Lung cancer is currently the leading cause of death due to malignancy in Japan. Since screening with chest radiography and sputum cytology has not been found to effectively decrease the mortality of lung cancer, trials using thoracic CT have recently been advocated. Encouraging results of screening using low-dose spiral CT have been reported in several articles, but many problems still exist.

Our institution provides occupational health service for all employees. Starting April 1998, we introduced lung cancer screening using low-dose spiral CT at annual health examinations of the employees. Based on the results of this thoracic CT screening over a 29-month period and involving 13,524 procedures, we tried to evaluate the following points: (1) prevalence of lung cancer detected at the baseline screening and its incidence at the repeat screening; (2) detectability of small, early lung cancer; and (3) selection of suitable candidates.
Materials and Methods

Subjects

All participants gave informed consent at presentation for CT screening, and filled out questionnaires about respiratory symptoms and smoking history. From April 1998 to August 2000, a total of 13,524 CT screening procedures were performed, consisting of 7,956 procedures as baseline screening and 5,568 procedures as repeat screening 1 year later. The characteristics of the participants are summarized in Table 1. The majority of participants were men, with ages ranging from 50 to 59 years. The frequency of current or former smokers was 62.1%.

CT Scanning

A spiral CT scanner (Radix TURBO; Hitachi Medical; Tokyo, Japan) was used for this study. The scanning parameters were 120 kilovolt peak, 50 mA, 10-mm collimation, and 2:1 pitch. The whole lung field was scanned and completed at deep inspiration during a single breath-hold of about 15 s. The total time between entering and leaving the room was only about 3 min. Ten-millimeter reconstructed images were stored on optical disks (2.6 gigabytes of volume per disk).

Interpretation

Cine-display images of 1-mm interpolation were displayed on the cathode ray tube (CRT) monitors of the diagnostic console (CT-DC-1A; Hitachi Medical; Tokyo, Japan). Both lung windows (window width, 1,400 Hounsfield units [HU]; window level, −700 HU) and mediastinal windows (window width, 400 HU; window level, 60 HU) were shown on the CRT monitors. The two CRT monitors of diagnostic consoles provided images of almost equal quality for comparison. Two readers separately interpreted all cases. When they could not reach a consensus, the final decision was made at a weekly reading conference.

Follow-up Principle

Thoracic CT screening has been reported to detect many solitary pulmonary nodules (SPNs). In practice, however, the target of screening is a small, peripheral lung cancer, approximately 10 mm in size. When nodules were identified, we recorded the size (length and width) and location (lobe and level). The nodules showing extensive calcification, located in the same lobe that represented inflammatory changes, or more than six nodules, were classified as “benign” or “diffuse changes” and excluded from further evaluation.

When we detected noncalcified SPNs ≥ 8 mm, a detailed CT scan was carried out approximately 1 month later. The scanning parameters of the detailed CT scan were 120 kilovolt peak, 150 mA, 2-mm collimation, and 1:1 pitch. For SPNs ≥ 11 mm in size, we recommended biopsy by bronchoscopy, video-assisted thoracoscopy, thoracotomy, CT-guided fine-needle aspiration, or a combination of these methods according to the current standards for care.

SPNs measuring 8 to 10 mm in size were examined with detailed CT scans 3 months and 6 months later. If they showed no growth during this period, we recommended that the participants undergo annual routine screening. Those with SPNs from 5 to 7 mm in size were recommended to undergo annual routine CT screening. If there were several nodules (from two to six), we applied the same principle to each nodule. This follow-up principle is shown in Figure 1.

Table 1—Characteristics of Participants*

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Male Subjects</th>
<th>Female Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td></td>
<td></td>
</tr>
<tr>
<td>50–54</td>
<td>2,699</td>
<td>1,372</td>
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<tr>
<td>55–59</td>
<td>2,099</td>
<td>1,449</td>
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<tr>
<td>60–64</td>
<td>1,151</td>
<td>1,015</td>
</tr>
<tr>
<td>65–69</td>
<td>370</td>
<td>421</td>
</tr>
<tr>
<td>Total</td>
<td>6,319</td>
<td>4,257</td>
</tr>
<tr>
<td>Current or former smoker, No. (%)</td>
<td>4,869 (77.1)</td>
<td>3,350 (78.7)</td>
</tr>
</tbody>
</table>

*Data are presented as No. of participants unless otherwise indicated.

Figure 1. Follow-up scheme of small noncalcified SPNs.
Results

Prevalence of SPNs at Baseline Screening

During the baseline screening, a total of 2,865 noncalcified SPNs (in 2,099 patients) were detected in 7,956 patients (26.3%). The prevalence of SPNs by age and sex is shown in Figure 2. The prevalence of SPNs seemed to be high among the elderly participants. There was no significant difference by smoking history at any age.

Results of the Baseline Screening

Of the 7,956 participants, 541 patients (6.8%) were encouraged to undergo a detailed CT scan (Table 2). In total, 64 patients underwent additional examinations consisting of bronchoscopy, serum tumor marker, and biopsy. Thoracotomy, including video-assisted thoracic biopsy or surgery, was carried out on 51 patients, and 36 cases of primary lung cancer were histologically confirmed as of November 2000. One female patient had a double-lung cancer of stage I. The prevalence was 0.44% of participants. Current or former smokers represented only 14 of 36 cases.

Of the 36 patients (37 tumors), 28 patients were classified as stage IA (77.7%), 3 patients were classified as stage IB, 3 patients were classified as stage IIA, 1 patient was classified as stage IIB, and 1 patient was classified as stage IIIA. The mean size (greatest diameter) of the tumors on high-resolution CT images was 17 mm. The range of tumor sizes was as follows: 7 to 10 mm (n = 6), 11 to 15 mm (n = 14), 16 to 20 mm (n = 10), and 21 to 26 mm (n = 7).

Histologically, 28 tumors were well-differentiated adenocarcinoma, 7 tumors were moderately-differentiated adenocarcinoma, 1 tumor was large cell carcinoma, and 1 tumor was carcinoid. Thirteen of 28 well-differentiated adenocarcinomas (12 patients) were subclassified as bronchioloalveolar carcinoma. Nine of 12 cases of bronchioloalveolar carcinoma were in nonsmoking patients. There was no squamous cell carcinoma or small cell carcinoma. Additionally, five cases of atypical adenomatous hyperplasia were histologically diagnosed.

Ten cases were confirmed as false-positives. They included focal fibrosis, foreign body granuloma, and subpleural lymphoid tissue that could not be differentiated by detailed CT examination.

Results of the Annual Repeat Screening

Of the 5,568 participants, only 148 patients (2.7%) were recommended for detailed CT scan (Table 2). Seven patients underwent additional examinations.

Table 2—Comparison of Baseline and Repeat Screenings

<table>
<thead>
<tr>
<th>Variables</th>
<th>Baseline Screening</th>
<th>Repeat Screening</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants, No.</td>
<td>7,956</td>
<td>5,568</td>
</tr>
<tr>
<td>Male/female gender, No.</td>
<td>6,319/1,637</td>
<td>4,257/1,311</td>
</tr>
<tr>
<td>Cases with detailed CT, No. (%)</td>
<td>541 (6.8)</td>
<td>148 (2.7)</td>
</tr>
<tr>
<td>Cases with further investigation, No.</td>
<td>64</td>
<td>7</td>
</tr>
<tr>
<td>Cases of lung cancer, No.</td>
<td>36 (37 lesions)</td>
<td>4</td>
</tr>
<tr>
<td>Detection rate, %</td>
<td>0.44</td>
<td>0.07</td>
</tr>
<tr>
<td>Male/female gender, No.</td>
<td>24/12 (15 lesions)</td>
<td>4/0</td>
</tr>
</tbody>
</table>

Figure 2. Prevalence of SPNs at baseline screening by age and sex.
Thoracotomy, including video-assisted thoracic biopsy or surgery, was carried out on six patients, and four cases of primary lung cancer were histologically confirmed as of November 2000. The prevalence was 0.07% of participants. Two lesions were demonstrated as small SPNs approximately 3 mm in size at the baseline screening, and one lesion was diagnosed as benign at detailed CT. They were stage IA, and the mean size of tumors on high-resolution CT images was 16 mm. Histologically, one lesion was a well-differentiated adenocarcinoma, and two lesions were moderately differentiated adenocarcinoma. They were all found in male subjects with smoking histories. Only one case was negative at the baseline screening. This case was a moderately differentiated adenocarcinoma of stage IB, 23 mm in size. This lesion was in a nonsmoker. There were two cases of benign lesions newly developed at the repeat screening. One proved to be an inflammatory pseudotumor, and the other was a fibrotic scar that could not be classified as benign by our detailed CT examination.

**Other Incidental Neoplasms**

No handling policy for incidental mediastinal or thyroid masses had been established. We recommended further examinations for large masses with expanding features or suspicion of invasion to the surrounding tissue. Fourteen cases of thyroid, parathyroid, mediastinal, and chest wall neoplasms were diagnosed. Four cases were clinically malignant or potentially malignant diseases. Two cases were thymoma with invasive features, one parathyroid mass proved to be atypical adenoma, and a chest wall mass proved to be a recurrent plasmacytoma.

**Overall Lung Cancer Detection Rate**

The overall lung cancer detection rates by age and sex are presented in Table 3. The detection rate was rather high among female participants between 55 years and 64 years of age. All were nonsmokers, and were detected during the baseline screening.

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**Table 3—Overall Lung Cancer Detection Rate by Age and Sex**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Age, yr</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>50–54</td>
<td>55–59</td>
<td>60–64</td>
<td>65–69</td>
<td></td>
</tr>
<tr>
<td>Male participants, No.</td>
<td>4,071</td>
<td>3,545</td>
<td>2,166</td>
<td>791</td>
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</tr>
<tr>
<td>Cases of lung cancer, No.</td>
<td>11</td>
<td>8</td>
<td>71</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>Rate, %</td>
<td>0.27</td>
<td>0.23</td>
<td>0.32</td>
<td>0.25</td>
<td></td>
</tr>
<tr>
<td>Female participants, No.</td>
<td>1,063</td>
<td>1,131</td>
<td>601</td>
<td>153</td>
<td></td>
</tr>
<tr>
<td>Cases of lung cancer, No.</td>
<td>3</td>
<td>5</td>
<td>4</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Rate, %</td>
<td>0.28</td>
<td>0.44</td>
<td>0.66</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

1Three cases were detected by repeat screening.
2One case was detected by repeat screening.

**Discussion**

Henschke et al. reported that low-dose CT identified 233 individuals as having from one to six noncalcified nodules, among 1,000 participants. Our data were similar to those of their report, and we found these nodules in 26.3% of participants. Although the prevalence of CT-detected SPNs has not yet been reported in Japan, it seems to be high in view of the age of participants in this study (approximately 70% were 50 to 59 years old). The high prevalence of granulomatous disease, especially old tuberculosis of elderly people in Japan may be related to these results. Many SPNs detected by thoracic CT screening are benign, and it is essential to carefully select the correct cases for detailed CT examination. For this purpose, we determined our follow-up principle, and only 6.8% of the participants at the baseline screening and 2.7% at the repeated screening underwent detailed CT examination.

However, no handling policy for small SPNs detected by CT screening has yet been established. The economic or social burden for following up small SPNs must also be diminished. Annual repeat screening may play a role in the evaluation of small SPNs. The comparison between current and previous examinations is very useful in order to observe the interval change of small shadows. The diagnostic accuracy of small tumors < 10 mm in size must be improved. We constructed a follow-up scheme for these small SPNs as shown in Figure 1, and this proved to be practical and useful. However, the detection of minute growth of small SPNs is difficult. Three-dimensional volumetric analysis can improve the detection of growth in small peripheral lung cancer.

From the baseline screening, we diagnosed 36 cases of lung cancer. This prevalence of lung cancer at the baseline screening (0.44%) was similar to those in previous reports, and 31 cancers (86%) were stage I. These numbers are much higher than for screening using sputum cytology and chest radiography. It should be noted that the lung cancer detection rate in our study was rather high among female participants aged 55 to 64 years. These women had no smoking history. These results differ from our general concept of “high-risk groups,” such as smokers and elderly men. We could not confirm any occupational exposure that may raise the lung cancer risk in our population. Data about passive smoking are not available.
As described previously, the target of thoracic CT screening is peripheral lung cancers. Although squamous cell carcinoma and small cell carcinoma are strongly related to smoking, these central early-stage lung cancers may not be detected by CT screening. We could detect no cases of squamous cell carcinoma or small cell carcinoma by our CT screening. Smoking-cessation programs are probably still important for the prevention of squamous cell carcinoma and small cell carcinoma. When findings related to smoking such as emphysema or bronchiectasis are detected by CT screening, participants should be advised to stop smoking.\(^1\)\(^2\)\(^3\)

It is interesting that 12 cases of lung cancer were diagnosed in female participants without smoking histories at the baseline screening. The lung cancer mortality among female subjects has been increasing in many countries. In 1999, 45% of all new lung cancers in the United States were in female subjects.\(^4\) In Japan, 25.7% of all lung cancer death cases were in female subjects.\(^5\) Smoking history or existence of chronic obstructive lung disease may raise the risk of lung cancer in female subjects. Although we did not confirm their exposure to environmental tobacco smoke, all our female patients were nonsmokers. Thus women and nonsmokers should not be excluded from CT screening. We recommend that both men and women nonsmokers ≥ 50 years of age participate in the baseline CT screening.

The results of the annual repeat screening were quite different from those of the baseline screening. We detected only four cases of lung cancer, and the detection rate was only 0.07%. Three of these cases had small shadows at the baseline screening, and all were male subjects with smoking histories and stage IA lesions. Only one case was completely negative at the baseline screening and was in a nonsmoking male subject with stage IB disease. The efficiency of lung cancer screening markedly decreased at repeat screening. There was no lung cancer detected among female participants. This result was quite different from the baseline screening. It seems necessary to select participants suitable for annual repeat screening. The selection can be based on gender, smoking history, and the results at the baseline screening. Participants with smoking histories and small SPNs detected at the baseline screening may be recommended to receive repeat screening. The frequency of screening can be reduced for female or nonsmoking patients.

The hypothesis is advanced that the biological features of CT-detected lung cancer are different in male and female subjects. In female subjects, the majority of lung cancers are relatively slow-growing tumors (for example, well-differentiated adenocarcinoma) that appear as faint peripheral nodules. These lesions will be suitable for CT screening, and will be detected at the baseline screening. However, lung cancers in male subjects may have various biological features due to smoking and other additional factors.

Most lung cancers that were detected at the repeat screening in retrospect showed small nodules at the baseline screening. The interval growth of small SPNs in these patients at the repeated screening strongly suggested the possibility of lung cancer and led to diagnosis. Although they were, histologically, mostly moderately differentiated adenocarcinomas, they were all stage I lesions. These results at the repeat screening were different from a previous report\(^7\) and suggest that repeat screening is useful for detecting lung cancers at an early stage.

In conclusion, lung cancer screening using low-dose spiral CT is feasible as a part of general health examinations. The sensitivity of the baseline screening was very high, but decreased markedly at the repeat screening 1 year later. This casts a serious doubt about whether early lung cancer detection should be performed by routine yearly CT screening. Our project is now in its the third cycle, and we hope to accumulate more data in order to determine how often CT screening should be performed and how to select suitable candidates.

ACKNOWLEDGMENT: We thank Katsuyuki Endo, MD; Noboru Yanai, MD; Masataka Irokawa, MD; and Shimao Fukai, MD for thorough examination and treatment of screened cases, and also all related staff who took part in this screening program.

REFERENCES


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