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CT Screening for Lung Cancer: Five-year Prospective Experience[1]

PURPOSE: To report results of a 5-year prospective low-dose helical chest computed tomographic (CT) study of a cohort at high risk for lung cancer.

MATERIALS AND METHODS: After informed written consent was obtained, 1520 individuals were enrolled. Protocol was approved by institutional review board and National Cancer Institute and was compliant with Health Insurance Portability and Accountability Act, or HIPAA. Participants were aged 50 years and older and had smoked for more than 20 pack-years. Participants underwent five annual (one initial and four subsequent) CT examinations. A significant downward shift was evaluated in non–small cell lung cancers detected initially from advanced stage down to stage I by using a one-sided binomial test of proportions. Poisson regression and Fisher exact tests were used for comparisons with Mayo Lung Project.

RESULTS: In 788 (52%) men and 732 (48%) women, 61% (927 of 1520) were current smokers, and 39% were former smokers. After five annual CT examinations, 3356 uncalcified lung nodules were identified in 1118 (74%) participants. Sixty-eight lung cancers were diagnosed (31 initial, 34 subsequent, three interval cancers) in 66 participants. Twenty-eight subsequent cases of non–small cell cancers were detected, of which 17 (61%; 95% confidence interval: 41%, 79%) were stage I tumors. Diameter of cancers detected subsequently was 5–50 mm (mean, 14.4 mm; median, 10.0 mm). Analysis for a more than 50% shift in proportion of stage I non–small cell cancer detection did not show statistical significance. Forty-eight participants died of various causes since enrollment. Lung cancer mortality rate for incidence portion of trial was 1.6 per 1000 person-years. There was no significant difference in lung cancer mortality rates of cancers detected in subsequent examinations between this trial and Mayo Lung Project after separation of participants into subsets (2.8 vs 2.0 per 1000 person-years, $P = .43$).

CONCLUSION: CT allows detection of early-stage lung cancers. Benign nodule detection rate is high. Results suggest no stage shift.

Lung cancer is a major public health concern. No advantage in mortality has been demonstrated with the use of chest radiographic screening (1–5). Investigators have shown (6–9) that screening with helical computed tomography (CT) allows detection of more early-stage lung cancers that are smaller in size than those detected with chest radiography and in current clinical practice. It is unclear whether the detection of early-stage disease represents a true stage shift or overdiagnosis. Screening studies have raised issues regarding false-positive findings, overdiagnosis, quality of life, and unnecessary surgical procedure expense, morbidity, and mortality. No professional health care organizations currently recommend screening for lung cancer.

The National Lung Screening Trial was established to address these and other issues. It is a randomized controlled trial with results expected near the end of this decade.

The purpose of this study was to report the results of a 5-year prospective low-dose helical chest CT study of a cohort at high risk for lung cancer.

MATERIALS AND METHODS

Research was funded by the National Cancer Institute (CA 79935–01) and Mayo Clinic.

Participants

We enrolled 1520 individuals into the study after written informed consent was obtained. Participants were recruited by means of local and regional television and newspaper coverage that relayed information regarding the general outline of the study, eligibility requirements, and funding by a National Institutes of Health grant. Participants were asymptomatic men and women aged 50 years and older. Participants had to be current or former (ie, they quit less than 10 years ago) cigarette smokers. A history of cigarette smoking of at least 20 pack-years was necessary for entrance into the study.

Participants were ineligible if they received supplemental oxygen or if they had a history of any cancer within 5 years other than nonmelanomatous skin cancer, cervical cancer in situ, or localized prostate cancer. Only mentally competent individuals considered healthy enough to undergo pulmonary resection were able to participate in the study. Any person with a serious illness that decreased life expectancy to less than 5 years was excluded. This protocol was approved by the Mayo Foundation institutional review board and by the National Cancer Institute. It was compliant with the Health Insurance Portability and Accountability Act, or HIPAA.

All participants consented to undergo an initial CT examination and four subsequent annual examinations; the fourth subsequent annual examination was not part of the original study objectives and hence required repeat patient consent. Annual induced sputum samples were obtained the same day of CT examination for immediate cytologic analysis. Blood was obtained from each participant and stored for subsequent DNA analysis. Spirometry (forced expiratory volume in 1 second) was performed for each participant at baseline. The results of DNA analysis and spirometry will be reported separately.

Imaging and Image Review

All scans were acquired with a four–detector row helical CT scanner at low radiation-dose levels (LightSpeed model QX/I; GE Medical Systems, Milwaukee, Wis) by using the following technique: 5-mm section width with 3.75-mm reconstruction interval, high-speed mode, pitch (ratio of table travel per rotation to total beam width) of 1.5, exposure time of 0.8 seconds per rotation, table feed of 30 mm per rotation of 37.5 mm/sec, 120 kVp, and 40 mA. Effective radiation dose was 0.65 mSv (65 mrem). All scans were acquired without a scout view to limit radiation dose. Scans were obtained from the level of the sternal notch to the iliac crests. No intravenous contrast material was administered.

All CT images were viewed at a computer workstation by one of four investigative radiologists. All four were chest radiologists (S.J.S., T.E.H., A.M.S., G.L.A.). Years of experience after board certification ranged from 7 to 26 years, with a mean of 15½ years. Images were viewed at standard lung (width, 1500 HU; level, −600 HU), soft tissue (width, 400 HU; level, 40 HU), and bone (width, 1000 HU; level, 200 HU) window settings.

The location and size (ie, average of the largest and perpendicular transverse diameters) of the six largest uncalcified nodules per patient were tabulated. A nodule was defined as a discrete round or oval (ie, the largest diameter measurement did not exceed two times the smallest diameter measurement) opacity with a smooth or irregular margin. It could be solid but could be cavitated or of ground-glass opacity.

All nodules identified in the baseline year were considered initial (prevalence) nodules. Any prevalence nodule that was diagnosed as cancer at a later time was considered a prevalence cancer. All nodules identified in subsequent annual CT examinations were considered incidence nodules. Cancers discovered between annual screenings were classified as interval cancers.

TABLE 1
False-Positive Rates for Lung Cancer

Nodule Type	Presence of Prevalence Cancers			Presence of Incidence Cancers*		
	Yes	No	False-Positive Rate (%)	Yes	No	False-Positive Rate (%)
All nodules	31	749	96.0	32	773	96.0
Nodules > 4 mm	31	404	92.9	31	378	92.4

Note.—Data are number of nodules, unless indicated otherwise. Calculations are based on one or more nodules detected at prevalence or incidence CT examination only.

* Excludes the three interval cancers. Two patients with cancer detected at prevalence CT examination had a new primary lung cancer detected on an incidence CT scan and were excluded from incidence analyses.

Follow-up and Recommendations

The CT reports and a letter from either one of the two investigative pulmonologists (J.R.J., D.E.M.; board certified with average subspecialty experience of 19½ years) were sent to each participant and his or her designated physician. Interval scans for nodule follow-up performed outside of the protocol were acquired at numerous institutions; the technique used was not dictated by the study protocol.

Nodule management recommendations were made in the letter to the attending physician on the basis of an internally developed management algorithm for indeterminate prevalence or incidence lung nodules: *(a)* For a nodule smaller than 4 mm, follow-up low-dose screening CT should be performed after 6 months. (The follow-up interval was increased to 12 months in the past year based on our experience with nodules smaller than 4 mm.) *(b)* For nodules 4–7 mm, follow-up diagnostic CT should be performed after 3 months. *(c)* For nodules 8–20 mm, diagnostic CT should be performed as soon as possible; CT nodule enhancement protocol (10) or positron emission tomography (PET) (11) should be considered. *(d)* For nodules larger than 20 mm, CT should be performed as soon as possible; PET and biopsy or removal should be considered as indicated.

Nodules were considered benign if they were stable or smaller in size over a 2-year period of observation or if they contained benign-pattern calcification (eg, diffuse central, laminated, chondroid). Nodules that did not meet these criteria were considered radiologically indeterminate. These criteria and surgical outcome were our reference standards. Although we made specific recommendations for follow-up of every nodule on the basis of size, we did not otherwise direct management

TABLE 2
Histologic Findings of Primary Lung Cancers

Cancer Type and Stage	Diameter (mm)	No. of Adeno-carcinomas	Adenocarcinoma with Bronchioloalveolar Carcinoma Features	Bronchiolo-alveolar Carcinoma	Large Cell Neuro-endocrine Carcinoma	Mixed Large and Small Cell Carcinoma	Non–Small Cell Carcinoma (Not Otherwise Specified)	Squamous Cell Carcinoma	Small Cell Carcinoma
Prevalence cancers (n = 31)									
IA	4–7	3	0	0	0	0	0	1	0
	7–20	6	4	3	0	0	1	2	0
IB	7–20	1	0	1	0	0	0	0	0
IIA	7–20	2	1	0	1	0	0	0	0
IIIA	>20	1	0	0	0	0	0	1	0
IV	7–20	0	1	0	0	0	0	0	0
Limited (small cell carcinoma)	>20	0	0	0	0	0	0	0	2
Total prevalence cancers		13	6	4	1	0	1	4	2
Incidence and interval cancers (n = 35)*									
IA	4–7	0	0	4	0	0	1	0	0
	7–20	0	0	3	0	1	1†	6	0
IB	7–20	1	0	0	0	0	0	0	0
IIA	7–20	1	0	0	0	0	0	0	0
	>20	1	0	0	0	0	0	0	0
IIB	>20	1	0	0	0	0	0	1	0
IIIA	4–7	1	0	0	0	0	0	0	0
	7–20	1	0	0	0	0	1†	1	0
IIIB	7–20	0	0	0	0	0	0	2	0
IV	<4	0	0	0	0	0	0	0	0
	4–7	0	0	0	0	0	0	0	0
	>20	0	0	0	0	0	0	0	0
	Unknown	0	0	0	0	0	1	0	0
Limited (small cell carcinoma)	>20	0	0	0	0	0	0	0	6†
Total incidence and interval cancers		6	0	7	0	1	4	10	6

* One cancer was of unknown histology, stage, and size and was not included in the Table but was included in incidence analyses. Two patients with cancer detected on a prevalence CT scan had a new primary lung cancer detected on an incidence CT scan and were excluded from incidence analyses and were not included in the Table.

† One tumor in this grouping was staged with CT, PET, and mediastinoscopy.

decisions made by the attending local physician and the patient.

Our team of research coordinators attempted to make contact with all participants at least two times per year (in person at the annual screening examination or by telephone if scanning was not performed and by mail 6 months after each screening examination). One of 1520 participants was lost to follow-up.

A member of our research coordination team recorded all information in our database. Sources of study data included patient records, radiology reports, death certificates, and surgical reports. Data recorded included nodule size, nodule growth or stability, location and calcification, cancer size and stage, cell type, follow-up scans, surgical procedures, illnesses, other diagnoses, cause and date of death, and additional findings. Diagnosis of cancer was assigned with histologic or cytologic findings in all cases. Staging was determined at surgery, if performed, and according to supportive biopsy results as available (or by means of PET and/or CT in the absence of other data). Information obtained through May 26, 2004, with regard to participants and status of their health was included in the current summary and analysis.

Statistical Analysis

Roughly 40%–50% of non–small cell lung cancers detected by means of chest radiography or sputum cytology in the previous major screening studies were stage I. This estimate is relatively consistent in the literature (1–5). Our primary aim was therefore to test the null hypothesis that the percentage of stage I non–small cell lung cancers observed at diagnosis is 50% or less versus the one-sided alternative that helical CT can substantially increase detection of the proportion of stage I non–small cell lung cancers to more than 50%.

A sample of 1500 subjects followed for 4 years (approximately 6000 person-years of screening) was targeted for accrual to identify at least 26 incidence non–small cell lung cancers. This sample provides at least 80% power to detect a more than 50% shift in the proportion of stage I non–small cell lung cancers at diagnosis (eg, from 50% stage I to 75% stage I), given that the true shift in the proportion of stage I non–small cell lung cancers is at least 75% (one-sided binomial test of proportions, with the significance threshold set at $P = .05$).

Incidence results from this study were compared with a historical control, the Mayo Lung Project (4). This exploratory comparison was conducted to see how results from the current study compared with what was observed in the past. The Mayo Lung Project was conducted in the 1970s, when lung cancer diagnosis, treatment methods, smoking practices, and patient histologic examination, among many other factors, were probably very different from today. To facilitate a reasonably fair comparison, we accounted for the known confounding factors of patient sex, age, and years of follow-up; however, other factors, such as smoking exposure, cigarette filters, and treatment methods, could not be controlled statistically because of lack of available data.

The Mayo Lung Project included only men more than 45 years of age who smoked 1 pack or more of cigarettes daily. Participants were randomized between screening (chest radiographic and sputum cytologic examinations every 4 months) and control ("normal care") groups. The initial follow-up was conducted from late 1971 to mid-1976. To compare the lung cancer mortality rates in a similar subset in the two screening trials, we included only men 50 years of age and older in both trials.

In addition, only the first 4 years of follow-up were included for the Mayo Lung Project. Since the lung cancer mortality rates were nearly identical in the control and screening groups of the Mayo Lung Project (3.2 vs 3.0 per 1000 person-years), we combined the two arms when computing the lung cancer mortality rates for the Mayo Lung Project. We recognize that there is inadequate power for such comparisons; however, the goal of this analysis is to help put the mortality estimates in perspective. These results should be viewed as exploratory and hypothesis generating rather than definitive.

Poisson regression and Fisher exact tests were used for comparisons of lung cancer incidence rates and mortality estimates between the sexes and between studies. False-positive rates were computed separately for the prevalence and incidence scans. A false-positive finding was defined as an uncalcified lung nodule detected at either prevalence or incidence CT that was not reported as a cancer (proved benign by means of surgery or observation) during the study period.

RESULTS

From January 20, 1999, to December 15, 1999, 1520 participants were enrolled and underwent baseline prevalence helical CT scanning. Enrollment was denied to 421 other applicants because they did not meet the eligibility criteria. The reasons for ineligibility were insufficient smoking history (198 patients), no interest in the study after informed consent was obtained (84 patients), history of cancer within 5 years (37 patients), congestive heart failure (18 patients), insufficient age (31 patients), enrollment in a conflicting research study (four patients), respiratory insufficiency (seven patients), and miscellaneous health or personal situations (42 patients). The final incidence CT examination was completed in December 2003. We report here the results through May 26, 2004, including the baseline and all four annual incidence CT scans. Our results through 2001 were reported previously (12).

TABLE 3
Overall Mortality Rates for Participants Who Underwent at Least One Incidence CT Examination

Cause of Mortality	No. of Participants ($n = 1453$)	Mortality Rate*
Lung cancer	9	1.6
All causes	33	6.0

Note.—Mortality rates are per 1000 person-years of follow-up. Prevalence cancers excluded.
* For a total of 5481.5 person-years.

There were 788 (52%) men and 732 (48%) women. All were 50 years of age and older (median age, 59 years; range, 50–85 years). Sixty-one percent (927 of 1520) were current smokers, and 39% were former smokers. The median number of pack-years was 45 (range, 20–230 pack-years). The compliance rates for the annual incidence CT examinations were 98% for year 1, 96% for year 2, 95% for year 3, and 80% for year 4. As already noted, the fourth annual incidence scan was not part of the original study objectives; hence, repeat patient consent was required. One of 1520 participants was lost to follow-up.

After five annual CT examinations (one prevalence and four incidence examinations), 3356 uncalcified nodules were identified in 1118 (74%) participants. The distribution of nodules is as follows: 2038 (61%) nodules smaller than 4 mm, 1034 (31%) nodules 4–7 mm, 268 (8%) nodules 8–20 mm, and 16 (<1%) nodules larger than 20 mm. A total of 780 (51%) of the 1520 participants had 1646 prevalence nodules identified prospectively. Participants had 847 new nodules (not present in

TABLE 4
Incidence Lung Cancer Stage Distribution (Age-matched Men Only)

Cancer Type and Stage	Mayo Lung Project			Helical CT
	Overall Population	Screened Population	Control Population	Overall Population
Unknown	0 (0.0)	0 (0.0)	0 (0.0)	1 (100.0)
Non–small cell lung carcinoma				
Carcinoma in situ	3 (2.7)	3 (4.6)	0 (0.0)	0 (0.0)
IA	23 (20.9)	16 (24.6)	7 (15.6)	7 (46.7)
IB	19 (17.3)	12 (18.5)	7 (15.6)	0 (0.0)
IIA	8 (7.3)	8 (12.3)	0 (0.0)	2 (13.3)
IIB	8 (7.3)	5 (7.7)	3 (6.7)	1 (6.7)
IIIA	24 (21.8)	11 (16.9)	13 (28.9)	2 (13.3)
IIIB	0 (0.0)	0 (0.0)	0 (0.0)	2 (13.3)
IV	25 (22.7)	10 (15.4)	15 (33.3)	1 (6.7)
Total	110 (100.0)	65 (100.0)	45 (100.0)	15 (100.0)
Small cell lung carcinoma				
Limited	0 (0.0)	0 (0.0)	0 (0.0)	1 (100.0)

Note.—Data are numbers of cancers. Numbers in parentheses are percentages.

previous examinations in retrospect) detected over the 4 years of incidence screening and had 863 nodules detected that were present in retrospect on previous scans. Fifty-eight participants had more than six nodules (nodules detected after the first six are not included in the totals provided earlier).

Rates of false-positive findings (uncalcified lung nodules proved benign by means of observation or surgery) ranged from 92.4% to 96.0% (Table 1). A total of 69% of our participants had at least one false-positive finding to date. Thirteen participants underwent 15 surgeries for benign disease without surgical mortality.

We documented 68 primary lung cancers in 66 participants (4% of 1520 participants and 2% of 3356 nodules), of which 31 were prevalence, 34 were incidence, and three were interval lung cancers (Table 2). Two cases were detected by means of sputum cytology only (one incidence case and one prevalence case). Two patients with cancer detected at prevalence CT scanning had a new primary lung cancer detected on an incidence scan. These two patients (one with stage IB adenocarcinoma and one with stage IA squamous cell carcinoma) were excluded from incidence analysis. (Therefore, for all incidence analyses, including the lung cancer mortality estimates and comparisons with the Mayo Lung Project, we combined the incidence and the interval lung cancers, for a total of 35 cancers [Table 2]).

Prevalence Cancers

There was a significant difference in the number of prevalence lung cancers (n = 31) between men and women (10 vs 21, Fisher exact test, P = .03). Prevalence non–small cell lung cancers ranged in size from 5 to 47 mm (mean, 13.9 mm; median, 12.0 mm). The most common histologic findings were adenocarcinoma (42%), adenocarcinoma with bronchioloalveolar carcinoma features (19%), and bronchioloalveolar carcinoma (13%). See Table 2 for more details on other histologic findings.

Incidence Cancers

Incidence non–small cell lung cancers (n = 35, including the three interval cancers) ranged in size from 5 to 50 mm (mean, 14.4 mm; median, 10.0 mm). The most common histologic findings were adenocarcinoma (17%), bronchioloalveolar carcinoma (20%), and squamous cell carcinoma (29%). See Table 2 for more details on other histologic findings. A total of 28 non–small cell lung cancer incidence cases were detected, of which 17 (61%; 95% confidence interval: 41%, 79%) were stage I tumors. Analysis for a more than 50% shift in the proportion of stage I non–small cell lung cancers detected did not show statistical significance (P = .17). A comparison of lung cancer incidence rates between the sexes per 1000 person-years of follow-up revealed no significant difference (18 women with a total follow-up of 2622 person-years = rate of 6.86, vs 17 men with a total follow-up of 2877 person years = rate of 5.91; Poisson regression, P = .66).

Mortality

Forty-eight participants died since enrollment. Deaths were from lung cancer (n = 9), cardiovascular disease (n = 4), primary brain cancer (n = 3), respiratory failure (n = 5), laryngeal cancer (n = 2), esophageal cancer (n = 2), bladder cancer (n = 2), pancreatic cancer (n = 2), lymphoma (n = 1), prostate cancer (n = 1), leukemia (n = 1), melanoma (n = 1), drowning (n = 1), suicide (n = 1), and unknown cause (n = 13). One of the lung cancer deaths was postoperative.

Thirty-three of the 1453 participants who had at least one incidence scan died since enrollment. The total mortality rate (excluding prevalence cancers) was 6.0 per 1000 person-years, and the overall lung cancer mortality rate was 1.6 per 1000 person-years (Table 3).

We compared the lung cancer mortality rates between our current CT study and the Mayo Lung Project in a similar age and sex subset. There was no difference in the incidence lung cancer mortality rates between the two studies in the subset of men 50 years of age and older with 4 years of follow-up (2.8 vs 2.0 per 1000 person-years; Poisson regression, P = .43) (Tables 4, 5).

Stage Distribution Comparisons

We compared the stage distribution at diagnosis between the incidence portion of our current CT study and the Mayo Lung Project in a similar subset of age and sex. There was no difference in the percentage of patients diagnosed with stage I non–small cell lung cancers, including carcinoma in situ (47% vs 41%; Fisher exact test, P = .78). There was, however, a substantially larger proportion of stage IA cancers detected with CT versus chest radiography in this subset analysis (47% vs 21%; Fisher exact test, P = .05) (Tables 4, 5).

DISCUSSION

CT screening for lung cancer offers the possibility of reducing mortality from lung cancer. Our preliminary results do not support this possibility and may raise concerns that false-positive results and overdiagnosis could actually result in more harm than good.

Stage Distribution

A national cancer database report (13) indicates that, in usual clinical practice, 20% of patients with lung cancer have stage I disease at the time of presentation. On the surface, our relatively high percentage of stage I incidence non–small cell lung cancers (61%) appears to be a positive result. However, this could re-

TABLE 5
Comparison of Lung Cancer Mortality Rates per 1000 Person-Years

Study	No. of Patients	Deaths due to Lung Cancer	Deaths due to All Causes	Deaths from Other Causes in Patients with Lung Cancer	Person-Years
Mayo Lung Project					
Overall population	6910	54 (2.0)	592 (22.4)	5 (3.8)	26 483.1
Screened population	3460	24 (1.8)	318 (24.2)	4 (5.4)	13 218.2
Control population	3450	30 (2.3)	274 (20.7)	1 (1.8)	13 264.9
Current helical CT study					
Overall population	778	8 (2.8)	37 (12.9)	0	2876.5

Note.—Data are numbers of patients, unless indicated otherwise. Numbers in parentheses are mortality rates. Prevalence cancers were excluded. Only age-matched men included.

flect any combination of selection, length, overdiagnosis, and lead-time biases.

The proportion of advanced-stage cancers in the incidence portion of our screened population relative to the Mayo Lung Project was similar (33% vs 45%; Fisher exact test, $P = .58$), which raises questions concerning whether there has been a true stage shift with CT. To demonstrate a stage shift, one must show not only an increase in early-stage disease but also a concomitant decrease in late-stage disease when compared with a nonscreened population.

Mortality Estimates

Our exploratory analysis demonstrates no difference in the observed incidence lung cancer mortality rate relative to a historic benchmark (2.8 vs 2.0 per 1000 person-years). This observation is consistent with estimates of lung cancer mortality from CT trial results (14).

There are data that positively frame the debate for advocates who see an opportunity for earlier detection with CT screening to substantially reduce mortality from lung cancer. In the national cancer database report (13), the overall 10-year survival of 392 238 patients with lung cancer was a dismal 7%. The 5-year survival rate, after resection of stage IA non–small cell lung cancer, ranges from 62% to 82% (13,15). The outcome of patients who decline treatment for stage I cancers is usually fatal (16). However, our preliminary mortality results should cause physicians to pause and reexamine their positions if they are performing routine CT screening outside of a clinical trial.

False-Positive Findings

Our false-positive rates were high (92.4%–96.0%) and affected most participants (69%). False-positive rates at CT screening appear to be reflective of technologic advances, independent of geographic location in the world (6,7,12, 17–19).

Intervention for benign nodules is common and has substantive financial, mortality, morbidity, and quality of life costs (20–30).

Overdiagnosis

Overdiagnosis bias is in part the result of slow-growing relatively indolent lung cancers that a patient dies with and not from. If CT screening truly leads to overdiagnosis of lung cancer, one would expect an increase in stage I disease, an increase in resectability, a longer 5-year survival, and an increase in the total number of cancers but no change in the number of advanced cancers and no decrease in lung cancer deaths (31–33). This is exactly what was found in the chest radiographic Mayo Lung Project (4).

In current clinical practice, approximately 30%–40% of lung cancer deaths are expected to be associated with histologic findings of adenocarcinoma (13). One could speculate that the higher rate of adenocarcinomas (especially bronchioloalveolar carcinoma) observed in the current study (74% prevalence, 37% incidence) raises the possibility of overdiagnosis in this high-risk cohort. This is a substantially higher percentage than one would expect from the overall mortality rates of lung cancer, indicating that slower-growing adenocarcinomas (especially bronchioloalveolar carcinomas) that are not lethal may be identified with CT screening. A substantially larger proportion of adenocarcinomas has been identified in recent trials (8,34–36).

As investigators look more closely at the lung with CT, we appear to be finding more tumors than with chest radiography and more than what one would expect from mortality data. It is unlikely that all of these tumors are clinically important (ie, lethal). Surgical intervention for nonlethal cancers could result in more harm than good.

There are limitations to our study. It is a single-arm prospective cohort study that could have a selection bias. It is not randomized and has no internal control group. There were only 4 years of follow-up since the first incidence examinations; therefore, the benefit of early detection may not yet be evident. There may be stage migration bias caused by staging technology differences relative to historical controls. The number of observed lung cancer deaths could be higher in the current study because of temporal improvements in the detection and diagnosis of lung cancer as the cause of death determination. In other words, some lung cancer deaths in the Mayo Lung Project may have been misattributed to other causes.

There are shortcomings to using the Mayo Lung Project as a benchmark for comparison, but we believe that it is the best available historical comparison group. We were able to separate our participants into subsets to achieve reasonable demographic similarity. The limitations of this comparison are *(a)* the relatively small sample size in the CT subset (778 participants with a total of 2877 person-years), *(b)* the absence of a comparison group for women, and *(c)* the small number of lung cancer deaths in the CT group that results in insufficient power to make any definitive conclusions. Other shortcomings include different diagnostic and therapeutic era, different histologic mix, different cigarettes, and different smoking pack-years.

In conclusion, the ramifications of widespread CT screening for lung cancer are mostly unknown (37). Our findings

answer some questions and raise many others. Screening of patients at high risk for lung cancer with CT allows for detection of many early-stage lung cancers that are smaller than those seen in our usual clinical practice today or with chest radiographic screening (6–9,35). It is unclear if this represents a true stage shift and/or overdiagnosis. CT screening allows for detection of a large number of benign uncalcified lung nodules (false-positive result) that will be expensive to diagnose and may impact quality of life and mortality from intervention. Our data do not suggest a mortality benefit; whether CT for lung cancer meets the criteria for an effective screening test remains to be proved (33).

The National Lung Screening Trial, funded by the National Cancer Institute, is a randomized controlled trial that will determine whether there is a disease-specific mortality benefit (38). Before the National Lung Screening Trial is completed, screening should be performed in the setting of a clinical trial or only after informed consent is obtained from a fiduciary without financial interest (39,40).

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