ORIGINAL ARTICLE

Long-Term Follow-up Results of the DANTE Trial, a Randomized Study of Lung Cancer Screening with Spiral Computed Tomography

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Abstract

Rationale: Screening for lung cancer with low-dose spiral computed tomography (LDCT) has been shown to reduce lung cancer mortality by 20% compared with screening with chest X-ray (CXR) in the National Lung Screening Trial, but uncertainty remains concerning the efficacy of LDCT screening in a community setting.

Objectives: To explore the effect of LDCT screening on lung cancer mortality compared with no screening. Secondary endpoints included incidence, stage, and resectability rates.

Methods: Male smokers of 20+ pack-years, aged 60 to 74 years, underwent a baseline CXR and sputum cytology examination and received five screening rounds with LDCT or a yearly clinical review only in a randomized fashion.

Measurements and Main Results: A total of 1,264 subjects were enrolled in the LDCT arm and 1,186 in the control arm. Their median age was 64.0 years (interquartile range, 5), and median smoking exposure was 45.0 pack-years. The median follow-up was 8.35 years. One hundred four patients (8.23%) were diagnosed with lung cancer in the screening arm (66 by CT), 47 of whom (3.71%) had stage I disease; 72 control patients (6.07%) were diagnosed with lung cancer, with 16 (1.35%) being stage I cases. Lung cancer mortality was 543 per 100,000 person-years (95% confidence interval, 413–700) in the LDCT arm versus 544 per 100,000 person-years (95% CI, 410–709) in the control arm (hazard ratio, 0.993; 95% confidence interval, 0.688–1.433).

Conclusions: Because of its limited statistical power, the results of the DANTE (Detection And screening of early lung cancer with Novel imaging TEchnology) trial do not allow us to make a definitive statement about the efficacy of LDCT screening. However, they underline the importance of obtaining additional data from randomized trials with intervention-free reference arms before the implementation of population screening.

Keywords: lung neoplasms; early diagnosis; screening; spiral computed tomography; randomized controlled trial

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*A complete list of members may be found before the beginning of the References.

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At a Glance Commentary

Scientific Knowledge on the Subject: Screening for lung cancer with low-dose spiral CT (LDCT) has been shown to reduce lung cancer mortality by 20% compared with screening with chest radiography in the National Lung Screening Trial, but uncertainty remains concerning the efficacy and cost-effectiveness of CT screening in a community setting.

What This Study Adds to the Field: In this randomized trial of LDCT screening versus annual clinical review, stage I lung cancer was detected in 47 out of 1,264 participants (3.72%) in the LDCT arm and in 16 out of 1,186 (1.35%) in the control arm. A 31% lung cancer excess rate in the LDCT arm was observed, but no stage shift was evident. Lung cancer and all-cause mortality did not differ significantly between the two arms. The results of the DANTE (Detection And screening of early lung cancer with Novel imaging TEchnology) trial underline the importance of obtaining additional data from randomized trials with intervention-free reference arms before recommending population screening with LDCT.

Localized, surgically curable stage I–II lung cancers represent only approximately 16% of clinically detected cases (1), a statistic that has remained stagnant for decades. For this reason, screening of high-risk subjects to detect lung tumors before progression to advanced disease was proposed early in the second half of the last century as a potential strategy to curtail lung cancer mortality (2).

However, the randomized trials that followed in the 1970s (3–5) did not demonstrate a reduction in lung cancer mortality with chest X-ray (CXR) screening compared with conventional care despite a significant increase (up to ~50%) in stage I detection rates. Although several aspects of those studies were eventually criticized (6, 7), the subsequent large Prostate, Lung, Colorectal, and Ovarian cancer screening trial in 2011 also reported that no reduction in lung cancer mortality could be obtained with CXR screening (8). The insufficient sensitivity of CXR was the most credited explanation for such failures.

In 1999, the ELCAP (Early Lung Cancer Action Program) study showed low-dose spiral computed tomography (LDCT) to be far more sensitive than CXR for small lung nodules, with 80% of the cancers detected by LDCT being stage I (9). Indeed, 5-year survival rates of 80 to 90% have been reported in a number of uncontrolled trials for patients whose lung cancers were detected by a screening LDCT (10–13). Despite the enthusiasm for such results, it was also acknowledged that more data were needed from randomized controlled trials to avoid a biased and misleading interpretation of available evidence (14). In 2001, we therefore started the DANTE study (Detection and Screening of Early Lung Cancer with Novel Imaging Technology and Molecular Assays), a randomized trial of LDCT versus clinical review at annual intervals for five rounds to explore the effect of screening with low-dose spiral CT on lung cancer mortality.

Financial considerations precluded a large trial capable of addressing the question as a stand-alone study, but we were confident that more similar trials would follow and that pooling our data with other research groups would eventually become possible.

In 2003, the large National Lung Screening Trial (NLST), which included 53,000 high-risk patients, was initiated in the United States, and in 2011 the NLST investigators reported a 20% reduction of lung cancer–specific mortality with three annual rounds of LDCT screening compared with three rounds of CXR screening (15). Several major organizations have subsequently recommended screening with LDCT for high-risk subjects under certain conditions (16, 17). However, many significant issues remained, in particular regarding the most appropriate target population (18, 19), false positives (20, 21), optimal nodule workup (22–24), potential harm (25), the costs of large-scale implementation (26), and the impact on lung cancer mortality achievable in a community setting (27). The European CT screening trials collaborative group therefore recommended in 2013 that all ongoing randomized studies of LDCT screening versus usual care be continued until their natural conclusion and analyzed thoroughly (28). Here, we present and discuss the final, long-term results of the DANTE study.

Methods

The trial methodology has been reported previously and is briefly described below (29, 30).

The research was coordinated by the Humanitas Research Hospital, Milan, Italy. The study was advertised through family doctors, the media, the internet, and in-hospital boards and leaflets.

Subject recruitment began in March 2001 and ended in February 2006. The Humanitas-Gavazzeni Hospital in Bergamo and the Humanitas Oncology Center in Catania contributed to enrollment during the last year. Eligible subjects included 60- to 74-year-old male smokers or former smokers of at least 20 pack-years who had quit less than 10 years before recruitment. Subjects with severe comorbid conditions carrying a life expectancy of less than 5 years, those deemed unable to comply with the follow-up protocol for any reason, and those with a history of previous malignancy within 10 years before recruitment were ineligible.

Applicants were interviewed on the phone to assess their age, sex, and whether they were current or former smokers. Applicants were randomized if appropriate, and an appointment was made at a weekly outpatient clinic for subsequent formal enrolment. At that time, prospective participants were briefed on the study purpose and procedures and were required to give written informed consent and to fill out a detailed questionnaire on their smoking exposure, occupational and medical history, and present health condition. A structured medical interview and physical examination were conducted to verify their baseline health status, reassess eligibility in depth, and confirm enrolment.

All enrolled subjects had a baseline CXR and 3-day sputum cytology testing regardless of their allocation, but only subjects in the LDCT arm also received a baseline CT scan of the thorax on the same day.

Four subsequent yearly LDCT screening rounds were planned in the LDCT arm in addition to a more concise version of the baseline medical interview and a physical examination focused on

reassessing smoking habits, recent medical history, and new signs and symptoms since the last assessment.

Control subjects underwent the same yearly clinical review only. The physician in charge could order a CXR as a first-line test in the case of respiratory complaints and/or abnormal findings. All participants were reinvited to attend annually by phone. After the last round, active follow-up through phone interviews was continued until 2012. Life status data and death certificates were requested for the entire study population from local health registries. The follow-up cut-off date was May 15, 2013.

Death certificates were cross-checked with hospital records and/or with written reports provided by the attending physicians or by the family doctor. A panel blinded to patients' assignment reviewed the clinical cases whenever several competing causes of death were possible.

Statistical Methods

Subjects were randomized by a 1:1 scheme in blocks of four and stratified by center according to a computer-generated list supplied by the data center each week before enrolment sessions. Endpoints of the study included lung cancer mortality and all-cause mortality. Secondary endpoints included lung cancer incidence, stage at detection, and resectability rates.

A sample size of 2,400 subjects was calculated assuming a 50% mortality reduction in the LDCT arm. Sensitivity, specificity, and predictive values of the screening protocol were calculated on a per-patient basis (31). Proportions between groups were compared using the χ^2 test or the Fisher's exact test if needed; means were compared using the t test unless stated otherwise. Confidence intervals (CIs) for means and proportions were calculated by the Gaussian approximation method. Survival functions were estimated using the Kaplan-Meier method and compared using Cox regression analysis. Related hazard ratios were provided, with CIs calculated by the Wald method.

Additional details on the trial methodology are provided in the online supplement.

Results

An outline of patient recruitment and outcomes is presented in Figure 1. Revision of the database for this final report led to

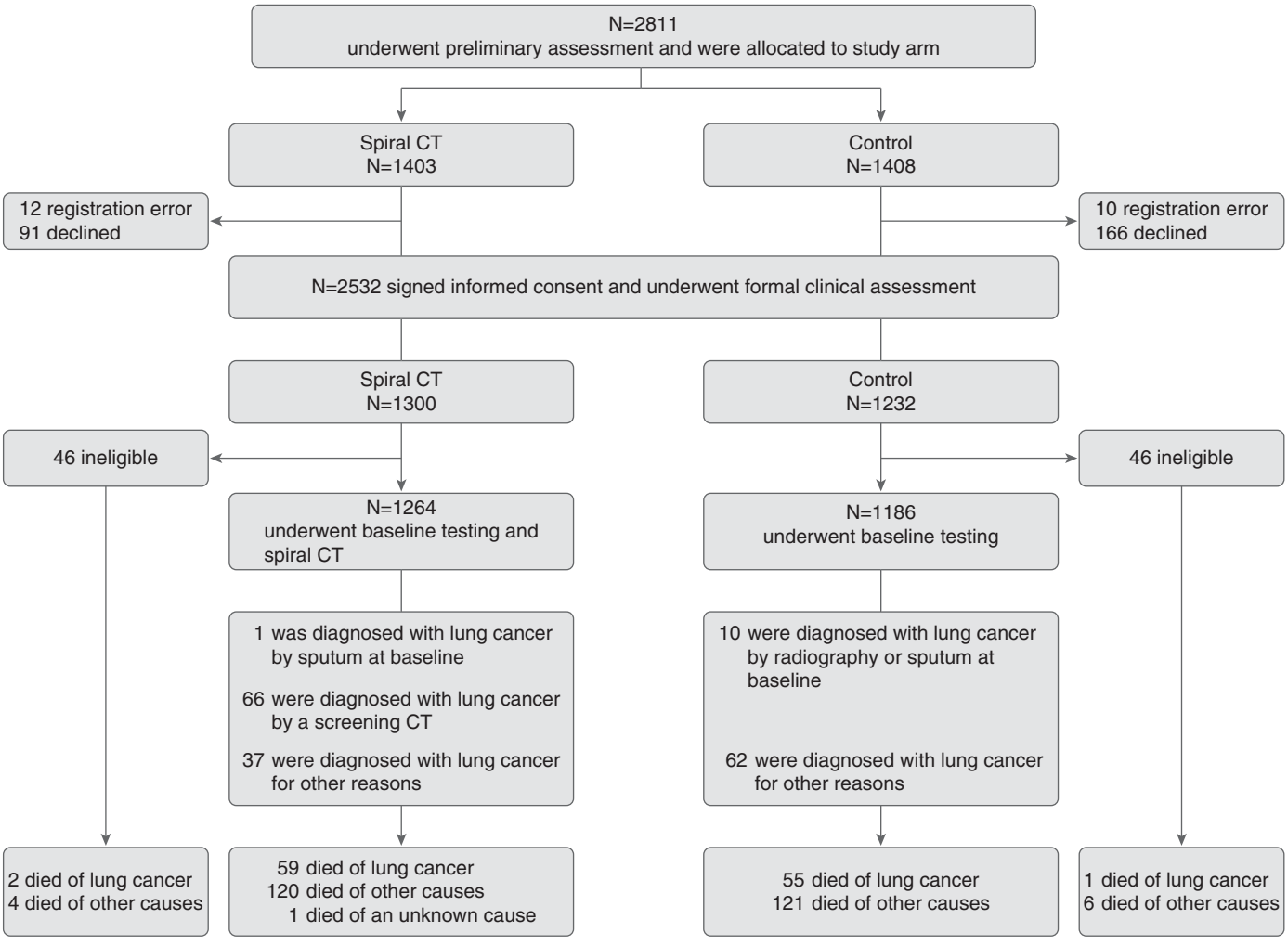


Figure 1. Outline of patient recruitment and outcomes in the DANTE (Detection and Screening of Early Lung Cancer with Novel Imaging Technology and Molecular Assays) trial. CT = computed tomography.

the discovery of 20 duplicate registrations and two test records, so the actual number of evaluable subjects was 1,264 in the LDCT arm versus 1,186 in the control arm. As per the inclusion criteria, all subjects were male.

Age, smoking, and professional exposures were consistent between the two groups. Respiratory comorbidity was slightly more prevalent among subjects in the LDCT arm (35 vs. 31% $P = 0.0321$), but all other comorbid conditions were evenly distributed. By the end of the study, 1,184 (93%) subjects in the screening arm received all five CT scans (Table 1).

During the active phase, at least one abnormality was observed by LDCT in 471 out of 1,264 (37%) subjects in the screening arm (Table 2 and *see* Table E1 in the online supplement), and 355 (28%) underwent further testing, receiving in total 562 additional CT scans. Four patients in the LDCT arm underwent further investigation due to abnormal pulmonary cytology at baseline; one of these patients was diagnosed with a radiologically occult superficial squamous lung cancer.

In the same period, 38 control subjects (3%) underwent further evaluation after a baseline screening CXR, eight underwent further evaluation for abnormal sputum cytology, and 144 (12%) received a CXR after a planned clinical review. CXR obtained for such a reason prompted further investigation by a chest CT in seven control subjects, none of whom had lung cancer.

Significantly more invasive procedures of any type and more surgical procedures for potential cancer lesions were recorded in the spiral CT arm of the study (Tables 2 and E2).

The overall rate of surgical procedures that did not reveal any cancer was 17 out of 96 (17.7%) in 90 patients (18.9% of those who underwent surgery for possible lung cancer in the screening arm).

Three patients with lung cancer in the LDCT arm died postoperatively (3.3% surgical mortality): two died after lobectomy (from sudden cardiac death and suture-line failure), and one died after pneumonectomy (ARDS). One patient (3.2%) in the control arm died after pneumonectomy due to suture-line failure and ARDS. There were no deaths associated with surgical procedures for benign lesions in either arm.

Detection modality, stage, histology, and resectability rates for all lung cancer patients observed in the DANTE trial are summarized in Tables 3 and E3.

As of May 15, 2013, 104 patients in the LDCT group (8.23%) had developed 118 lung cancers, including four patients with two synchronous primary tumors and eight patients with metachronous second primaries. Overall, 66 of 104 patients (63%) were diagnosed with lung cancer by a screening CT, and one patient was diagnosed with lung cancer by sputum cytology. Thirteen patients were diagnosed with lung cancer due to symptoms between two screening rounds, two patients who did not comply with the screening protocol were diagnosed for other reasons within 5 years of recruitment, and two patients were diagnosed for other reasons within 1 year from the final screening round. Finally, 20 patients were diagnosed more than 1 year after their final negative CT scan. By intention-to-treat analysis, the sensitivity of the screening protocol for primary lung cancer detection during the active phase was therefore 0.7952 (95% CI, 0.7716–0.8169), and its negative predictive value was 0.9813 (95% CI, 0.9718–0.9878) (Table E4).

Forty-two (63.6%) cases of CT-detected lung cancer were stage I disease, as opposed to only four (10.5%) of those detected for any other reason. By comparison, 72 patients in the control group (5.98%) were diagnosed with 75 lung cancers by the end of the study, including one patient with a radiologically occult synchronous squamous cancer and one patient who developed two subsequent metachronous cancers (both were successfully resected). Ten out of 72 (14%) patients were diagnosed with lung cancer by CXR and/or sputum at baseline, three (4%) were detected clinically during a scheduled annual review, and 59 (84%) were detected due to symptoms or other reasons, including two patients who received a CT scan inappropriately (one due to an error in allocation and one who received a CT scan at another institution).

In the screening arm, significantly fewer patients were detected with lung cancer for any reason other than a screening LDCT compared with lung cancer patients in the control arm detected for any reason other than a baseline chest radiograph; additionally, significantly more patients with lung cancer were amenable to complete surgical resection in the LDCT group than in the control group (Tables 3 and E3).

Table 1. Patient Characteristics

	LDCT	Control	All
Patients enrolled, n (%)	1,264 (51.59)	1,186 (48.41)	2,450 (100)
Current smokers, n (%)	714 (56.48)	681 (57.41)	1,395 (56.93)
Age, yr			
Mean (95% CI)	64.6 (64.3–64.8)	64.6 (64.4–64.9)	64.6 (64.4–64.8)
SEM	0.14	0.12	0.09
Median (IQR)	64.0 (5)	64.0 (5)	64.0 (5)
Pack-years			
Mean (95% CI)	47.3 (45.7–49.0)	47.2 (45.5–49.0)	47.3 (46.1–48.5)
SEM	0.8	0.9	0.6
Median (IQR)	45.0 (28.5)	45.0 (32.5)	45.0 (30.0)
Occupational exposure, n (%)*	391 (31.33)	402 (34.13)	793 (32.69)
Comorbidities, n (%)			
Respiratory†	446 (35.28)	370 (31.20)	816 (33.31)
Hypertension	456 (36.08)	447 (37.69)	903 (36.86)
Cardiac	159 (12.58)	165 (13.91)	324 (13.22)
Peripheral vascular	130 (10.28)	107 (9.02)	237 (9.67)
Diabetes	105 (8.31)	99 (8.35)	204 (8.33)
Other	452 (35.76)	426 (35.92)	878 (35.84)
Compliance, n (%)			
Had ⩾3 CT scans	1,223 (96.76)		
Had 5 CT scans	1,184 (93.67)		
Median follow-up, yr	8.35	8.35	8.35

Definition of abbreviations: CI = confidence interval; CT = computed tomography; IQR = interquartile range; LDCT = low-dose spiral computed tomography.
Percentages are calculated based on group totals.
*Chemical industry, insulation, construction industry, metallurgy, agriculture, and mining.
†$P = 0.0321$.

Table 2. Abnormal Findings and Downstream Investigation Procedures

	LDCT	Control	All	*P* Value
Study subjects, n (%)	1,264 (51.59)	1,186 (49.41)	2,450 (100)	
Reasons for further investigation, n (%)*				
Baseline CXR (only)	—	38 (3.20)		
Baseline sputum	4 (0.31)	8 (0.34)	12 (0.49)	
Baseline LDCT	169 (13.37)			
Annual LDCT after baseline	186 (14.71)			
Annual clinical review	4 (0.31)	144 (12.14)		
Symptoms	31 (2.45)	61 (5.14)	92 (3.76)	
Other reasons	165 (13.05)	192 (16.19)	357 (14.57)	
FDG-PET scan	96 (7.59)	17 (1.43)	113 (4.61)	<0.0001
Invasive procedures, n (%)†				
Any invasive procedure‡	144 (11.39)	64 (5.39)	208 (8.49)	<0.0001
After screening test	112 (9.65)	17 (1.43)	129 (5.27)	
Surgery for lung cancer	90 (7.12)	31 (2.62)	121 (4.94)	<0.0001
Lung cancer confirmed	73 (5.78)	26 (2.20)	99 (4.04)	<0.0001
Number of procedures§	96	34	130 (5.31)	
Surgery for a benign lesion‖	17 (1.34)	5 (0.42)	22 (0.9)	0.0176
Surgery for other conditions¶	7 (0.55)	2 (0.17)	9 (0.37)	

Definition of abbreviations: CXR = chest X-ray; FDG-PET= ^{18}F-fluorodeoxyglucose positron emission tomography; LDCT = low-dose spiral computed tomography.

Data were collected during the active observation period (no data available after January 2012). Data refer to single patients; percentages refer to column totals.

*Includes additional computed tomography (CT) earlier than 12-month follow-up, contrast-enhanced CT, FDG-PET, or biopsy.

†Invasive procedures performed for staging purposes are not presented.

‡Includes bronchoscopy, percutaneous biopsy, video-assisted thoracoscopy (VATS), mediastinoscopy, or thoracotomy.

§Including repeat surgery for metachronous lung cancers.

‖LDCT: three mediastinoscopies, seven VATS wedge resections, and six open wedge resections. Control: two VATS biopsies, two VATS wedge resections, and one open wedge resection.

¶LDCT arm: one open biopsy, one extrapleural pneumonectomy for mesothelioma, two esophagectomies for cancer, one esophageal leiomyoma VATS resection, two VATS thymectomies, and one lobectomy for aspergilloma. Control: one open lung biopsy for hilar lymphoma and one VATS thymectomy.

A significantly higher number and proportion of patients with stage IA–IB primary lung cancer was observed the spiral CT arm than in the control arm (47 vs. 16; $P = 0.0002$), whereas patients with stage II–IV lung cancer accounted for 50 cases in each arm. The distribution of all histological types was similar in the two study arms, with the exception of lepidic–predominant adenocarcinomas (Table 3).

In 19 patients with LDCT, definitive diagnosis and treatment were delayed 12 to 91 months after the lesion(s) became detectable by CT for the following reasons: small size (n = 3), ground-glass nodules (n = 6), multiple indeterminate lesions (n = 2), missed or misinterpreted in the previous CT scan (n = 5), and patient noncompliance with our recommendations (n = 3).

As retrospectively determined, 14 such patients were likely to have stage I disease at the outset, five of whom eventually progressed while being observed. Three such patients died of lung cancer; in one patient the lesion had been misinterpreted as benign, in one patient it had been missed, and one patient refused further investigation until accelerated progression occurred 8 years later. Including the above patients, 27 out of 66 patients (41%) detected by a screening CT and 32 out of 38 (84%) cases detected for any other reason died of lung cancer in the LDCT arm.

Active follow-up was terminated in February 2012, and vital status information as of May 15, 2013 was obtained through health registries for the whole study population, reaching a median follow-up of 8.35 years.

Death certificates could be cross-verified in 279 out of 356 cases (78%): 105 out of 114 (91%) lung cancer deaths, 90 out of 113 (80%) nonpulmonary cancer deaths, and 84 out of 127 (76%) noncancer deaths. In the remaining cases, the cause of death was known through death certificates alone or remained unknown in two subjects (Table 4).

In the LDCT arm, the lung cancer–specific mortality rate was 543 per 100,000 person-years (95% CI, 413–700) versus 544 per 100,000 person-years (95% CI, 410–709) in the control arm (hazard ratio [HR], 0.993; 95% CI, 0.688–1.433), and all-cause mortality rate was 1,655 per 100,000 person-years (95% CI, 1,422–1,916) versus 1,742 per 100,000 person-years (95% CI, 1,494–2,019) in the control arm (HR, 0.947; 95% CI, 0.769–1.165) (Figures 2 and 3).

Discussion

In 2001, the DANTE trial began enrolling patients in a randomized fashion with the aim of exploring whether LDCT screening could reduce lung cancer mortality compared with no screening. Several other groups in Europe eventually started their own randomized LDCT screening trials, all sharing the same methodology of comparing LDCT screening with no screening (32–37). DANTE, the first and smallest of these trials, holds several distinctive features: it had a unique control regimen, only male subjects were eligible, and a lower age limit of 60 years was chosen to maximize the efficiency of screening.

Table 3. Lung Cancer Detection Modality, Stage, and Histology

	LDCT	Control	All	*P* Value
Study subjects, n (%)	1,264 (51.59)	1,186 (49.41)	2,450 (100)	
Total patients with LC, n (%)	104 (8.23)	72 (6.07)	176 (7.18)	0.0418
Mode of detection, n (%)				
Baseline CXR or sputum only	1*	10†		
Baseline CT	29 (2.29)		29	
Follow-up CT	37 (2.92)	2‡	39 (1.59)	
Symptoms/other	37 (2.92)	62 (5.24)	99 (4.04)	0.0040
Complete resection	57 (4.51)	21 (1.77)	78 (3.18)	0.0001
Stage of primary, n (%)				
IA	31 (2.45)	6 (0.50)	37 (1.51)	<0.0001
IB	16 (1.26)	10 (0.84)	26 (1.06)	
II	7	5	12 (0.49)	
IIIA	9	6	15 (0.61)	
IIIB	8	6	14 (0.57)	
IV	26 (2.06)	33 (2.78)	59 (2.41)	0.2915
Missing§	7	6	13	
Histology of primary, n (%)				
Adenocarcinoma	44 (3.48)	19 (1.60)	63 (2.57)	0.0032
Lepidic-predominant	17 (1.34)	1 (0.08)	18 (0.73)	0.0002
Other subtypes	27	18	45 (1.84)	0.2930
Squamous	25	17	42 (1.71)	0.3510
Non–small cell, NOS	7	8	15 (0.61)	
Other	7	6	13 (0.53)	
Small cell	9 (0.71)	6 (0.51)	15 (0.61)	
Missing§	12 (0.95)	16 (1.35)	28 (1.14)	

Definition of abbreviations: CT = computed tomography; CXR = chest X-ray; LC = lung cancer; LDCT = low-dose spiral computed tomography; NOS = not otherwise specified.
Data refer to single patients. Percentages refer to column totals. Invasive procedures performed for staging purposes are not presented. Patients for whom the data are missing (five patients with LDCT and four control subjects) and one patient in each group with a contralateral radiologically occult tumor that was not resected are counted as incomplete resections.
*Radiologically occult; detected by baseline sputum examination.
†One patient inappropriately enrolled despite having already had stage IV lung cancer diagnosed elsewhere.
‡Two control patients were diagnosed by CT due to breach of protocol.
§Diagnosis established clinically or obtained by a death certificate.

The two arms of the trial appear well balanced except for a slightly higher prevalence of clinically detected respiratory comorbidity among subjects in the LDCT arm. In the LDCT arm of the DANTE trial, recalls, false positives, and stage I disease detection rate are comparable with those in the other European randomized trials (28) and with the LDCT arm of the NLST (15); however, the proportion of subjects diagnosed with lung cancer is the highest among all trials performed so far (Table 5).

A higher rate of surgical procedures (7%) and of surgical biopsies for benign lesions (1.34%) also occurred in the DANTE trial, although only six patients (0.47%) had a thoracotomy for such a reason. Early during the trial, video-assisted thoracoscopic biopsies for undetermined nodules were indeed more commonly performed; however, selection factors may in part account for such results in the DANTE cohort, where the median age of participants was 64 years. More false-positive findings, together with an increased lung cancer detection rate, were also reported for the Medicare-eligible (65-yr-old and above) subset of NLST participants (38).

In the DANTE study, patients with both early and advanced disease were increasingly detected in the LDCT arm after a drop after the baseline screen (*see* Figure E1 in the online supplement), and in the end no stage shift could be observed. Lung cancer–specific and all-cause mortality were unfortunately similar in the screening and in the control arm (Figures 2 and 3).

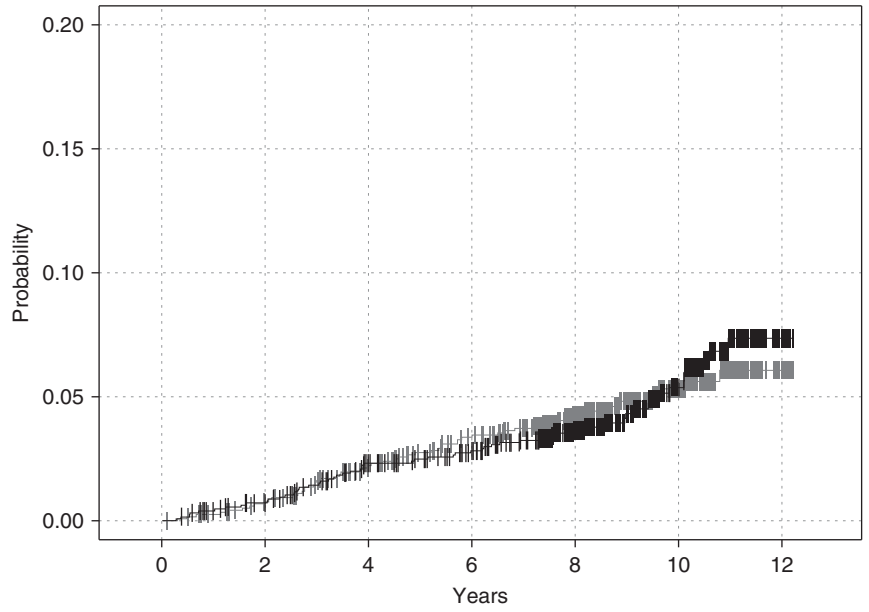
Thirty-two more lung cancer patients were diagnosed in the screening arm compared with the control arm, representing a lung cancer excess rate of 30.76% in the face of an unchanged mortality rate, indicating some degree of overdiagnosis.

There may be several reasons why the positive results of the NLST trial could not be replicated in the DANTE study. Sample size was a known limitation at the outset, but rather than yet another (even large) observational trial, we opted for a small, randomized study, choosing a large effect

Table 4. Lung Cancer–Specific and All-Cause Mortality Rates (per 100,000 Person-Years)

	LDCT	Control	All
Study subjects, n (%)	1,264 (51.59)	1,186 (49.41)	2,450 (100)
FU, person-years	10,875	10,104	20,979
Cause of death, n (%)			
Cancer of the lung	59 (4.66)	55 (4.64)	114 (4.65)
Cancer of other organs	54	59	
Nonneoplastic disease	65	62	
Unknown*	2	—	
Total deaths	180 (14.24)	176 (14.84)	356 (14.53)
Lung cancer mortality (95% CI)	543 (413–700)	544 (410–709)	543 (448–653)
All-cause mortality (95% CI)	1,655 (1,422–1,916)	1,742 (1,494–2,019)	1,697 (1,525–1,883)

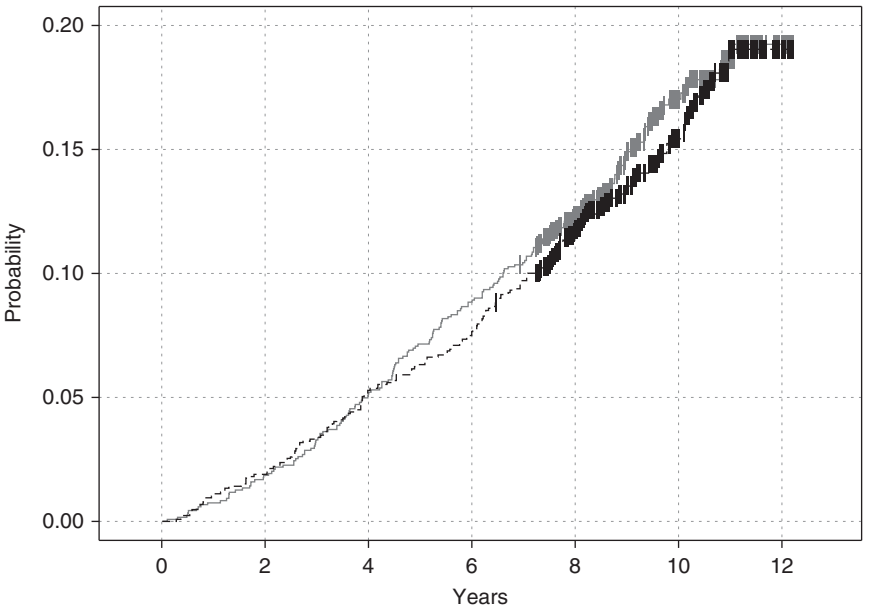
Definition of abbreviations: CI = confidence interval; FU = follow-up; LDCT = low-dose spiral computed tomography.
*One patient died of disseminated cancer of unknown origin, and one patient died of unknown causes in a foreign country.



At risk							
Control	1184	1162	1122	1078	748	335	20
LDCT	1264	1239	1197	1167	807	373	15

Figure 2. Cumulative probability of death from lung cancer. Hazard ratio = 0.993 (95% confidence interval, 0.688–1.433). LDCT = low-dose spiral computed tomography.

size as an endpoint based on optimistic assumptions. DANTE is therefore an inconclusive study. Second, a borderline interaction between sex- and lung-cancer–specific mortality, with greater benefit expected for female patients, has been reported (39) in a recent *post hoc* analysis of the NLST data. In our study, only male patients were enrolled, as in all earlier screening trials of CXR screening versus standard care, which was our only comparison when we started the DANTE trial. Our eligibility criteria might therefore have reduced the ability of this study to detect a small mortality advantage in favor of LDCT screening. Third, a baseline CXR and sputum examination and a yearly clinical review were offered to all to attract potential participants. It was anticipated that this control regimen would further limit the power of the study, and we acknowledged that it would not fully reflect what is likely to occur in the community setting. Nevertheless, it was also believed that media pressure in favor of LDCT screening and competition with neighbor institutions would otherwise make recruitment into our randomized study very difficult and that the impact of this regimen in the control arm would be modest, as our data show (Tables 2 and 3).



At risk							
Control	1184	1162	1122	1078	748	335	20
LDCT	1264	1239	1197	1167	807	373	15

Figure 3. Cumulative probability of death from all causes. Hazard ratio = 0.947 (95% confidence interval, 0.769–1.165). LDCT = low-dose spiral computed tomography.

Our disappointing results might also be due to the low sensitivity of the screening protocol. Multidetector scanners and workstations became available after 2003 and were only used for follow-up CT scans. In addition, a 3-mm reconstruction interval, 5-mm slice thickness, and two-dimensional evaluations were used for nodule assessment, whereas in most major trials, 0.7- to 2.5-mm reconstruction intervals and 1- to 3-mm slice thickness were adopted, and in several cases, volumetric software was used (15, 24, 27, 32, 33, 35, 40, 41). Indeed, the proportion of cancers that escaped detection by LDCT during the active phase of the study is higher than in all other trials (Table 5). Nevertheless, 47 out of 1,264 screened subjects (3.72%) were also diagnosed with stage I lung cancer by CT in the DANTE LDCT arm; therefore, stage I disease was also proportionally intercepted in the screened population much more frequently than in all other randomized trials (Table 5) and in major observational studies (10, 11, 13, 23, 42), suggesting that our high "miss rate" may not be due to low sensitivity alone.

Issues related to the evaluation of nodules might have contributed to decreasing the effectiveness of intervention in the LDCT arm because definitive diagnosis or treatment were delayed in 19 patients, and 5 (9.6%) out of 52 patients with stage I disease (five of whom were

Table 5. Detection Rates and Mortality Data in Selected Lung Cancer Screening Trials

Study (Reference[s])	Group	N	Age (*yr*)	Lung Cancers*		LDCT Detected		Stage I			Died, Lung Cancer	
				n	%	n	%	n	%	FU†	n	%
NELSON (22, 49)	LDCT	7,915	50–75	211	2.67	200	2.53	148	1.87	—	—	—
	Usual	7,907								—	—	—
ITALung (34, 50)	LDCT	1,406	55–69	40	2.84	38	2.7	23	1.64	—	—	—
	Usual	1,593		0	0					—	—	—
DLCST (32, 47)	LDCT	2,052	50–75	70	3.41	69	3.36	47	2.29	4.81	15	0.73
	Usual	2,052		24	1.17			5	0.24	4.81	11	0.54
MILD (37)‡	LDCT1	1,190	⩾50	34	2.86	29	2.44	18	1.51	4.4	12	1.01
	LDCT2	1,186		25	2.11	20	1.69	14	1.18		6	0.51
	Usual	1,723		20	1.16	—				4.4	7	0.41
DANTE	LDCT	1,264	60–74	104	8.23	67	5.3	47	3.72	8.35	59	4.67
	Clinical	1,186		72	6.07	10	0.84	16	1.35	8.35	55	4.64
NLST (15)	LDCT	26,309	55–74	1,060	4.03	649	2.47	400	1.52	6.5	356	1.35
	CXR	26,035		941	3.61	279	1.07	131	0.5	6.5	443	1.70
PLCO (8)§	CXR	77,445	55–74	1,696	2.19	307	0.4	462	0.6	11.9	1,213	1.57
	Usual	77,456		1,620	2.09	—	—	374	0.48	11.9	1,230	1.59
MLP (3, 6)	CXR	4,618	⩾45	206	4.46	90	1.95	68	1.47	7	122	2.64
	Usual	4,593		160	3.48	—	—	31	0.67	7	115	2.50

Definition of abbreviations: CXR = chest X-ray; DANTE = Detection And screening of early lung cancer with Novel imaging TEchnology; DLCST = Danish Lung Cancer Screening Trial; FU = follow-up; LDCT = low-dose spiral computed tomography; MILD = Multicentric Italian Lung Detection trial; MLP = Mayo Lung Project; NELSON = Dutch-Belgian Randomized Lung Cancer Screening Trial (Dutch acronym); NLST = National Lung Screening Trial; PLCO = Prostate, Lung, Colorectal, Ovary cancer screening trial.

Data reported on a per-patient basis. Percentages refer to entire study populations.

*Non–screen-detected cases include interval cases and cases detected for any reason more than 1 yr after the last screening round. Interval cases are defined as non–screening-detected cases occurring within 1 yr of the previous or last negative screening computed tomography.

†Median follow-up in years.

‡In the MILD trial, LDCT1 and LDCT2 indicate annual and biennial screening.

§PLCO and MLP data are included as a reference term for the control arm of the NLST.

retrospectively identified) progressed while being observed. However, false negatives (i.e., lung cancer nodules that were either misinterpreted as benign or missed and eventually progressed beyond stage I) have occurred with similar or greater frequency (8–17%) in other major screening trials as well (42–44). Such data are not yet available for the NLST trial.

Surgical mortality in the DANTE trial was 3.3%, whereas it was only 1% in the NLST. Because advanced age, male sex, and comorbidity negatively affect postoperative mortality in lung cancer surgery (45), case selection may have contributed to our less favorable results, which, however, are close to the 3.4% surgical mortality in the U.S. National Cancer Database (46).

Besides the NLST, three more randomized trials of lung cancer screening with LDCT have so far produced mortality data: the Danish Lung Cancer Screening Trial (47), the Multicentric Italian Lung Cancer Detection (MILD) trial (37), and DANTE. Although these studies are far smaller than the NLST, they all compared LDCT screening with conventional care or, as in DANTE, with something closely approximating it. In all three studies, a significant excess rate (30–66%) of lung cancer detection by CT was observed (in the NLST, it was only 11%), and unfortunately none of them was able to demonstrate a stage shift or any mortality advantage with CT screening.

The results of DANTE also suggest that aggressive cancers (that escape detection by LDCT) may appear with increasing frequency as the screened population gradually grows older and that the relative proportions of indolent, moderately progressive (suitable for early detection), or highly aggressive cancers in a given population may largely account for the results of LDCT screening rather than test sensitivity for small nodules. Even though the NLST was an outstanding trial, based on which the Centers for Medicare and Medicaid Services has finally approved financial coverage for LDCT screening in the United States (48), there is still some concern, at least in Europe (28), as to what extent it will eventually be possible to replicate those positive results in a community setting.

Given the limited statistical power of the DANTE trial, our data do not allow making a definitive statement about whether or not LDCT screening is effective in reducing lung cancer mortality. Yet such results suggest that additional information should be obtained from all randomized trials of LDCT screening for lung cancer that use intervention-free reference arms, in particular the NELSON study (44), and thoroughly evaluated before population screening can be recommended in Europe. Pooled analyses of European studies will include 37,000 subjects and will hopefully be able to provide the answers of paramount importance that are still needed concerning lung cancer screening with LDCT. ■

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