality registers. At that date, 7 years had passed since the last trial participant was recruited (April 2011), and the average follow-up time was 8.8 years. With regard to lung cancer incidence, given an approximate 2-year lag-time till completeness of data reporting from active either follow-up or from the cancer registry, for the present analyses, we considered incidence data to be complete only till April 30, 2016.

### Statistical analyses

*Basic description.* For description of screening performance (LDCT arm only), lung cancer cases were assigned to that screening round in which the respective nodule was first deemed suspect, triggering follow-up (i.e., 3- or 6-month surveillance) imaging and/or further clinical work-up towards lung cancer diagnosis. Interval cancers—defined as lung cancer cases clinically diagnosed between annual screens that had remained undetected—were assigned to the latest screening round in which they might have been detected, and included lung cancers diagnosed within 12 months after an individual's final LDCT screen.

*Evaluation of screening effects.* The effects of screening on the incidence of advanced lung cancer and on mortality outcome (disease-specific or overall) were evaluated with Cox-proportional hazards regression and cumulative incidence and mortality plots. In these analyses, the occurrences of lung cancer and other outcomes in the two study arms were examined by time since randomization, using the date of lung cancer diagnosis (mostly date of biopsy) or death as the date for outcome occurrence, and with age as an adjustment variable. For some lung cancer cases, the date of confirmed diagnosis was more than 9 months after first suspicion. Interaction terms were used to test for heterogeneity of screening-related mortality reduction by sex. The proportional hazards assumption for all estimated Cox models was evaluated by testing the independence between their Schoenfeld residuals and time, log(time) and time.[2] No violations of proportionality were observed for models with lung cancer mortality as end-point (sex-stratified or combined), and for sex-stratified models with incidence (overall, or classified by early/late stage) as end point.

*Estimation of screening sensitivity.* The sensitivity of screening was computed by two approaches: The most frequent view is to relate the screen-detected cases (without the number M of interval cancers) to all observed cancers in the screening group $I_{\text{screen}}$ which include the interval cancers, that is, $\text{Se}_{\text{screen}} = (I_{\text{screen}} - M)/I_{\text{screen}}$. This quantity, however, is biased towards higher sensitivity the greater the overdiagnosis. Therefore, following a more conservative approach frequently applied

in mammography screening (incidence method),[18] we alternatively used the number of observed cases in the control group as a measure of baseline lung cancer incidence unbiased by possible overdiagnosis, using the formula $Se_{control} = (I_{control} - M)/I_{control}$.

## Results

### Characteristics of participants

About two-thirds of the 4,052 participants were men and one third were women; 62% of participants were current smokers and 38% ex-smokers (Table 1). On April 30, 2018, after an average observation time of 8.8 years, 3,741 subjects were documented to be still alive, whereas and 298 had deceased; 13 were lost to follow-up. In the LDCT arm, 85 lung cancers were detected or observed (59 males, 26 females), and 67 in the control arm (46 males, 21 females). Besides lung cancer, the predominant causes of death were other malignant neoplasms and cardiovascular diseases. There were 69 lung cancer deaths, 29 in the LDCT arm (25 males and 4 females) and 40 in the control arm (27 males and 13 females).

### Compliance with screening rounds and trial protocol

Attendance to LDCT screening was above 90% in each of the five screening rounds (Table 2), and 93% of the screeners had at least three LDCT screens, 90% at least four screens and 84% (1,706 subjects) completed all five screens (data not shown in table). Over the first 5 years of prospective follow-up (time points $T_1$–$T_5$) total annual response rates to questionnaires varied from 95.9% ($T_5$) to 97.6 (T3) in the screening arm (responses either at LDCT visits or by mail), and from 91.6% (T1) to 96.5% (T3) in the control arm (data not shown). Cumulatively over time, 98.4% of the screening participants and 95.7% of the controls had provided questionnaire responses covering a time period of at least 5 years postrandomization, whereas 97.4% and 94.0%, respectively, had provided response covering a minimum of 7 years (Supporting Information Table S2). During the active screening period (first 5 years postrandomization) 98 participants in the control group and 12 in the screening group reported self- or clinician-initiated radiological pulmonary imaging outside the study protocol (mostly, X-ray, in a small proportion also CT) for general surveillance purposes without symptomatic indication and one lung cancer was detected that way in the control arm. After the active screening period, self- or clinician-initiated thorax imaging was performed in 81 participants in the LDCT arm and in 134 of the control arm, leading to the identification of one further lung cancer case in the control arm and four cases in the LDCT arm (Table 1). Finally, two further Stage I lung cancers in the control group were found incidentally during diagnostics indicated by COPD and a melanoma, and one Stage IIIa interval cancer in screening round 4 was found incidentally when staging lymphoma.

### Suspicious findings and biopsy rate (LDCT arm)

The identification rate for suspicious pulmonary nodules dropped from 22% in the first round, where suspicious nodules were detected mostly by size (largest diameter), to about 4–5% in the subsequent rounds, where nodule growth over time (VDT) was a major concurrent detection criterion (Table 2). The detection rate for nodules confirmed to be malignant dropped from 1.2% in the first screening round to 0.5–0.6% in the subsequent rounds. Immediate recall in 174 individuals resulted in 21 bronchoscopies, 29 VATS procedures, 15 thoracotomies, 4 positron emission tomography and 21 antibiotic treatments (data not shown in table) with a total of 84 biopsies (Table 2). The biopsy rate was 1.7% of participants in the first (prevalence) screen and dropped to 0.6–1.0% in the subsequent (incidence screening) rounds. The benign/malignant ratio of biopsies in individual screening rounds ranged from 1/2.1 to 1/9, with an overall ratio of 1/2.7.

### Lung cancer incidence during active screening period, by study arm, stage and histology

The cumulative number of advanced lung cancers (UICC stage II and more)—a potential surrogate measure for forthcoming mortality—was almost identical in the two study arms for the first 2 years after randomization but started diverging from the third year onwards (Fig. 1*a*). At the end of the active screening period (5 years postrandomization), 33 advanced lung cancer cases had been observed in the control arm and 20 in the screening arm, and the incidence rate of advanced lung cancers in the screening arm was reduced by about 39% (HR = 0.61 [95% CI: 0.35–1.07], $p = 0.083$). Over the full observation time, inclusive of all further follow-up years, the incidence rate of advanced tumors was about 39% lower than in the control group (HR = 0.61 [95% CI: 0.40–0.92], $p = 0.02$). For early-stage (UICC stage I) tumors screening caused an overall increase in diagnosis during the active screening period, as compared to the control arm (for the first 5 years postrandomization: HR = 14.1 [95% CI: 4.37–45.5], $p < 0.0001$; Fig. 1*b*), and also led to a significant increase in tumor diagnosis for early and advanced-stage tumors combined (HR = 1.76 [95% CI: 1.17–2.66], $p < 0.01$). Analyses based on an alternative classification of Stage I and II tumors as nonadvanced and stage III/IV as advanced showed a pattern similar to that in Figure 1 (see Supporting Information Fig. S2). Additional details on lung cancer incidence by stage, sex, study arm, by follow-up time (0–5 *vs.* >5 years) since randomization in given in Supporting Information Table S3. Through April 2018, based on (as of yet) incomplete follow-up data on lung cancer incidence and over a postrandomization time period of 8.8 years, screening resulted in an overall excess of lung cancer diagnosis (HR = 1.28 [95% CI: 0.93–1.77], $p = 0.13$). Depending upon mode of calculation, the estimated sensitivity of LDCT screening ranged from about 83% to 91% ($Se_{screen}$ = 91.3% [0.84–0.98], $Se_{control}$ = 82.9% [0.70–0.95]).

As already reported for earlier phases of our study,[11] LDCT detection (first 5 years after randomization) led to a predominance of diagnosed adenocarcinomas in the screening arm as compared to the control arm, and this was more strongly the case among women than among men (Fig. 2), although this difference did not reach statistical significance

**Table 1.** Basic characteristics of the study participants of the German lung cancer screening study LUSI at time of randomization (2007–2011) and vital status at end of follow-up (April 30, 2018)

| Characteristic (at time of randomization) | Intervention arm (% of characteristic, by arm) | Control arm (% of characteristic, by arm) | *p*-value | Total (% of entire cohort) |
|---|---|---|---|---|
| Total number | 2,029 (50.1) | 2,023 (49.9) | | 4,052 (100) |
| Gender | | | | |
| Males | 1,315 (50.1) | 1,307 (49.9) | 0.92[1] | 2,622 (64.7) |
| Females | 714 (49.9) | 716 (50.1) | | 1,430 (35.3) |
| Age | | | | |
| Median 50–54 | 55 | 55 | 0.94[2] | 55 |
| 55–59 | 942 (50.3) | 932 (49.7) | | 1,874 (46.3) |
| 60–64 | 518 (49.5) | 528 (50.5) | | 1,046 (25.8) |
| 65–69 | 344 (50.2) | 341 (49.8) | | 685 (16.9) |
| | 225 (50.3) | 222 (49.7) | | 447 (11.0) |
| Smoking status | | | | |
| Current smokers | 1,259 (50.2) | 1,248 (49.8) | 0.84[1] | 2,506 (61.9) |
| Ex-smokers | 770 (49.8) | 775 (50.2) | | 1,546 (38.1) |
| Median observation time (years) (as of April 30, 2018) | 8.89 | 8.89 | 0.97[2] | 8.89 |
| Number of subjects lost to follow-up | 5 (0.2%) | 8 (0.4%) | 0.58[1] | 13 (0.3%) |
| Total number of lung cancers (males/females) | 85 (59/26) | 67 (46/21) | 0.16[1] | 152 (105/47) |
| Identified in CR[3] and FU[4] | 47 | 27 | 0.12[1] | 74 |
| Identified only in CR | 16 | 21 | | 37 |
| Identified only in FU | 21 | 8 | | 29 |
| Identified only in DC[5] | 1 | 11 | | 12 |
| Number of deaths (m/f) | 148 (126/22) | 150 (123/27) | 0.93[1] | 298 (249/49) |
| Cause of death by ICD group: | | | | |
| All cancers (C[6]) | 72 (60/12) | 79 (60/19) | | 151 (120/31) |
| Cardiovascular system (I[6]) | 37 (33/4) | 34 (31/3) | | 71 (64/7) |
| Respiratory system (J[6]) | 11 (9/2) | 7 (5/2) | | 18 (14/4) |
| Gastrointestinal system (K[6]) | 5 (4/1) | 8 (6/2) | | 13 (10/3) |
| Unspecified (R[6]) | 8 (8/0) | 5 (5/0) | | 13 (13/0) |
| Others (B, D, E, F, G, M, N, S, T, X, Z[6]) | 15 (12/3) | 17 (16/1) | | 32 (28/4) |
| Number of deaths from lung cancer (m/f) | 29 (25/4) | 40 (27/13) | 0.19[1] | 69 (52/17 |
| Self- or clinician-initiated X-ray or LDCT diagnostics for screening purposes | | | | |
| a. During the active screening period (1st 5 years of FU) | 12 | 98[7] | ‹0.001[1] | 110 |
| b. After the active screening period/after first 5 years of FU[8] | 81[9] | 134[9] | ‹0.001[1] | 215 |

[1]*p*-Value from a chi-squared test for the distribution of categories in the two study arms.
[2]*p*-Value from a Mann–Whitney *U* test for the difference in continuous variables between the two study arms.
[3]Cancer registry.
[4]Follow-up.
[5]Death certificate.
[6]Leading character of the respective ICD10 group.
[7]One stage I lung cancer was found.
[8]Sixty-nine (30 in the control arm and 39 in the LDCT arm) such diagnostics were CT examinations, alone or in combination with X-rays.
[9]One lung cancer was found in the control arm and four in the treatment arm after the active screening period by means of self- or clinician-initiated X-rays or LDCT for screening purposes.

($p$ = 0.075, test stratified by sex, men and women combined). In both arms, the distribution of histologic subtypes differed significantly between men and women, with women showing a higher proportion of adenocarcinomas, and a much smaller percentage of small cell tumors, than men (Fig. 2).

Table 2. Results of the five screening rounds in the LDCT arm

| Screening round (time point of contact) | Number invited to LDCT and number screened (compliance in %) | Unsuspicious LDCT (only first screening round: no nodules detected/nodules detected, but all ‹5 mm | Suspicious LDCT with early recall after 6 months/3 months/immediately; overall early recall rate | Number of biopsies (biopsy rate); benign/malignant biopsies (ratio) | Confirmed lung cancers and detection rate | Interval cancers[1] |
|---|---|---|---|---|---|---|
| 1 ($T_0$) | 2,029<br>2,028[2]<br>(99.9%) | 1,577<br>(980/597) | 330/68/53<br>22.2 | 52<br>(2.6%)<br>30/22<br>(1.36) | 25<br>1.23 | 1 |
| 2 ($T_1$) | 2,000<br>1,892<br>(94.6%) | 1,804 | 36/16/36<br>4.7 | 31<br>(1.6%)<br>19/12<br>(1.58) | 11<br>0.58 | 0 |
| 3 ($T_2$) | 1,978<br>1,849<br>(93.5%) | 1,775 | 26/23/25<br>4.0 | 23<br>(1.2%)<br>12/11<br>(1.09) | 12<br>0.65 | 2 |
| 4 ($T_3$) | 1,954<br>1,826<br>(93.4%) | 1,722 | 46/25/33<br>5.7 | 26<br>(1.4%)<br>16/10<br>(1.6) | 10<br>0.55 | 1 |
| 5 ($T_4$) | 1,925<br>1,810<br>(94.0%) | 1,711 | 49/23/27<br>5.5 | 26[3]<br>(1.4%)<br>13/12<br>(1.08) | 11<br>0.61 | 2 |

[1]Interval cases were cases of lung cancer clinically diagnosed in the screening arm between annual screens, or within 12 months since a participant's last screen, but which had remained undetected by LDCT.
[2]In one case, the CT could not be drawn due to overweight; the participant was excluded from the study.
[3]In one case, no biopsy result could be obtained.

### Cumulative number of lung cancer deaths and overall mortality

The overall cumulative number of lung cancer deaths diverged from the second year postrandomization onwards (Fig. 3*a*), resulting in a (statistically nonsignificant) hazard ratio of HR (HR = 0.74 [95% CI: 0.46–1.19], $p = 0.21$). Separate analyses by sex showed a statistically significant reduction in lung cancer mortality among women (HR = 0.31 [95% CI: 0.10–0.96], $p = 0.04$), but not among men (HR = 0.94 [95% CI: 0.54–1.61], $p = 0.81$), and this heterogeneity was close to statistical significance ($p_{\text{heterogeneity}} = 0.09$) (Fig. 3*b*). LDCT screening had no significant impact on all-cause mortality (for men and women combined, HR = 0.99 [95% CI: 0.79–1.25], $p = 0.95$; Fig. 4).

## Discussion

The LUSI trial is the German contribution to a series of European trials to examine the efficacy of LDCT screening to reduce lung cancer mortality. Over an average follow-up time of 8.8 years postrandomization, among men and women screened by LDCT (combined) we observed an overall hazard ratio for lung cancer mortality of HR = 0.74 [95% CI: 0.46–1.19]—an estimate that, although not statistically significant, is in line with overall mortality reductions reported by the NLST and several of the European trials. Secondary analyses, however, suggest a significant reduction of lung cancer mortality among women (HR = 0.31 [95% CI: 0.10–0.96], $p = 0.04$), but not among men (HR = 0.94 [95% CI: 0.54–1.61], $p = 0.81$).

Based on the occurrence of interval cancers, we estimated the sensitivity of LDCT screening at 83–91%, depending on the mode of calculation, and during the active screening period (5 years postrandomization) LDCT detection led to a major shift in tumor stage at detection and a 39% reduction in the occurrence of advanced (UICC stage II and higher) lung cancers. From the second screening round onwards, the diagnostic protocol for detecting lung suspicious nodules used led to a relatively small proportion (4–5%) of trial participants requiring 3- or 6-month control examinations. Biopsy rates were also low, especially from the second screening onwards (0.6–1.0%), and overall five screening rounds, the ratio of benign to malignant biopsies taken was 1/2.7.

In terms of compliance with study design, the LUSI trial showed successful baseline randomization to the LDCT and control arms with regard to past smoking history and other risk factors. Furthermore, the trial showed excellent participation in annual LDCT screens, excellent response to annual questionnaire surveillance, and very low contamination by self-initiated or medically initiated X-ray or CT for lung cancer diagnostics outside the screening protocol. Mortality outcomes were determined on the basis of population registers providing complete, population-wide coverage and lung cancer as main cause of death was assessment with full blinding as to which study arm LUSI participants were assorted to. In contrast, a limitation of LUSI as of to date is that,

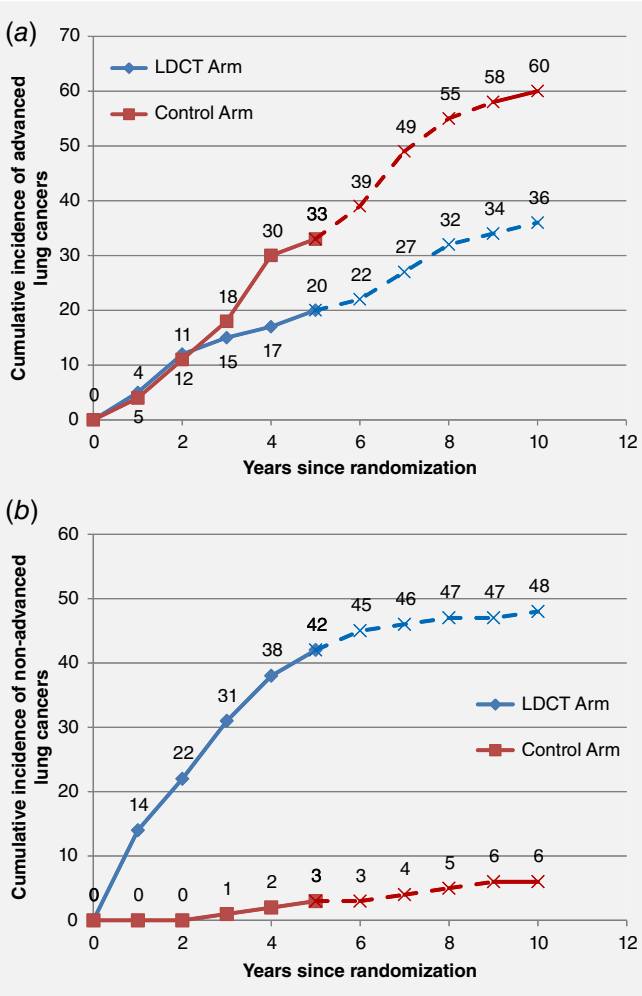


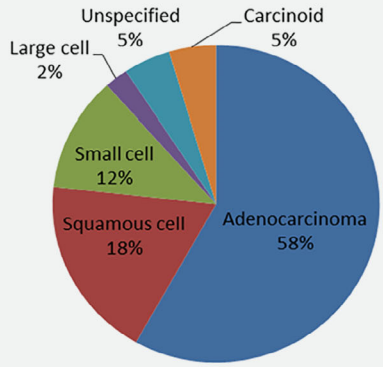

**Figure 1.** Cumulative number of advanced (panel *a*—Stages II–IV) and nonadvanced (panel *b*—Stage I) lung cancers in the LDCT arm and the control arm by time since randomization (shown in 12 month intervals). Follow-up for cancer incidence is considered complete till April 30, 2016, which corresponds to 5 years postrandomization for all study participants; prospective case ascertainment is partially complete for follow-up times between April 2016 and April 2018. *For one incident lung cancer case, in the LDCT arm, stage information was missing. Dashed line corresponds to years post randomization for which follow-up was only partially complete until April 2018. [Color figure can be viewed at wileyonlinelibrary.com]

due to lag-times in prospective case ascertainment, data for lung cancer incidence do not yet cover a sufficient duration of follow-up time and with high enough completeness of case ascertainment to allow an estimation of lung cancer overdiagnosis.

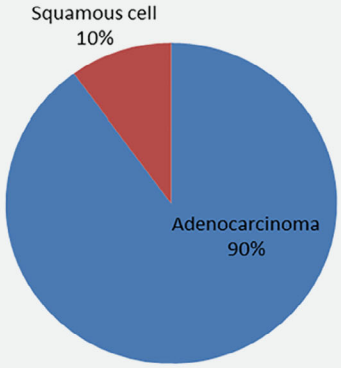
An intriguing observation in LUSI is the apparent heterogeneity (although only borderline significant, $p_{heterogeneity}$ = 0.09) in the effect of LDCT screening on lung cancer mortality by sex, suggesting a mortality reduction among the women only. Analyses of NLST data stratified by sex, smoking history, and lung cancer histology had already indicated a stronger mortality reduction by LDCT screening among women than among men (risk ratio of 0.73 *vs.* 0.93, respectively; $p_{interaction}$ = 0.08),[19] and the preliminary findings reported from NELSON also suggest a stronger mortality reduction among women (HR of 0.39–0.61, depending on follow-up time point) than among men (HR = 0.74 [0.59–0.91]).[15] Detailed analyses of the NLST data further indicated that the heterogeneity in mortality reduction may have resulted from a gender difference in mortality from histologic tumor subtypes. By tumor histology, mortality relative risks in NLST were 0.75 for adenocarcinoma, 0.71 for all nonsmall cell lung cancers except squamous, 1.23 for squamous cell carcinoma and 0.90 for small cell carcinoma. Between men and women, relative risks were similar for mortality due to nonsquamous nonsmall cell lung cancers (0.71 and 0.70, respectively), whereas relative risks for mortality related to small cell and squamous cell carcinoma was found to be heterogeneous between sexes. It is worth noting in this context that, compared to men, the women in LUSI (both study arms) had a stronger overall predominance of adenocarcinomas and a much lower diagnosis of small cell carcinomas (entirely absent among women in the LDCT arm). However, numbers of cancer deaths in LUSI were too small to examine whether the apparent heterogeneity in relative mortality hazards for men and women could be explained by differences in tumor histology, or whether it could have been entirely due to chance.

Further to NELSON, a total of five smaller European trials (LUSI included) have now reported on the effect of LDCT screening on lung cancer mortality, for a total of 17,911 trial participants. In all studies, LDCT screening was prospectively compared to a control arm without screening intervention (total $n$ = 8,577), and each of the five smaller trials used annual screening, although one study (MILD[9]) also included a further, biennial screening arm ($n$ = 1,186). Like LUSI, the ITALUNG (Tuscany, Italy,[8]) showed a rate ratio below 1.0 (0.70 [95% CI 0.48–1.03]) for lung cancer mortality, although contrary to LUSI this mortality benefit started to appear only 5–6 years after randomization. A combined analysis of data from DANTE and MILD, using multivariable adjustments for study, sex, age, pack-years of cigarette smoking and baseline lung function, showed an overall 17% decrease in lung cancer mortality (HR = 0.83 [95% CI 0.61–1.12]).[14] The Danish DLCST study reported a clear null result with regard to lung cancer mortality (HR = 1.03 [95% CI 0.66–1.06]).[6] Thus, although none of the smaller European studies showed a statistically significant effect of LDCT screening on lung cancer mortality, their overall findings appear to point mostly towards a moderate mortality reduction.

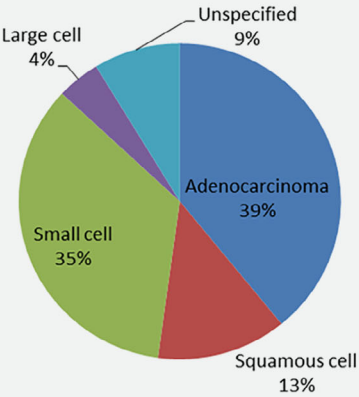
The European studies differed only moderately in the choice of screening eligibility criteria (age, smoking history), but varied more substantially with regard to radiologic criteria used for lung cancer detection at baseline and incidence screens, the total number of screens performed, and screening intervals. Besides random variations in tumor occurrences due to small individual study sizes, further factors that theoretically may have contributed to between-study heterogeneity in findings include population differences in general risk profiles and/or medical care, or differences in duration of follow-up since randomization. Furthermore,



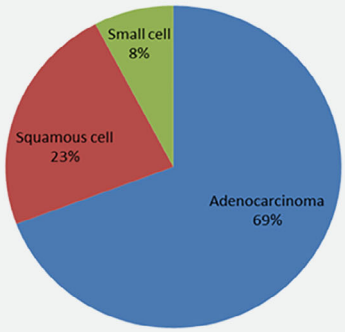

LDCT arm, men: 43 cases




LDCT arm, women: 20 cases




Control arm, men: 23 cases




Control arm, women: 13 cases

| | LDCT arm | | | Control arm | | | |
|---|---|---|---|---|---|---|---|
| Subtype | Men | Women | Subtotal | Men | Women | Subtotal | Total |
| Adenocarcinoma | 25 | 18 | 43 | 9 | 9 | 18 | 61 |
| Squamous cell | 8 | 2 | 10 | 3 | 3 | 6 | 16 |
| Small cell | 5 | 0 | 5 | 8 | 1 | 9 | 14 |
| Large cell | 1 | 0 | 1 | 1 | 0 | 1 | 2 |
| Unspecified | 2 | 0 | 2 | 2 | 0 | 2 | 4 |
| Carcinoid | 2 | 0 | 2 | 0 | 0 | 0 | 2 |
| Total | 43 | 20 | 63 | 23 | 13 | 36 | 99 |

| | Men | | | Women | | | |
|---|---|---|---|---|---|---|---|
| | Control | LDCT | Subtotal | Control | LDCT | Subtotal | Total |
| Adenocarcinoma | 9 | 25 | 34 | 9 | 18 | 27 | 61 |
| Squamous cell | 3 | 8 | 11 | 3 | 2 | 5 | 16 |
| Small cell | 8 | 5 | 13 | 1 | 0 | 1 | 14 |
| Large cell | 1 | 1 | 2 | 0 | 0 | 0 | 2 |
| Unspecified | 2 | 2 | 4 | 0 | 0 | 0 | 4 |
| Carcinoid | | 2 | 2 | 0 | 0 | 0 | 2 |
| Total | 23 | 43 | 66 | 13 | 20 | 33 | 99 |

**Figure 2.** Histologic distribution of incident lung cancers in the LDCT arm and the control arm during active screening period (0–5 years postrandomization), by sex. Both within the LDCT arm and the control arm, the distributions of histologic lung cancer subtypes differed significantly between men and women ($p = 0.026$ and $p = 0.049$, respectively, as based on Pearson's chi-square test for independence). Within strata of sex, the $p$ values for test of independence of histologic distributions between LDCT and control arms were 0.14 for men and 0.24 for women, respectively). [Color figure can be viewed at wileyonlinelibrary.com]

randomized screening trials can be subject to bias, for example, due to imperfect randomization between screening and control arms with regard to major cancer risk factors (e.g., imbalances in smoking history, as reported by DLCST[6] or MILD[9]), or between-arm biases (imperfect blinding) in the ascertainment and verification of lung cancer deaths. Pooled (re)analyses of the data

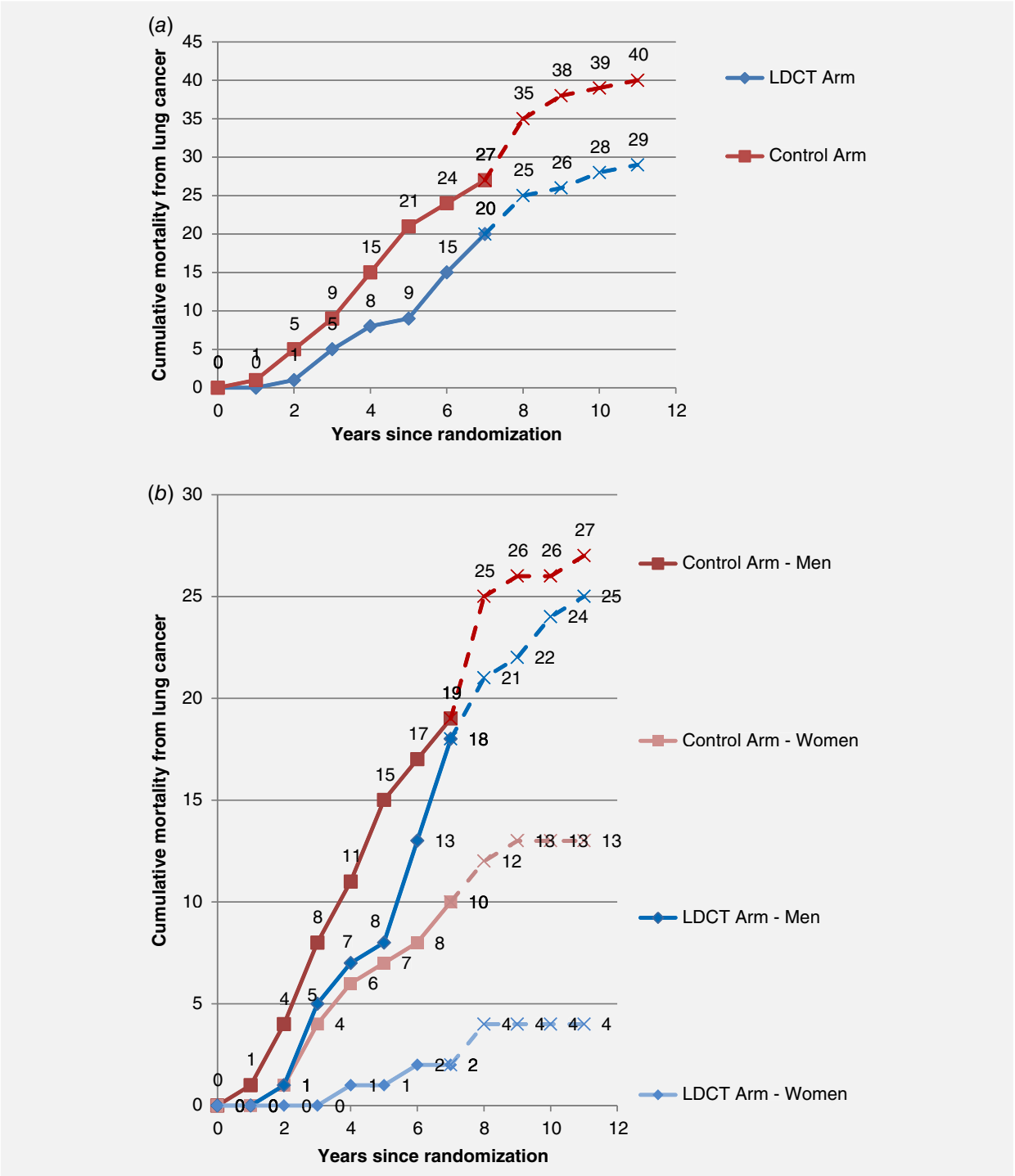



**Figure 3.** Cumulative number of deaths from lung cancer by time since randomization (shown in 12-month intervals) and study arm, overall and by sex. Follow-up for lung cancer mortality is complete for all study participants till April 30, 2018, which corresponds to 7 years postrandomization for all study participants; after April 2018, only part of study participants had reached longer postrandomization follow-up times longer than 7 years. Dashed line corresponds to years post randomization for which follow-up was only partially complete until April 2018. [Color figure can be viewed at wileyonlinelibrary.com]

accumulated in all European trials may provide further clues for observed heterogeneity in study findings for lung cancer mortality, including possible differences in screening efficacy by sex and/or histologic tumor subtype. In addition, pooled data analysis of European trial data may allow a more precise, quantitative estimation of overdiagnosis, as all European trials compared the

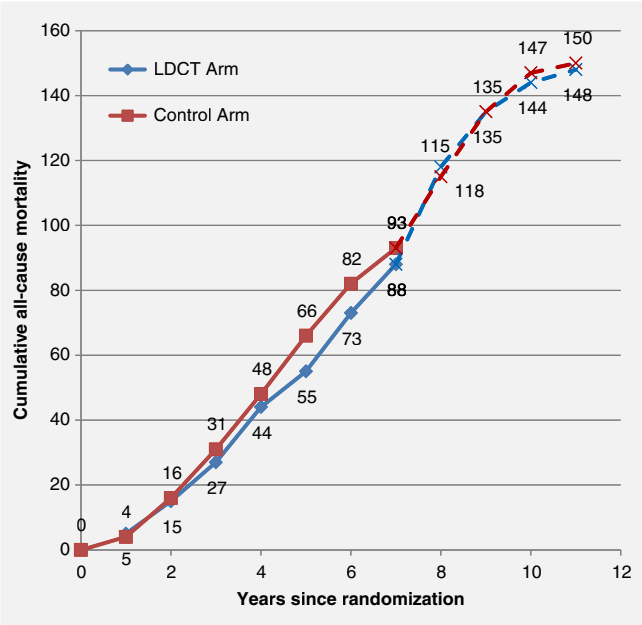



**Figure 4.** Cumulative all-cause mortality in the LDCT arm and in the control arm by time since randomization (shown in 12-month intervals, until April 31, 2018). Dashed line corresponds to years post randomization for which follow-up was only partially complete until April 2018. [Color figure can be viewed at wileyonlinelibrary.com]

screening group to a control group not subjected to any form of screening (contrary to NLST, where the control arm received annual screening by standard X-ray[20]). To contribute to the estimation of overdiagnosis, the LUSI study remains continuing its prospective ascertainment of incident lung cancer, so as to reach a more complete prospective case ascertainment for all study participants over an extended follow-up time of at 8 and more years after randomization and minimally 4 years after last screen.

In conclusion, the collective evidence from the NELSON and the five smaller European trials, LUSI included, now clearly appears to argue in favor of introducing systematic lung cancer screening in Europe, confirming initial findings from the NLST. However, some critical questions remain, such as the optimization of risk-stratified recruitment strategies, further optimization of radiologic criteria for early lung cancer diagnosis and nodule management, risk stratification and determination of individualized screening intervals on the basis of radiologic images, and assessment of the effects of comorbidity on rapidity of diagnosis and treatment and on survival. Also, more precise estimates are needed for potential lung cancer overdiagnosis—a major potential adverse effect of LDCT screening. In combination, the pooled European trial data can provide a rich resource to further address these remaining questions, in order to define optimal guidelines for lung cancer screening in Europe.

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## Author Contributions

Study design and grant application: Miller AB, Becker N, Delorme S. Study implementation and conduct: Becker N, Motsch E, Trotter A (epidemiology); Delorme S, Heussel CP, Kauczor H-U (radiology); Schnabel PA (pathology); Dienemann H (surgery). Data evaluation: Becker N, Motsch E, Trotter A, Maldonado SG, Kaaks R. Article writing: Becker N, Kaaks R, Motsch E, Trotter A, Delorme S.

## Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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