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Lung Cancer Screening with CT: Mayo Clinic Experience[1]

PURPOSE: To evaluate a large cohort of patients at high risk for lung cancer by using screening with low-dose spiral computed tomography (CT) of the chest.

MATERIALS AND METHODS: A prospective cohort study was performed with 1,520 individuals aged 50 years or older who had smoked 20 pack-years or more. Participants underwent three annual low-dose CT examinations of the chest and upper abdomen. Characteristics of pulmonary nodules and additional findings were tabulated and analyzed.

RESULTS: Two years after baseline CT scanning, 2,832 uncalcified pulmonary nodules were identified in 1,049 participants (69%). Forty cases of lung cancer were diagnosed: 26 at baseline (prevalence) CT examinations and 10 at subsequent annual (incidence) CT examinations. CT alone depicted 36 cases; sputum cytologic examination alone, two. There were two interval cancers. Cell types were as follows: squamous cell tumor, seven; adenocarcinoma or bronchioloalveolar carcinoma, 24; large cell tumor, two; non–small cell tumor, three; small cell tumor, four. The mean size of the non–small cell cancers detected at CT was 15.0 mm. The stages were as follows: IA, 22; IB, three; IIA, four; IIB, one; IIIA, five; IV, one; limited small cell tumor, four. Twenty-one (60%) of the 35 non–small cell cancers detected at CT were stage IA at diagnosis. Six hundred ninety-six additional findings of clinical importance were identified.

CONCLUSION: CT can depict early-stage lung cancers. The rate of benign nodule detection is high.

In the United States, lung cancer is the most common fatal malignancy in both men and women. Approximately 175,000 new cases are diagnosed each year, of which 75%–80% represent non–small cell lung cancer. More than 50% of patients will have distant metastases at diagnosis, and only 20%–25% of patients will have lesions that are localized and potentially resectable for cure (1).

In the 1970s, the National Cancer Institute supported a lung cancer mass-screening program in which chest radiography and sputum cytologic examination were used for screening at the Mayo Clinic (2–4). No mortality difference was observed between the subjects who underwent screening and those in the control groups (5), even with extended follow-up through 1996, even though 48% of cancers in those who underwent screening were early-stage cancers: stages 0, I, and II (6). Similar results were found in a Czech study (7). As a result of these and other studies, no organizations recommend screening (8).

Investigators have more recently considered the use of low-dose computed tomography (CT) for screening (9–15). Authors of these studies have suggested that screening with spiral CT can depict lung cancers that are of a smaller size (<2 cm in diameter) and earlier stage (85%–93% at stage I) than those observed at chest radiography and in current clinical practice.

It is unclear whether the earlier-stage disease detected represents a true stage shift and whether detection at an earlier stage improves mortality rates. Screening studies have raised issues regarding false-positive findings, overdiagnosis, quality of life, and unnecessary surgical procedure expense, morbidity, and mortality.

To further examine some of these questions, a protocol was developed to evaluate a large cohort of patients at high risk for lung cancer by using screening with low-dose spiral chest

CT. Results were compared with those of previous studies (2–6) of screening with chest radiography and those of current clinical practice (1).

MATERIALS AND METHODS

Participants

All individuals participating in the study were enrolled after they provided written informed consent. Individuals volunteered for the study in response to local and regional television and newspaper coverage that provided information regarding the general outline of the study, the eligibility requirements for the study, and the fact that the study was funded in part by a National Institutes of Health grant. Participants were men and women who were 50 years of age or older and asymptomatic.

From January 20, 1999, to December 15, 1999, 1,520 participants (785 men, 735 women; mean age, 59 years; age range, 50–85 years) were enrolled and underwent baseline (prevalence) CT. Participants had to be current or former (ie, they had to have 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. Ineligible were those applicants with 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 entered into 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 institutional review board of the Mayo Foundation and by the National Cancer Institute.

All participants agreed to undergo prevalence CT and three subsequent annual (incidence) CT examinations. Annual induced sputum samples were obtained and subjected to immediate cytologic analysis. Blood was obtained from each participant and stored for subsequent DNA analysis. Spirometry to determine forced expiratory volume in 1 second was performed in each participant at baseline. The results of DNA analysis and spirometry will be reported separately.

Imaging and Image Review

All scanning for each of the 3 years was performed with a multisection spiral CT scanner (LightSpeed Model QX/i; GE Medical Systems, Milwaukee, Wis) at low dose levels with the following technique: 5.00-mm section width; 3.75-mm reconstruction interval; high-speed mode; pitch (ratio of table travel per rotation to total beam width), 1.5; exposure time, 0.8 second per rotation; table feed, 30.0 mm per rotation (37.5 mm/sec); 120 kVp; and 40 mA. Effective radiation dose was 0.65 mSv (65 mrem). All scans were obtained without a scout view. Scans were obtained from the level of the sternal notch to the iliac crests.

All CT images were viewed in cine formats at a computer workstation by one of four investigator radiologists (S.J.S., T.E.H., A.M.S., G.L.A.); all four were chest radiologists who had 5–24 years (average, 13.5 years) of experience after board certification. Images were viewed at standard lung, soft-tissue, and bone window settings.

The location and size of each uncalcified nodule were tabulated. A nodule was considered to be uncalcified, and therefore radiologically indeterminate, if it did not contain a benign pattern of calcification—diffuse, central, laminated, or chondroid. All nodules identified in the baseline year were considered prevalence nodules. All nodules identified at subsequent annual CT examination were considered incidence nodules, regardless of whether they were present in retrospect on scans from the baseline CT examination.

Follow-up and Recommendations

CT reports and a letter from either one of the two investigator pulmonologists were sent to each participant and his or her physician, as designated by the participant. Interval scans for nodule follow-up outside of the protocol were obtained at numerous institutions; the technique used was not dictated by the study protocol. Most medical centers used standard-dose chest CT with thin sections (1–3 mm) for nodule analysis. Nodule management recommendations were communicated in the letter to the attending physician on the basis of an untested, internally developed management algorithm for indeterminate pulmonary nodules. Recommendations were as follows: for nodules smaller than 4 mm, perform CT in 6 months; for nodules 4 mm or larger but smaller than 8 mm, perform CT in 3 months; for 8–20-mm nodules, perform CT as soon as possible and consider a CT nodule enhancement protocol or positron emission tomography; for nodules larger than 20 mm, perform biopsy.

Nodules were considered benign if they were stable or became smaller during 2 years of observation. Nodules not meeting these criteria were considered radiologically indeterminate. Our team of research coordinators attempted to make contact with all participants at least two times per year. A member of our research coordinator team recorded all data 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 obtained, surgical procedures performed, illnesses, other diagnoses, cause and date of death, and additional findings.

RESULTS

We report here the results though 2001, including results from the baseline and first two annual incidence CT examinations. Our results through 2000 were previously reported (16).

Enrollment was denied to 421 other applicants because they did not meet the eligibility criteria. The reasons for ineligibility were as follows: insufficient smoking history, 198; not interested in study after informed consent, 84; history of cancer within 5 years, 37; congestive heart failure, 18; age less than 50 years, 31; enrollment in a conflicting research study, four; respiratory insufficiency, seven; and miscellaneous health or personal situations, 42. Of the 1,520 participants, 742 (49%) were previous Mayo Clinic patients; the remaining patients were new to Mayo Clinic. Sixty-one percent were current smokers; 39% were former smokers. The median number of pack-years was 45 (range, 20–230 pack-years).

Nineteen participants had died since enrollment. Three of the participants died in 1999, six in 2000, and 10 in 2001. Five of the deaths were due to lung cancer (two were small cell lung cancers). Other known causes of death were cardiovascular disease ($n = 4$); infection ($n = 2$); and laryngeal cancer, esophageal cancer, pancreatic cancer, lymphoma, melanoma, and suicide ($n = 1$ each). The cause of death was unknown in two patients. The man who committed suicide had a 2-mm pulmonary nodule not thought to be cancer and a 4-cm abdominal aortic aneurysm.

Of the 1,511 living participants, 1,478 (98%) returned for the first of their three annual incidence examinations. Two

TABLE 1
Forty Primary Lung Cancers Found during This Investigation

Case No.	Histologic Finding	Cancer Stage	Type of Examination	Size (mm)
1	Large cell neuroendocrine tumor	IIA	Prevalence	8
2	Squamous cell tumor	IA	Prevalence	10
3	Adenocarcinoma	IA	Prevalence	14
4	Adenocarcinoma*	IA	Prevalence	20
5	Adenocarcinoma	IIA	Prevalence	15
6	Adenocarcinoma	IIIA	Prevalence	31
7	Squamous cell tumor	IIIA	Prevalence	47
8	Bronchioloalveolar tumor	IA	Prevalence	10
9	Adenocarcinoma*	IB	Prevalence	9
10	Squamous cell tumor†	IA	Prevalence	5
11	Adenocarcinoma	IA	Prevalence	15
12	Adenocarcinoma	IIA	Prevalence	13
13	Squamous cell tumor	IA	Prevalence	15
14	Small cell carcinoma	Limited	Prevalence	28
15	Small cell carcinoma‡	Limited	Prevalence	55
16	Adenocarcinoma	IA	Prevalence	7
17	Adenocarcinoma*	IA	Prevalence	20
18	Adenocarcinoma	IA	Prevalence	20
19	Adenocarcinoma	IA	Prevalence	14
20	Adenocarcinoma	IA	Prevalence	8
21	Bronchioloalveolar tumor	IA	Prevalence	20
22	Adenocarcinoma*	IIA	Prevalence	16
23	Adenocarcinoma*	IA	Prevalence	9
24	Non–small cell lung cancer	IA	Prevalence	12
25	Adenocarcinoma	IB	Prevalence	11
26	Adenocarcinoma	IA	Prevalence	15
27	Adenocarcinoma	IA	Prevalence	6
28	Small cell carcinoma†‡	Limited	Incidence	2
29	Squamous cell tumor‡	IIB	Incidence	60
30	Squamous cell tumor	IIIA	Incidence	8
31	Adenocarcinoma§	IIIA	Incidence	17‖
32	Squamous cell tumor‡	IA	Incidence	20
33	Bronchioloalveolar tumor	IA	Incidence#	5
34	Non–small cell lung cancer	IA**	Incidence	7‖
35	Large cell tumor††	IA	Incidence	20
36	Bronchioloalveolar tumor	IA	Incidence#	6
37	Adenocarcinoma‡‡	IB	Incidence#	8
38	Adenocarcinoma	IIIA	Incidence#	5‖
39	Non–small cell lung cancer‡	IV	Interval	Unknown
40	Small cell carcinoma	Limited	Interval	20

* With features of bronchioloalveolar carcinoma.
† Found at screening by means of sputum cytologic examination alone.
‡ Fatal lung cancer.
§ Metastatic carcinoma found in mediastinal lymph node.
‖ Size was measured from CT findings if the nodule was not removed at surgery.
Present in retrospect at prior annual CT.
** No pathologic stage (T1NXMX); the IA stage was assigned on the basis of CT findings.
†† Mixed large cell and small cell histologic findings.
‡‡ Second lung cancer in the same participant; the first cancer was case number 9.

hundred seven (14%) had one or more new nodules. None of these new nodules was present in retrospect on the baseline CT scans.

Of 1,501 living participants, 1,438 (96%) returned for their second annual incidence screening examination. One hundred twenty-nine (9%) had one or more new nodules. None of these new nodules was present in retrospect on scans from either the baseline or first annual CT examinations.

After 3 years of annual scanning (one prevalence examination and two incidence examinations), 2,832 uncalcified pulmonary nodules were identified in 1,049 (69%) of the 1,520 participants. The nodules were distributed in size and number as follows: smaller than 4 mm, 1,735 (61%); 4 mm or larger but smaller than 8 mm, 950 (34%); 8–20 mm, 136 (5%); larger than 20 mm, 11 (0.4%).

We documented 40 primary lung cancers (2.6% of 1,520 participants; 1.4% of 2,832 nodules). Thirty-six were non–small cell carcinomas, and four were limited-stage small cell carcinomas (Table 1). Twenty-six lung cancers were identified at prevalence CT, and 10 were identified at incidence CT. Two were interval cancers. Thirty-eight were detected with CT alone, and two (one prevalence and one incidence nodule) with sputum cytologic examination alone. The incidence nodule detected at sputum cytologic examination alone represented small cell cancer and was present in retrospect on baseline CT scans. According to cell type, seven cancers were squamous cell, 24 were adenocarcinoma or bronchioloalveolar carcinoma, two were large cell, three were non–small cell, and four were small cell. The mean size of the non–small cell lung cancers detected at CT was 15.0 mm. The mean size of the two small cell lung cancers detected at CT was 41.5 mm. One small cell lung cancer was detected at sputum cytologic examination only; the other was an interval lung cancer.

Potentially curative pulmonary resection was performed in 31 of 40 participants with lung cancer—lobectomy in 26, segmentectomy in one, and wedge excision in four. Cancer stage was IA in 22 participants, IB in three, IIA in four, IIB in one, IIIA in five, IV in one, and limited small cell in four. Cancer staging was based on information from surgery, if performed; otherwise, staging was based on clinical data, including results from imaging, bronchoscopy, and other forms of biopsy. Twenty-one (60%) of the 35 non–small cell cancers detected at CT were stage IA at diagnosis.

Eight patients underwent removal of benign lesions—seven underwent a wedge excision, and one, a lobectomy. Five participants who underwent resection of benign nodules had radiologic evidence of nodule growth. The diagnoses (one patient had two nodules) were inflammatory changes in three, granuloma in two, hamartoma in one, intrapulmonary lymph node in one, scarring in one, and pulmonary embolus or infarct in one. There was no surgical or perioperative mortality in any of the surgeries for cancers or benign nodules. All remaining nodules were managed with observation and were considered radiologically indeterminate. Nodules were considered benign if they were stable or became smaller during 2 years of observation. Nodules not meeting these criteria were considered radiologically indeterminate. Although we made specific recommendations for follow-up of every nodule on the basis of size, we did not otherwise dictate management decisions on the part of the attending local physician and the patient.

After 3 years of scanning, we identified 696 additional CT findings that we

judged to be of clinical importance (Table 2). Seventy-nine percent (1,208 of 1,520) of participants had one or more pulmonary nodules or an additional finding. The findings were considered clinically important if they required further evaluation (eg, an adrenal mass) or had substantive clinical implications (eg, aortic aneurysms). We identified 18 nonpulmonary tumors (Table 2). We did not consider coronary arterial calcification, angiomyolipomas, and renal or hepatic cysts clinically important because they are benign and do not warrant an additional examination or procedure.

DISCUSSION

Our results both raise hope that screening CT could be an effective tool to decrease mortality from lung cancer and raise concern that false-positive results and potential for overdiagnosis at screening CT could result in more harm than good.

Symptomatic lung cancer is generally advanced-stage disease (stage III or stage IV). Low-dose CT screening for lung cancer offers the possibility of earlier detection and reduction of mortality. The 5-year survival rate after resection of stage IA non–small cell lung cancer is 62%–82% (17–25). The outcome in patients who decline treatment for stage I cancers is almost universally fatal (19). This is why so many in the medical community are hopeful that CT screening may offer the answer for lung cancer.

The usefulness of CT screening is clearly unproved, however, and we believe that existing data do not justify its widespread use in the general population beyond scientific studies. Although most (60%) of the non–small lung cancers detected at CT in the present study were stage IA, it is not clear whether there was a true stage shift. The relatively high percentage of stage IA non–small cell lung cancers detected with CT in the present study could reflect any combination of selection, length, overdiagnosis, and lead-time biases. 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.

Our findings are consistent with those of the study by Kaneko et al (11) in which 15 cancers were found during a series of 3,457 CT examinations. Only four of the cancers were evident at chest radiography; 93% of the lung cancers were stage I (11). The same investigators (15) also reported detection of 42 lung cancers with a median diameter of 1.5 cm; 81% were stage IA. These findings were corroborated by those in an article published 3 years later by the Early Lung Cancer Action Project conducted by investigators at Cornell and New York Universities (12).

Clearly, we miss the majority of lung cancers smaller than 2 cm at chest radiography (14,26,27). It appears that CT allows detection of a majority of lung cancers at a size of less than 2 cm. It is possible that with double reading of the scans we could have detected lung cancers at an even smaller mean size. A shortcoming of the current study is that we did not analyze interobserver or intraobserver variability.

Although intuitively it may make sense that earlier detection will result in decreased mortality, this has not been proved. Questions have been raised as to whether there is any correlation at all between earlier detection and decreased mortality. Patz et al (28) reviewed a series of 510 patients and found no relationship between tumors less than 3 cm and survival; patients with 3-cm masses had the same survival as those with 1-cm nodules. In another related study (29), there was no relationship between stage at presentation and size of tumor; investigators found similar stage distributions for 1-cm and 2–3-cm lung cancers. Is the propensity to metastasize predetermined by genetics? Do most lung cancers metastasize at a size smaller than can be routinely detected at CT?

TABLE 2
Additional CT Findings in Patients Who Underwent Screening for Lung Cancer: Three-Year Summary

Finding	No. of Findings
Renal cell cancer	4
Indeterminate renal mass	63
Renal calculi	81
Bronchial carcinoid	2*
Indeterminate tracheal nodule	18
Lobar collapse	2
Diffuse lung disease	9
Bronchiectasis	23
Nontuberculous mycobacterial infection	4
Breast cancer	3
Indeterminate breast nodule	28
Atrial myxoma	1
Renal arterial aneurysm	1
Splenic arterial aneurysm	2
Abdominal aortic aneurysm	114
Splenosis	1
Pericardial effusion	12
Pleural effusion	9
Pulmonary arterial calcification	1
Lymphadenopathy	231
Ovarian carcinoma	1
Indeterminate ovarian mass	1
Lymphoma	2
Spinal metastasis	1
Pancreatic carcinoma	1
Indeterminate hepatic mass	21
Cirrhosis	1
Indeterminate adrenal mass	56
Pheochromocytoma	1
Gastric tumor	2
Total	696

* One atypical.

False-Positive Findings

After 3 years of this study, we identified 2,832 uncalcified pulmonary nodules in 69% of 1,520 participants who underwent screening. Of the 40 lung cancers detected, only 36 were demonstrated at protocol CT; two cancers were detected with sputum cytologic examination only, and two were interval cancers. The number (n = 2,832) of uncalcified pulmonary nodules reported as detected is also an underestimation of the real number because we did not track more than six nodules in any participant. We estimate that the majority of the 2,792 uncalcified pulmonary nodules (2,832 nodules minus 40 cancers) were benign given that most were stable at the 1-year and 2-year incidence CT examinations.

Approximately 1.3% (36 of 2,832) of the pulmonary nodules that were demonstrated are known to have been cancers. Therefore, we estimate that approximately 99% of the remaining nodules represent false-positive findings (1–6,8–15). Assuming that the annual rate of new indeterminate pulmonary nodules seen in this study continues to be 9%–13%, almost all patients will have at least one false-positive CT examination result after several more years of screening.

Overdiagnosis

Overdiagnosis refers to diagnosis of cases of slow-growing, relatively indolent lung cancers (eg, some cases of bronchioloalveolar carcinoma and adenocarcinoma) that a patient dies with and not of. The issue of competing risks (eg, heart disease, stroke, and chronic obstructive pulmonary disease) is an important consideration that must be analyzed in the context of the overall effectiveness of a screening examination.

Is overdiagnosis a concern with CT screening? As we continue to look more closely at the lung with CT, will we find

more tumors? Will all of these tumors be clinically important (ie, lethal)? Autopsy data also raise concerns regarding overdiagnosis. Results of one study (30) have shown that one-sixth of lung cancers at autopsy were not clinically recognized and not related to the patient's death. Are these "extra" cancers ones that patients would be dying of, or are they pseudodisease (31–34)?

Sone et al (13) found a large proportion of lung cancers in individuals who never smoked. These researchers found approximately the same rate of lung cancer at screening (approximately 0.5%) in smokers and in individuals who never smoked (13). This finding does not fit with clinical experience, in which we see that most patients who die of lung cancer have a history of heavy long-term smoking.

The volume-doubling time of the cancers in those who never smoked in one series (35) was more than twice as long as that of the cancers in smokers. In that series, 31% of 61 cancers examined were well-differentiated adenocarcinomas. These cancers had a mean size of 10 mm, and only one of 19 was seen at chest radiography. One hundred percent of them were stage I. Their mean doubling time was 813 days (35). A volume-doubling time of 813 days means that it would take 16 years for a 3-mm lung cancer to double in volume seven times to get to 15 mm in diameter. Are these cancers deadly?

If CT screening truly leads to overdiagnosis of lung cancer, one would expect the following findings (31–33): an increase in stage I disease, an increase in resectability, a longer 5-year survival rate, an increase in the total number of cancers, no change in the number of advanced cancers, and no decrease in lung cancer deaths. This is exactly what was found in the Mayo Lung Project from the 1970s; the data from that study have recently been reviewed and updated by researchers at the National Cancer Institute (6). Overdiagnosis bias was suggested as the most likely explanation for these findings. Is the overrepresentation of adenocarcinoma (60% [24 of 40]) also an indication of overdiagnosis?

Potential Harms from False-Positive Findings and Overdiagnosis

The potential harms of managing both false-positive nodules and overdiagnosed cancers include financial and emotional costs, as well as the morbidity and mortality associated with radiation, biopsy, and surgical procedures.

Unfortunately, it is difficult and costly to distinguish benign from malignant nodules. It may be impossible to distinguish pseudodisease from truly lethal cancers. After 3 years of this study, eight of the participants had undergone surgery for removal of a benign nodule. These surgeries represented approximately 21% (eight of 39) of the surgeries that were performed for pulmonary nodules or masses in the study cohort. The most recent data from multicenter studies in both the United States and Europe show that approximately 50% of pulmonary nodules removed at surgery are benign (36–39). That rate of resection of benign nodules would clearly be unacceptable for a mass-screening endeavor given the number of nodules detected at CT.

A much greater concern, however, is the morbidity and 3.8% mortality seen with wedge resection of a pulmonary nodule in the community hospitals where most of the surgeries would be performed (40). A substantial concern is that the rate of surgery for benign nodules could dramatically increase when CT screening is endorsed or promoted.

Additional Findings

Our protocol included low-dose spiral CT of the chest and upper abdomen through the level of the kidneys. We identified 696 additional findings of importance in the cohort of 1,520 participants. Seventy-nine percent (1,208 of 1,520) of the participants in our study had one or more positive findings in the chest and/or abdomen after 3 years of this study. All of these findings required further diagnostic testing and/or intervention. Most represent false-positive results.

Informed Consent

There are serious ethical questions about advertising directly to citizens for entrepreneurial screening ventures. A primary concern is that of informed consent (41). If the claim is that lung cancer can be found early, the inference may well be that the message is "we can save your life." The citizen reading an advertisement could reasonably assume that the scientific studies have been performed and that the recommendation in the advertisement is from evidence-based medicine. This is particularly true if physicians are involved in the promotion. The practice of self referral by someone with a financial conflict of interest is a serious matter about which our profession must be concerned (42).

Conclusions

Our findings answer some questions and raise many others. Screening with low-dose spiral CT in patients at high risk for lung cancer allows detection of many early-stage lung cancers. It is not clear if this is a true stage shift or overdiagnosis. Will there be a decrease in the number of advanced-stage cancers detected with CT screening? CT screening enables detection of a large number of benign but uncalcified pulmonary nodules—false-positive results—that are expensive to diagnose. Subsequent diagnostic procedures and the possibility that a patient may have cancer (but might not know for up to 2 years) may negatively affect quality of life. Clearly, CT is much more sensitive than is chest radiography for detection of small lung cancers (9–16). Also established is that CT depicts more early-stage lung cancers than does chest radiography (9–16).

Unproved is whether CT meets the criteria for an effective screening test (34). False-positive findings raise serious issues regarding quality of life and radiation exposure. Surgery for false-positive findings could lead to more morbidity and mortality among subjects who underwent screening than could be saved with any reduction in disease-specific mortality.

Additional findings raise hopes for decreased mortality from many conditions, including abdominal aortic aneurysms and renal cell carcinoma, but overdiagnosis and surgical mortality issues mute the enthusiasm here (43,44). Further study is needed.

A randomized control trial that shows disease-specific mortality benefit may be the best way to settle the controversy. The National Lung Screening Trial, funded by the National Cancer Institute, is a randomized controlled trial that is now underway.

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