Lung Cancer Screening
A Different Cancer Paradigm

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Thoracic computed tomography (CT) is a sensitive method for detecting early lung cancer but has a high false-positive rate and is not sensitive for detecting central preinvasive and microinvasive cancer. Our hypothesis was that automated quantitative image cytometry (AQC) of sputum cells as the first screening method may improve detection rate by identifying individuals at highest risk for lung cancer. A total of 561 volunteer current or former smokers 50 years of age or older, with a smoking history of more than or equal to 30 pack-years, were studied. Among these, 423 were found to have sputum atypia defined as five cells or more with abnormal DNA content using AQC. Noncalcified pulmonary nodules were found in 46% (259/561). Of the 14 detected cancers, 13 were detected in subjects with sputum atypia—nine by CT and four carcinoma in situ/microinvasive cancers by autofluorescence bronchoscopy. One cancer was detected by CT alone. AQC of sputum cells improved the detection rate of lung cancer from 1.8 to 3.1%. CT scan alone would have missed 29% of the cancers. This screening paradigm shift has the additional potential of reducing the number of initial CT scans by at least 25% with further savings in follow-up investigations and treatment.

**Keywords:** lung neoplasms; tomography, X-ray computed; bronchoscopy; diagnostic imaging; cytology

Lung cancer remains the largest cause of cancer death despite 50 years of antismoking efforts and advances in treatment (1). Overall, 5-year survival remains disappointing at 15% (1). The majority of lung cancers are inoperable at presentation, thereby limiting available treatment and potential cure (2). Patients with earlier stage disease have better survival rates but constitute a small proportion of presenting cases (2–4). Lung cancer will continue to be an enormous burden as over 20% of the population continue to smoke (5, 6). In addition, former smokers remain at risk, and nearly half of newly diagnosed lung cancers occur in this group (7).

The concept that earlier detection of lung cancer may improve the outcome of this disease has been a subject of controversy over the last 30 years. Results of previous screening studies using chest X-ray and sputum cytology contributed to the negative opinion regarding the benefit of lung cancer screening (8–13). However, chest X-ray has been shown to fail to detect up to 77% of computed tomography (CT)–detected cancers (14). The earlier screening studies were also underpowered to show a small benefit of screening using chest X-ray.

Rapid technological advances in multidetector spiral CT that scan the entire thorax at high resolution within 15 to 20 seconds have reigned interest in lung cancer screening. Several studies in the last decade have shown that CT detects lung cancer at an earlier stage and smaller size compared with chest X-ray (14–23). Unfortunately, improved sensitivity is associated with a higher false-positive rate. The frequency of noncalcified pulmonary nodules varies from 5 to 50%, with higher rates noted with thinner slices (14–23). Over 90% of these nodules are nonmalignant. In addition, CT scan is not sensitive for detection of superficial, preinvasive/microinvasive cancers in the central airways. There is increasing interest in the use of sputum biomarkers such as immunohistochemical, methylation, and molecular markers as well as automated quantitative cytometry (AQC) to detect gross genomic alterations present in early lung cancer (24–31). We have previously reported that AQC of sputum cells can identify individuals harboring lung cancer both in the central airways as well as in the peripheral airways (32). We hypothesized that if we use a sputum biomarker such as AQC of sputum cells as the first screening method, we could identify individuals at highest risk to improve the lung cancer detection rate by spiral CT and autofluorescence bronchoscopy. Some of the preliminary results of this study have been previously reported in abstract form (33, 34).

**METHODS**

**Study Subjects**

As a subcontract of an National Cancer Institute–sponsored chemoprevention trial, thoracic CT was added to the protocol between April 1, 2000 and April 1, 2002. Volunteer current and former smokers, between 50 and 74 years of age with a smoking history of more than or equal to 30 pack-years, were recruited from the community (Figure 1). After an interview and questionnaire, a sputum sample was obtained using inhalation of nebulized 3% hypertonic saline and high-frequency chest wall oscillations for 12 minutes with a ThAIRapy Vest (Advanced Respiratory Inc., St. Paul, MN) (35). Subjects were instructed to cough during induction and at least 2 hours afterwards to produce sputum. Samples were fixed in 50% ethanol, then cytospun onto a glass slide and stained with Feulgen-thionin. An investigational automated high-resolution image cytometer (Cyto-Savant Perceptronix Medical Inc., Vancouver, BC, Canada) was used to measure the DNA content of at least 3,000 epithelial cells per sample (36, 37). Diploid cells have a DNA index of 1.0. Atypia was defined as the presence of five cells or more that had a DNA index higher than 1.2 (32). A thoracic CT scan was booked at the time of the interview and sputum collection. A small subset of subjects with normal sputum, screened before the National Cancer Institute funding, who were eligible for the CT study were retrospectively invited to take part. All subjects were offered an autofluorescence bronchoscopy using the LIFE-Lung device (Xillix Technologies Corp., Richmond, BC, Canada) (38, 39). Areas of abnormal fluorescence were biopsied, fixed in 10% buffered formalin, stained with hematoxylin and eosin and graded according to World Health Organization criteria (40).

Approval was obtained from the Clinical Research Ethics Board of the University of British Columbia and the scientific review committee

(Rceived in original form January 31, 2003; accepted in final form July 23, 2003)

Supported by the U.S. Public Health Service contract N01-CN-85188 from the National Cancer Institute.

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This article has an online supplement, which is accessible from this issue’s table of contents online at www.atsjournals.org

Originally Published in Press as DOI: 10.1164/rccm.200301-144OC on July 25, 2003
Internet address: www.atsjournals.org
of the British Columbia Cancer Agency. Written informed consent was obtained from all participants.

Spirometry
FEV1 and FVC were measured using a flow-sensitive spirometer (Presto Flash Portable Spirometer Version 1.2; Spacelab Burdick Inc, Deerfield, WI) (41). FEV1 was expressed as a percent of the predicted value based on age, height, and sex of subjects by using the predicted equation of Crapo and coworkers (42).

Thoracic CT Scan
Baseline scans between June 1, 2000 and August 30, 2001 were performed on a single slice GE CTi scanner (General Electric Medical Systems, Milwaukee, WI) using 7-mm collimation, 120 kVp, 40 mA, 1-second scan time, and pitch of 1.5. After September 1, 2001 scans were performed on either a four track (GE QXi Lightspeed Plus) or eight track (GE QXi Lightspeed Ultra) CT scanner. Images were acquired in four-slice mode using 1.25-mm detector aperture, 120 kVp, 80 mA, 0.5-second rotation time and pitch of 1.5. An abnormal CT was defined as the presence of a noncalcified pulmonary nodule or an area of nonsolid density. A nodule was considered benign if it showed benign calcification pattern (central, diffuse, laminated, popcorn). Follow-up was arranged in subjects with an abnormal result. Lesions of 4 mm or less were reexamined at 6, 12, and 24 months. Lesions between 4 and 9 mm were reexamined at 3, 6, 12, and 24 months. Lesions of 10 mm or more were assessed on an individual basis for further investigation.

Statistical Analysis
Statistical analysis was performed using SPSS version 10.1 (SPSS Inc, Chicago, IL). The initial analysis of subjects was performed according to the sputum result. The baseline characteristics of subjects, general CT characteristics, and bronchoscopy results were evaluated by the χ2 and t-tests. Analysis of nodule size and nodules per subject was evaluated using the Mann–Whitney test. The analysis comparing results for the two different CT scan techniques was performed by the same methods.

RESULTS
A total of 561 subjects were enrolled in the study, 423 with sputum atypia and 138 with normal sputum by image cytometry (Figure 1, Table 1). All of the subjects with sputum atypia were enrolled prospectively. Among subjects with normal sputum 121/138 (88%) were prospectively enrolled. An additional 17 subjects with normal sputum who were screened before the National Cancer Institute funding and who were eligible for the CT study were retrospectively invited to take part.

Autofluorescence bronchoscopy was performed in 378 subjects (67%), with 309 subjects in the sputum atypia group (73%) and 69 subjects in the normal sputum group (50%) (Table 1).

The mean FEV1% predicted was 86 ± 20% and the range was 15 to 134%. The majority of subjects (82%) had an FEV1 more than or equal to 70% predicted, 13% of subjects had an FEV1 between 50 and 69% predicted, and only 5% of subjects had an FEV1 less than 50% predicted. Smoking status included 61% current smokers and 39% former smokers.

All subjects with an abnormal baseline CT scan are being followed with serial CT scans as part of our protocol. At present, the median follow-up duration is 14 months (range 3–33 months). Subjects with a normal baseline CT were not being actively followed unless they were part of the chemoprevention study. The outcome of the remaining subjects was tracked through the Cancer Registry. In British Columbia, pathology laboratories are required by law to report all newly diagnosed cancers to the Registry. Up to February 28, 2003, there were no other cases of lung cancer in this cohort besides the ones included in this report.

CT Findings
An abnormal result was found in 46% (259/561) of the subjects. In total, there were 572 noncalcified solid nodules and 28 nonsolid densities detected. The mean number of nodules detected was 2.3 per subject (range between 1 and 18). The mean size of the solid nodules was 4 mm and that of the nonsolid density was 8.8 mm. The majority of nodules (73%) were less than or equal to 4 mm diameter (Table 2). When the CT findings were analyzed according to the sputum result (sputum atypia vs. no atypia), there was no significant difference in the mean number of nodules per subject, or the presence of emphysema, previous granulomatous disease, or coronary artery calcification. However, when the size of the nodule was evaluated, the sputum atypia group was found to have statistically larger nodules than the normal sputum group (mean nodule size 4.2 vs. 3.6 mm, respectively; p = 0.003).

Lung Cancers
A total of 14 primary lung cancers were detected, 10 with thoracic CT scan and 4 with autofluorescence bronchoscopy (CT occult).

### Table 1. Baseline Subject Characteristics

<table>
<thead>
<tr>
<th>Sputum</th>
<th>Atypia</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of subjects</td>
<td>423</td>
<td>138</td>
</tr>
<tr>
<td>Bronchoscopy performed</td>
<td>309</td>
<td>69</td>
</tr>
<tr>
<td>Abnormal CT</td>
<td>191</td>
<td>70</td>
</tr>
<tr>
<td>Men</td>
<td>227</td>
<td>70</td>
</tr>
<tr>
<td>Women</td>
<td>196</td>
<td>68</td>
</tr>
<tr>
<td>Mean age, yr</td>
<td>60 ± 6</td>
<td>61 ± 7</td>
</tr>
<tr>
<td>Mean pack/yr</td>
<td>49 ± 17</td>
<td>51 ± 23</td>
</tr>
</tbody>
</table>

*Definition of abbreviation: CT = computed tomography.*

*Results expressed as mean ± SD.*
There were seven men and seven women. The mean age of the patients with cancer was 63 years (Table 3). Thirteen cancers were found in subjects with sputum atypia, and one subject had normal sputum at baseline. Therefore, in subjects with sputum atypia by image analysis, the prevalence of lung cancer was 3.1% (13/423) with both CT and autofluorescence bronchoscopy. Overall, 79% of cancers detected were Stage 0/I, and 93% were Stage 0-II. Half the number of the subjects with lung cancer had an FEV1 less than 80% predicted compared with only 31% in subjects without lung cancer (mean FEV1% predicted 77 ± 13% vs. 86 ± 20%, respectively, p = 0.04).

The 10 CT-detected tumors included six adenocarcinoma, two squamous cell carcinoma, one poorly differentiated nonsmall cell carcinoma, and one mixed small/large cell carcinoma. The mean size of these malignancies on the screening CT scan was 16.7 mm. Surgical resection was performed in all of the CT-detected tumors. One subject with Stage IIIA adenocarcinoma received neoadjuvant chemoradiotherapy followed by surgical resection, and one subject with a mixed large/small cell carcinoma received postoperative adjuvant chemoradiotherapy. The lung cancer in the subject with normal sputum was a 2 mm lesion at the baseline CT scan that was not noted on the initial scan. Another small lesion was present at another site that prompted CT follow-up. Subsequent CT scan follow-up at 12 months retrospectively revealed that this lesion had increased in size to 15 mm, from 2 mm at baseline and 5 mm at 6 months. The repeat sputum cytometry at 12 months was abnormal.

Four cancers were found on autofluorescence bronchoscopy. They had no CT scan abnormality detected at the malignant site even on retrospective review by the study radiologist. These CT occult cancers included three squamous carcinoma in situ (TisN0M0) and one Stage IA squamous cell carcinoma (T1N0M0). This CT occult Stage IA tumor was initially diagnosed as carcinoma in situ on bronchial biopsies and treated with endobronchial electrocautery therapy. Follow-up bronchoscopy revealed that distal brushings remained positive, and the subject was referred for a lobectomy. Final pathology revealed disease distal to the treated area with one small area of microinvasion. In the other three CT occult tumors, two have received endobronchial electrocautery and remain disease-free at 27 and 12 months, respectively. The fourth case was treated by a standard lobectomy, as the tumor was located in bronchus B6b of the right lower lobe with extension into sub-sub-segmental bronchi making it difficult to treat with endobronchial techniques.

In addition to the 12 surgeries for lung cancer resection, three subjects underwent surgery for enlarging noncalcified pulmonary nodules that turned out to be nonmalignant. All of these nodules were detected at the baseline thoracic CT scans. One subject had a contrast-enhanced thoracic CT scan that showed enhancement of the nodule. The second subject had a transhiatal needle aspiration biopsy that was negative. He declined further follow-up and chose immediate surgery. The third subject chose immediate surgery rather than further investigation or observation. Two subjects had video-assisted thoracoscopic surgery with wedge resection, and one subject required a lobectomy. The final pathology was lymph node (2) and necrotizing granuloma (1). Thus, of the 15 subjects who had video-assisted thoracoscopic resection or standard lobectomies, three resections (20%) were for a benign condition.

Three subjects had transthoracic needle aspiration biopsy before surgery, two in subjects who were subsequently found to have lung cancer and the third was in a subject found to have a benign lesion at surgery. Two of the three subjects developed a small pneumothorax after the biopsy that did not require intervention.

**Coincidental CT Findings**

Other findings on thoracic CT scan included emphysema (27%), evidence of previous granulomatous disease (18%), and coronary artery calcification (46%). One subject was found to have a renal cell carcinoma. Three subjects had anterior mediastinal masses. In one subject, the mass was found to be long-standing and unchanged from previous CT scans. Two subjects underwent further investigation and resection. Final diagnoses included one bronchogenic cyst and one combined bronchogenic cyst and thymic hyperplasia. Two subjects were noted to have significant mediastinal lymphadenopathy at baseline that showed progressive enlargement on follow-up. Both underwent mediastinoscopy, and final diagnosis was sarcoidosis in one and benign reactive lymphadenopathy in the other subject.

**Spiral CT versus Multitrack CT Scan**

A total of 332 baseline thoracic CT scans were performed with the single slice GE CTi scanner using 7 mm collimation, and 229 were performed with the multitrack CT using 1.25 mm collimation. Baseline CT scans were reported as abnormal more frequently with the multitrack CT versus spiral CT (60 vs. 36%, respectively; p < 0.001). The mean nodule size was significantly smaller with the multitrack compared with single-slice CT scans (3.8 vs. 4.3 mm, respectively; p = 0.014). Increased detection of emphysema, coronary artery calcification, and previous granulomatous disease was also noted (41 vs. 17%, 59 vs. 38%, 33 vs. 7%, respectively, p < 0.001).

**Autofluorescence Bronchoscopy**

Among the 378 subjects who had an autofluorescence bronchoscopy, the proportion of subjects with dysplasia of any grade or

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**TABLE 2. SIZE DISTRIBUTION OF NONCALCIFIED PULMONARY NODULES**

<table>
<thead>
<tr>
<th>Size of nodule, mm</th>
<th>Sputum Atypia</th>
<th>Normal</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 4</td>
<td>307 (71%)</td>
<td>109 (77.3%)</td>
<td>416 (73%)</td>
</tr>
<tr>
<td>4—9</td>
<td>100 (23%)</td>
<td>26 (18.4%)</td>
<td>126 (22%)</td>
</tr>
<tr>
<td>≥ 10</td>
<td>24 (6%)</td>
<td>6 (4.3%)</td>
<td>30 (5%)</td>
</tr>
<tr>
<td>Total no. of nodules</td>
<td>431</td>
<td>141</td>
<td>572</td>
</tr>
</tbody>
</table>

**TABLE 3. SCREENING-DETECTED LUNG CANCERS**

<table>
<thead>
<tr>
<th>Subject</th>
<th>Cell Type</th>
<th>Stage</th>
<th>Detection</th>
<th>CT Size (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Adenocarcinoma</td>
<td>IA</td>
<td>CT</td>
<td>25</td>
</tr>
<tr>
<td>2</td>
<td>Mixed small/large cell carcinoma</td>
<td>IIIB</td>
<td>CT</td>
<td>20</td>
</tr>
<tr>
<td>3</td>
<td>Adenocarcinoma</td>
<td>IB</td>
<td>CT</td>
<td>18</td>
</tr>
<tr>
<td>4</td>
<td>Squamous cell carcinoma</td>
<td>0</td>
<td>Bronchoscopy</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>Squamous cell carcinoma</td>
<td>0</td>
<td>Bronchoscopy</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>Poorly differentiated NSCLC</td>
<td>IA</td>
<td>CT</td>
<td>10</td>
</tr>
<tr>
<td>7</td>
<td>Squamous cell carcinoma</td>
<td>IB</td>
<td>CT</td>
<td>20</td>
</tr>
<tr>
<td>8</td>
<td>Adenocarcinoma</td>
<td>IA</td>
<td>CT</td>
<td>12</td>
</tr>
<tr>
<td>9</td>
<td>Adenocarcinoma</td>
<td>IA</td>
<td>CT</td>
<td>9</td>
</tr>
<tr>
<td>10</td>
<td>Adenocarcinoma</td>
<td>IIIA</td>
<td>CT</td>
<td>23</td>
</tr>
<tr>
<td>11</td>
<td>Adenocarcinoma</td>
<td>IIA</td>
<td>CT</td>
<td>15</td>
</tr>
<tr>
<td>12</td>
<td>Squamous cell carcinoma</td>
<td>0</td>
<td>Bronchoscopy</td>
<td>0</td>
</tr>
<tr>
<td>13</td>
<td>Squamous cell carcinoma</td>
<td>IA</td>
<td>Bronchoscopy</td>
<td>0</td>
</tr>
<tr>
<td>14</td>
<td>Squamous cell carcinoma</td>
<td>IA</td>
<td>CT</td>
<td>15</td>
</tr>
</tbody>
</table>

*Definition of abbreviations: CT = computed tomography; NSCLC = nonsmall cell lung cancer.*
carcinoma in situ (CIS) was higher among those with sputum atypia versus those without atypia (48 vs. 32%, p = 0.05) (Table 4). All of the subjects with severe dysplasia or CIS were found in the sputum atypia group.

**DISCUSSION**

Previous noncomparative screening studies using thoracic CT scan have shown that CT is more sensitive than standard chest X-ray for detecting lung cancers at a smaller size and an earlier stage (14, 15, 17). Between 60 and 92% of CT scan-detected nonsmall cell lung cancers are Stage I and the mean size of CT-detected cancers is between 13 and 20 mm (14–23). Our study is comparable with these published results; 70% of CT-detected lung cancers were Stage I, and the mean size was 16.7 mm.

The unique findings in the current study are (1) 93% of lung cancers were found in those who had sputum atypia by AQC, (2) 29% of the lung cancers were CT occult, and (3) the histologic cell type distribution was more reflective of that seen in the general population using a combination of CT and autofluorescence bronchoscopy. With the exception of the study by Diederich and coworkers (22), the majority of cancers detected in other studies were adenocarcinoma or bronchoalveolar carcinoma (67–95%) (14–23). In our study, 43% of the cancers were adenocarcinoma and 43% were squamous cell carcinoma. Although the incidence of adenocarcinoma is rising worldwide, squamous cell carcinoma still accounts for approximately 37% of the lung cancers in men and 20% of the lung cancers in women in the United States and Canada (43). In Europe, a even higher proportion of lung cancers are squamous cell carcinoma—approximately 47 and 27% of the lung cancers in men and women, respectively (43). Adenocarcinoma and large cell carcinoma are usually located in the peripheral airways. They are readily detected by CT. On the other hand, the majority of the squamous cell carcinoma and small cell carcinoma are found in the central airways. In situ or microinvasive cancers in the central airways are not usually seen on CT. They are, however, visible by sensitive endoscopic methods such as autofluorescence bronchoscopy. Therefore, when we combined CT with autofluorescence bronchoscopy, the overall detection rate was improved and the histologic cell type distribution became similar to the general population.

Published CT screening studies have shown that suspicious pulmonary abnormalities are found in 5 to 51% of subjects screened (14–23). In our study, we observed a significantly greater number of subjects identified with an abnormal CT scan with the use of the multitrack scanner using 1.25 mm collimation compared with a single-slice spiral CT at 7 mm collimation (60% vs. 38%). The high frequency of noncalcified lung nodules (51%) observed in the Mayo Study (20, 21) compared with the 5 to 27% in the Early Lung Cancer Action Project, Anti-Lung Cancer Association Project, Sone, and Nawa studies (15, 16, 18, 19, 23) was previously believed to be related to the prevalence of histoplasmosis in the midwestern United States. The current study suggests that a major cause of the observed differences in nodule frequency could well be due to CT slice thickness. Thus, although technical advances allow better definition of solid pulmonary nodules and volumetric rendering (44), they have also led to higher false-positive rates and created important management issues. Currently, there is no international consensus as to the optimal scanning technique.

In a screening setting, even in a high-risk population, as defined by age, smoking history, and occupational exposure, the prevalence of lung cancer is low—approximately 1% on average. The positive predictive value of CT is therefore usually 12% or less (45). A screening test with a low positive predictive value has implications for unnecessary downstream investigations and treatment with associated morbidity or even mortality. In addition, greater costs will be incurred without corresponding benefits. In our study and those of others, 18 to 29% of all surgical resections, whether video-assisted thoracoscopic surgery or thoracotomy, were for nonmalignant disease (18–23). In other words, by participating in a CT screening study, there is a 0.1 to 0.5% risk of having an unnecessary invasive surgical procedure. Although volumetric rendering (44) holds promise in reducing the number of follow-up CT scans, our study and others showed that “growing” nodules are not always malignant. More aggressive CT-guided transthoracic needle biopsies could reduce the number of surgical resections for benign disease (15, 16), but one would have to accept a pneumothorax rate of at least 15 to 20% (46). In addition, dedicated CT scanners, highly gifted radiologists who can biopsy subcentimetre nodules, and on-site cytology service are not generally available. These limitations need to be taken into account if CT were used as the first screening procedure.

One potential solution is to improve the positive predictive value of CT by using another test to identify those at highest risk for lung cancer first and perform CT as a second step. This different screening paradigm was investigated in our current study. We showed that if CT alone were performed in all 561 at-risk subjects, the detection rate would be only 1.8% (10/561)—a figure that is similar to the 1.9% found in the Mayo study (20, 21). On the other hand, if AQC of sputum cells were used as the first screening tool and CT were restricted to those with sputum atypia, the proportion of initial CT scans alone could be reduced by approximately 25%. The lung cancer detection rate by CT alone in those with sputum atypia would be 2.1% (9/423). The addition of autofluorescence bronchoscopy would increase the overall detection rate further to 3.1% (13/423). The ability to detect CT occult carcinoma in situ or microinvasive cancers is important because these tumors are highly curable by simple endobronchial therapies (47–52). However, using sputum analysis alone as the first step in this pilot study would have missed the one subject with normal sputum at baseline that was eventually diagnosed on follow-up CT. In this subject, the lesion at baseline was very small and only seen in retrospect. As it enlarged, the sputum became abnormal. If CT follow-up had not been arranged for the observation of another lesion, this cancer would have been missed.

Our study also showed that a significant proportion of the subjects harbors preneoplastic lesions. In the current study, 5% of the subjects with sputum atypia had one or more areas of moderate dysplasia, another 0.7% had severe dysplasia, and 1.3% had CIS. It is important to detect these preneoplastic lesions because previous studies using serial autofluorescence bronchoscopy and biopsies showed that over two thirds of CIS and 11% of lesions with severe dysplasia progressed to invasive cancer within 2 years (53, 54). On autofluorescence bronchoscopy, detection of high-grade dysplasia would also allow investigation

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**TABLE 4. BRONCHOSCOPY RESULTS: HIGHEST PATHOLOGY GRADE PER SUBJECT**

<table>
<thead>
<tr>
<th>Sputum</th>
<th>Atypia</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects</td>
<td>309</td>
<td>69</td>
</tr>
<tr>
<td>Mild dysplasia, %</td>
<td>41</td>
<td>30</td>
</tr>
<tr>
<td>Moderate dysplasia, %</td>
<td>5</td>
<td>1.5</td>
</tr>
<tr>
<td>Severe dysplasia, %</td>
<td>0.7</td>
<td>0</td>
</tr>
<tr>
<td>Carcinoma in situ, %</td>
<td>1.3</td>
<td>0</td>
</tr>
</tbody>
</table>
of potential chemopreventive agents to prevent lung cancer (55). The role of autofluorescence bronchoscopy in the overall screening strategy needs to be investigated further.

Overdiagnosis is an important issue to consider as the early detection of a large number of clinically indolent cancers will not result in an improvement in mortality and will reduce the cost effectiveness of a screening program. The relative importance of overdiagnosis in a CT screening program for lung cancer has been a controversial issue and has recently been disputed by Henschke and colleagues (56, 57). They report that the majority of screening-detected cancers have doubling times of less than 300 days and that 90% of stage IA lung cancers are fatal. In our study, 50% of the adenocarcinoma cases detected by CT were more advanced than Stage IA, and one of the Stage IA cases was noted to have growth of the lesion over 6 months of CT follow-up. This certainly appears indicative of more aggressive behavior. Whether spiral CT can reduce lung cancer mortality is being addressed by the ongoing National Lung Screening Trial by the National Cancer Institute.

A recent review of the pathology of surgically resected lung cancers in the Mayo Lung Project (58) revealed that almost all of the CIS cases were from the screened group. The authors suggest that CIS may lead to overdiagnosis and contribute to the excess number of cancer cases in the screened group versus the control group as not all CIS lesions progress to invasive cancer. However, the large numbers of serial sections of the bronchi that were originally examined by the review pathologist (59) were not available for the review by Colby and coworkers (58). It is possible that foci of early invasion or microinvasion may not have been represented on the slides that were available for their later review. In the Mayo Lung Project, adenocarcinoma actually comprised a greater proportion of the “excess” cases of lung cancer in the screened group compared with the control group. It is therefore equally possible for adenocarcinoma to contribute to the excess lung cancer cases if overdiagnosis were the cause. It should also not be surprising that more cases of CIS were found in the screened group because 4-monthly sputum cytology examinations were performed compared with usual care (i.e., chest X-ray as indicated) received by subjects in the control group. CIS lesions do not usually produce symptoms, and they are not visible on chest X-ray. Because the CIS lesions observed by Colby and coworkers (58) were already resected, it would not be possible to determine their natural history. With the advent of autofluorescence bronchoscopy, it is now possible to study the natural history of bronchial dysplasia and CIS. Two recently published series report that more than two thirds of CIS lesions progress (53, 54). This is probably an underestimate as some smaller lesions would be removed by the initial diagnostic biopsy. However, the true percentage is difficult to assess, and the possibility remains that a small number of lesions may not have been represented on the slides that were available for their later review. In the Mayo Lung Project, adenocarcinoma actually comprised a greater proportion of the “excess” cases of lung cancer in the screened group compared with the control group. It is therefore equally possible for adenocarcinoma to contribute to the excess lung cancer cases if overdiagnosis were the cause.

Approximately half the number of subjects diagnosed with lung cancer in this study had an FEV1 less than 80% predicted, and the mean FEV1 was lower than that of the subjects without lung cancer. The association between airflow limitation and lung cancer has long been understood by the medical community (60). Certainly, these subjects constitute a high-risk group, but it is important to note that half the number of subjects with lung cancer in this study had normal lung function. If screening were only performed in subjects with airflow limitation, our study suggested that half of the lung cancer cases would be missed, thereby reducing the impact of an early detection program in a population setting.

Conventional sputum cytology, the only noninvasive method available to detect early lung cancer, has previously been shown to be unhelpful in screening (8–11). Although it has high specificity, the sensitivity was low (<15%) for detection of lung cancer especially for small peripheral lung cancer (17). In the current study, we used an optimized sputum collection method by combined hypertonic saline induction and high-frequency chest wall oscillation followed by postinduction collection to minimize unsatisfactory specimens (35). Automated analysis of a large number of sputum cells was then performed using quantitative image cytometry. The presence of five or more cells with abnormal DNA amount was found to be predictive of a higher lung cancer risk than using age and smoking history criteria alone. The use of DNA content was previously found to be predictive of the progression of patients with oral leukoplasia (61). The use of other nuclear features such as malignancy-associated changes (24, 32, 36) may further define the population who would benefit from secondary screening tests such as autofluorescence bronchoscopy and CT.

A number of cost-effectiveness analyses have recently been published using various hypothetical models to assess CT scan in lung cancer screening (62–64). Results were varied between the studies from $19,500 US/quality-adjusted life-year to $116,300 US/quality-adjusted life-year, but there were differences between the studies in the screening parameters such as age group screened, duration of screening and follow-up, and model design. However, these studies raise the important issue of the negative consequences of false-positive tests and resulting expensive downstream investigations and quality of life costs to the screened subjects.

The paradigm shift in screening strategy suggested by our pilot study may help provide better definition of the at-risk group. This would increase the disease prevalence in the population that would be screened by spiral CT and autofluorescence bronchoscopy, thereby improving the positive predictive value of these tests and improve the cost-effectiveness of a screening program.

This is the first reported study that uses the combined techniques of sputum analysis, autofluorescence bronchoscopy, and spiral CT for lung cancer screening. This paradigm, based on identification of subjects at highest risk using automated image analysis of sputum cells, increases the detection rate of early lung cancer, results in a histologic distribution of detected cancers similar to that seen in the general population, and has the potential of decreasing the number of unnecessary CT scans. Larger prospective studies should be conducted to confirm the results of our pilot study.

Conflict of Interest Statement: A.McW. has no declared conflict of interest; J.M. has no declared conflict of interest; S.McD. has no declared conflict of interest; J.C.B. has no declared conflict of interest; B.P. is a founder, and since January 2002 the CEO, of Perceptronix Medical Inc. where the technology was originally developed and currently is paid $70,000 CDN per year and has about 3% ownership in this privately held company; E.S. has no declared conflict of interest; S.L. received $65,000 CDN from Perceptronix Medical Inc. for participating in clinical trials between April 1, 2000 and March 31, 2002.

Acknowledgment: The authors thank Carol Astrop, Sharon Gee, Sukhinder Kathatra, Myles McKinnon, Suzan Ross, and Brenda Smith for their technical assistance in subject recruitment, sputum induction, quantitative image analysis, bronchoscopy, and data management. They also thank Yulia D’yachkova for assistance in statistical analysis and Advanced Respiratory Inc., St. Paul, MN for supplying the ThAllRap Vest for the sputum induction.

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