Lung cancer is the leading cancer killer in the United States and the world for both men and women. Tobacco smoking is the single most important risk factor for lung cancer. Environmental and occupational exposures to radon, asbestos, and other pollutants also are causes of lung cancers.

Advances in the diagnosis and treatment of lung cancer promise to extend patients’ lives, but the probability that treatment will be successful is inversely associated with tumor stage at diagnosis. Patients with metastatic disease face poor prognoses, and those diagnosed with a single well-localized small tumor can survive for many years.

Lung cancer can be prevented, and death rates associated with this disease can be reduced. Primary prevention efforts to avoid new cases include public health campaigns to discourage non-smokers from starting and encourage smokers to quit, along with home radon education and testing programs. The main form of secondary prevention is lung cancer screening. Secondary prevention efforts are aimed at early detection and intervention to slow the growth and spread of tumors that have already developed.

Low-dose helical computed tomography (LD-CT) has been validated by a large randomized clinical trial as superior to chest radiography in the screening and early detection of lung cancers. Although not every patient benefits from LD-CT lung cancer screening, and some patients undergo unnecessary follow-up procedures as a result of false-positive screening results, the research indicates that using this imaging modality to screen carefully selected high-risk patient populations for pulmonary tumors will prolong and save lives. Furthermore, every lung cancer screening represents an opportunity for educational interventions to encourage patients to pursue smoking cessation.
Screening and smoking cessation should be 2 parts of an integrated public health program to reduce the number of tobacco-associated lung cancer diagnoses and deaths.1

Epidemiology

The most important risk factor for all types of lung disease is tobacco smoking.1,3 Between 43 million and 55 million Americans smoke tobacco. Smoking ultimately contributes to the death of half of those who do not quit before developing a smoking-related disease, including cardiovascular disease or cancer of the lung, oropharynx, nasal cavity, esophagus, stomach, pancreas, kidney, bladder, or cervix, or acute myeloid leukemia.1,4,5

A strong dose-response association links the number of cigarettes smoked with the risk of developing lung cancer—a relationship long denied by tobacco companies but recognized in the medical literature since at least 1931.4 The U.S. Surgeon General’s report officially linking smoking to lung cancer risk was released in 1964.

A link between cannabis smoking and lung cancer risk remains unclear, however, in part because of legal restrictions on marijuana use. Further, research results are confounded by relatively heavy tobacco use among marijuana users.1,7

Once a rare disease—only about 2000 U.S. deaths were attributed to lung cancer in 1927—more than 1.5 million new cases are diagnosed each year around the world, and an estimated 221,130 of those are diagnosed in the United States.1 Lung cancer rates in the United States climbed dramatically throughout much of the 20th century, as smoking became more popular, and peaked in the 1980s before declining in the 1990s.1 Recent declines, particularly among men, presumptively resulted from tobacco-control legislation and education efforts.1 The absolute number of current smokers in the United States is similar to the 1960s, with up to 4.9 million active smokers and 50 million recovering or former smokers, yet the percentage of Americans who smoke has declined in recent decades.1

Today, 1 in 14 Americans will develop lung cancer.5 Like other leading types of cancer, lung cancer is largely a disease of late adulthood, rarely affecting people aged younger than 55 years.1 The median age at initial diagnosis is 71 years.8

Men of all ethnic groups have higher rates of lung cancer than women (see Table 1).1,4 Although the roots of this sex difference in lung cancer rates remain unclear, some believe it is a reflection of heavier smoking habits among men. This disparity has declined over time, with incidence rates of lung cancer decreasing among men as smaller proportions of men became smokers in recent decades.1 Unfortunately, cigarette smoking has declined more modestly among young women.7 Women also experience superior survival times compared with men.1 Disparities between the sexes in lung cancer incidence and mortality rates also might reflect biological differences mediated by estrogen.

Lung cancer incidence and mortality in the United States vary by ethnicity, income level, and geography. People with lower education levels and income are markedly more likely to develop lung cancer than are people with higher levels of education and income, even when smoking history is statistically controlled.1 Researchers have speculated that other inhalation exposures in the home or workplace, dietary factors, or poor access to health care and health information might contribute to the associations between lung cancer, education level, and income.1,9

Black Americans have markedly higher lung cancer incidence and mortality rates than do people of other ethnicities.6 Higher incidence rates among blacks are largely a reflection of higher tobacco smoking rates in this population.1 Racial disparities in survival outcomes after diagnosis, however, appear to be more complex. Outcomes involve levels of access to cancer screening and health care services and possible differences in the quality of care obtained. Black patients’ lung cancers frequently are diagnosed at more advanced stages of cancer than whites, but the 5-year survival rates among blacks is lower than those for whites for every stage.1

Despite having lower income and education levels overall than non-Hispanic whites, Hispanic people have lower rates of lung cancer and a decreased risk of overall mortality when they are diagnosed with the most common non–small cell forms of lung cancer.11 The reasons for this “Hispanic paradox” of better cancer rates and outcomes despite lower socioeconomic status remain unclear but might involve self-selection of healthier workers who migrate across the U.S.-Mexico border.11

Despite the strong association between tobacco use and lung cancer, an increasing number of lung cancers, particularly adenocarcinomas, has been noted in patients...
who have smoked fewer than 100 cigarettes in their entire lifetimes. These so-called never-smokers or non-smokers now represent between 15% and 25% of all lung cancer patients and an estimated 300,000 deaths each year. Lung cancers in never-smokers are believed to be caused by household air pollution, such as radon and secondhand tobacco smoke, and ambient or outdoor air pollution. Black nonsmokers have higher lung cancer incidence and mortality rates than white nonsmokers.

Radon is the second leading cause of lung cancer, representing 10% of lung cancer deaths. A decay product of uranium-238, radon produces polonium; both radon and polonium are \( \alpha \)-particle emitters. In high-radon geological regions, radon can accumulate in indoor air, particularly in houses with basements. This leads to chronic in-home exposure and increasing lung cancer risks.

Environmental or secondhand exposure to tobacco smoke, sometimes called passive smoking, appears to be involved in lung cancer rates among nonsmokers; the nonsmoking spouses of smokers face significantly increased risks of lung cancer compared with nonsmokers who do not live with smokers, for example. Similar research shows that lung function is harmed among workers who breathe tobacco smoke in the workplace—a finding that has led to workplace and public area smoking bans.

Other environmental and occupational exposures also have been implicated as lung cancer risk factors. Asbestos, used since the 1800s as a fire-resistant and insulating construction material, is associated with occupational lung diseases, including lung cancers, particularly a relatively rare form of lung cancer called mesothelioma. Limited evidence suggests that asbestos exposure also might increase the risk of other cancers, including malignancies of the throat, kidney, esophagus, colon, and rectum.

Table 1

<table>
<thead>
<tr>
<th>Race/Ethnicity</th>
<th>Overall Incidence</th>
<th>Incidence in Men</th>
<th>Incidence in Women</th>
<th>Overall Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>64.5</td>
<td>76.4</td>
<td>52.7</td>
<td>54.7</td>
</tr>
<tr>
<td>African American/Black</td>
<td>76.6</td>
<td>99.9</td>
<td>52.6</td>
<td>62.0</td>
</tr>
<tr>
<td>White</td>
<td>65.7</td>
<td>76.4</td>
<td>55.1</td>
<td>55.0</td>
</tr>
<tr>
<td>American Indian/Alaska Native</td>
<td>44.0</td>
<td>51.9</td>
<td>37.4</td>
<td>39.9</td>
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<tr>
<td>Asian/Pacific Islander</td>
<td>39.4</td>
<td>52.2</td>
<td>28.8</td>
<td>26.9</td>
</tr>
<tr>
<td>Hispanic/Latino</td>
<td>33.3</td>
<td>40.5</td>
<td>25.8</td>
<td>23.6</td>
</tr>
</tbody>
</table>

Ambient airborne particulate matter and sulfur dioxide from the combustion of fossil fuels such as diesel also are likely lung carcinogens. Infectious carcinogens such as HIV and human papillomavirus (HPV) also play a role in some lung cancers. HPV has been implicated in oropharyngeal and cervical cancers and is a target of recent preventive vaccination efforts. Tuberculosis infection history also is associated with lung cancer, even after tobacco smoking history is statistically controlled.

Preexisting pulmonary comorbidities that appear to increase the risk of lung cancer include:

- Emphysema or chronic obstructive pulmonary disease (COPD), which are associated with tobacco smoking.
- Pulmonary fibrosis, which is associated with asbestos inhalation and some autoimmune diseases.
- Asthma.
- Chronic bronchitis.

**Genetics and Genomics**

No single gene mutation is associated with every case of lung cancer, but inherited genes, genetic mutations, and genomic alterations are believed to be causally involved in lung cancer. These genetic and genomic alterations can result from environmental insults such as tobacco smoke inhalation or, in some cases, inherited genetic risk factors that render some individuals more vulnerable to carcinogenic exposures. As understanding of lung cancer genetics improves, new prevention strategies and targeted treatments are likely to emerge.
Targeted anticancer therapies such as engineered antibodies specifically suppress the tumor-promoting activity of mutations.

Gene mutations can contribute to cancer risk or tumor growth when they affect genes involved in cell division rates, apoptosis (programmed cell death), and angiogenesis (the development of new vasculature, which is necessary for tumor growth). Common gene mutations in lung tumors include \textit{EGFR}, \textit{ERBB2} (formerly \textit{HER2} or \textit{HER2/neu}), \textit{ERBB3}, \textit{ERBB4}, \textit{TP53}, \textit{CDKN2A}, \textit{K-RAS}, and \textit{PTEN}.\textsuperscript{1} Some gene mutations are seen more frequently in particular types of lung cancer.

In addition to these gene mutations, epigenetic alterations to the genome are increasingly recognized as factors in carcinogenesis.\textsuperscript{1} Epigenetic alterations are called \textit{methylation events}, in which the DNA sequence or structure of genes remains unaltered, but genes are chemically tagged in a manner that can trigger increased or decreased gene expression. When tumor-suppressor genes such as \textit{TP53} and \textit{K-RAS} are mutated or epigenetically altered in a manner that suppresses their normal activity, tumor growth becomes less controlled.\textsuperscript{1}

In addition to specific genetic point mutations and epigenetic methylation events, larger-scale genomic aberrations—gross chromosomal rearrangements—occur in many lung tumors. These rearrangements and disruptions of normal DNA replication during cell division can result in abnormal duplications or losses of entire chromosomal elements.

Gene mutations also are associated with lung cancer among never-smokers, but these mutations are not associated with mutations seen among smokers who develop lung cancer.\textsuperscript{1} \textit{EGFR} gene mutations are more frequent in never-smokers, for example.\textsuperscript{18} Sex differences in gene expression, possibly mediated by hormones such as estrogen, also might contribute to sex differences in lung cancer. For example, female smokers’ lung tissue cells usually express higher levels of cytochrome P450, family 1, subfamily A, polypeptide 1 (\textit{CYP1A1}) gene activity than men’s lung cells; \textit{CYP1A1} encodes an enzyme that helps break down and metabolize carcinogenic polycyclic aromatic hydrocarbons such as those that occur in tobacco smoke.\textsuperscript{1}

Gene mutations and epigenetic alterations that modulate cancer risk usually are acquired through genotoxic insults such as tobacco smoke exposure during a patient’s lifetime. But some families have heritable genetic alterations that increase cancer risk. Smokers and nonsmokers with family histories of lung cancer are up to twice as likely to develop lung cancer as those without such family histories.\textsuperscript{1} Some heritable familial “syndromes” that increase the risks of cancers, albeit only rarely lung cancers, include Bloom syndrome, Down syndrome, and Werner syndrome.\textsuperscript{1}

Relatively common gene variants, or alleles, appear to modulate lung cancer risk: variants of the \textit{CYP1A1} enzyme gene and glutathione-S-transferase (\textit{GSTM}1 and \textit{GSTT}1) alleles alter lung tissue metabolism of tobacco carcinogens, for example, and are associated with increased risk of lung cancer.\textsuperscript{1} Certain relatively common variants of DNA-repair genes such as \textit{XPC} and \textit{ERCC2} also are associated with lung cancer risk.\textsuperscript{1}

Other genes involved in lung cancer regulate acetylcholine nicotinic receptors and telomerase production, which is related to the rate of cellular aging.\textsuperscript{18}

**Prevention**

Clearly, it is easier to prevent cancer than to cure it. An appreciation of risk factors motivates effective cancer prevention. Tobacco control and cessation is central to lung cancer prevention. As inherited genetic predisposition and lung cancer–relevant gene mutations and genomic aberrations become better understood, prevention efforts should become better tailored to individual risks.

Primary prevention refers to avoiding carcinogenesis, and secondary prevention refers to preventing tumor progression or recurrence. Major public health campaigns to control lung cancer and other tobacco-associated diseases represent primary prevention strategies designed to discourage nonsmokers from initiating smoking habits or to encourage smokers to quit smoking before disease occurs. Antitobacco education programs in public schools and tobacco-control legislation such as workplace and public space smoking bans are examples of primary prevention efforts.

Radon detection is another primary prevention tool for lung cancer; many state health departments provide free radon detection kits. Houses with airborne radon levels greater than or equal to 4 pCi/L should undergo foundation and ventilation repairs.\textsuperscript{1} HPV vaccination campaigns are a primary prevention effort against cervical
cancer and might become important in efforts to curb oropharyngeal and possibly lung cancer.\textsuperscript{1,15}

**Lung Cancer Pathology**

*Lung Anatomy*

The respiratory system extends from the nasal passages and oral cavity to the physiologically active alveoli of the lungs, where inhaled oxygen is exchanged with carbon dioxide waste products and then exhaled. The pharynx is a muscular sac that routes air to the trachea and food to the esophagus. Air passes through the larynx and trachea and enters the lungs via the 2 bronchi. These large airways bifurcate repeatedly into smaller-diameter bronchioles, a network of dividing airways known as the tracheobronchial tree (see Figure 1).

The tracheobronchial tree is lined with mucus-covered epithelial cells, and ciliary movement on the surface of this lining pushes mucus and trapped particulates toward the pharynx. Between the 10th and 15th iterations of bronchiolar bifurcation, cartilage no longer supports the airways.\textsuperscript{17} These smallest terminal bronchioles of the conductive airways give way to physiologically active respiratory bronchioles and alveoli, where gas exchange occurs (see Figure 2). The average adult lung contains approximately 300 million alveoli, the total surface area of which is roughly equivalent to that of a tennis court.\textsuperscript{17} The bronchioles, alveoli, and associated capillary vasculature collectively are referred to as the lungs’ parenchymal tissues.\textsuperscript{17}

The surfaces of the lungs are divided by deep fissures into lobes: 3 on the right lung and 2 on the left lung. These lobes are subdivided into functional segments, each supplied by a major branch of the tracheobronchial tree. Thin pleural membranes line the outer surface of each lung, with an outer (parietal) pleura attaching to the thoracic wall and inner (visceral) pleura adhering to the lungs.\textsuperscript{17} Fluid between the pleural layers allows nearly friction-free movement of the lungs during inhalation and exhalation.

**Disease Process**

When cells within lung tissues accumulate certain genetic or genomic alterations, cellular division rates and apoptosis can become disorganized, yielding premalignant or precursor lesions called *carcinoma in situ*. Carcinoma in situ tumors sit atop the epithelial layer.
the primary or secondary bronchi and not the lungs’ peripheral tissues such as the alveoli.\textsuperscript{16} Any epithelial tumor other than small cell lung cancer is referred to as non–small cell lung cancer (NSCLC), the most common histological types of which are squamous cell carcinoma, large cell carcinoma, and adenocarcinoma.\textsuperscript{16} NSCLC tumors initially occur in the epithelium throughout the lungs, from the central bronchi to alveolar tissues. The histologic type of NSCLC depends on where it first occurred; squamous cell carcinomas usually emerge initially near the central bronchus, whereas adenocarcinomas and bronchioalveolar NSCLCs more commonly originate in peripheral lung tissues.\textsuperscript{18} Hispanics are significantly more likely to be diagnosed with bronchioalveolar carcinoma than are patients of other ethnicities.\textsuperscript{11}

All NSCLCs are associated with smoking history, but adenocarcinomas also are found in never-smokers.\textsuperscript{18} Small cell lung cancers are more responsive to chemotherapy and radiation therapy than NSCLCs.\textsuperscript{18}

When the disease is at advanced stages, patients with lung tumors often have symptoms and signs such as chest pain, weight loss, dyspnea, fatigue and malaise, wheezing, coughing, hemoptysis, difficulty swallowing, distention of the head and neck veins, and vocal hoarseness if a tumor compresses the laryngeal nerves.\textsuperscript{18} Microscopic examination of coughed sputum sometimes reveals cancer cells from lung tumors.

Lung tumors can compromise respiratory competency and metastasize to other vital organs. When lung tumors metastasize to the brain, they can cause pronounced, abrupt, and progressive neurological defects, including cognitive and personality changes.\textsuperscript{19} Bone pain accompanied by symptoms of lung cancer can indicate metastasis of lung tumors to bones. Pleural effusion, unresolved pneumonia, and lobar lung collapse frequently are seen in advanced lung cancers.\textsuperscript{19}

More than 50% of lung cancer patients are diagnosed only after cancers have advanced to metastatic disease, which is associated with a 5-year relative survival rate of 5% or less.\textsuperscript{24} Locally advanced, nonmetastatic lung cancer is seen in 22% of patients at the time of diagnosis and is associated with a 25% 5-year survival rate (see Table 2).\textsuperscript{14} Only 15% of lung cancers are diagnosed before tumors are at an advanced stage; more than half of these patients survive 5 years or longer.\textsuperscript{2,8}

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Stage Distribution and Survival for 2002-2008*</th>
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</thead>
<tbody>
<tr>
<td>Stage at Diagnosis</td>
<td>Stage Distribution (%)</td>
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<tr>
<td>Localized (confined to primary site)</td>
<td>15</td>
</tr>
<tr>
<td>Regional (spread to regional lymph nodes)</td>
<td>22</td>
</tr>
<tr>
<td>Distant (metastasized)</td>
<td>56</td>
</tr>
</tbody>
</table>

**Staging**

Determining the stage of lung cancer is crucial for accurate assessment of patient prognosis and development of a treatment or monitoring plan. Preoperative staging can be undertaken with imaging and clinical data, but definitive diagnosis and pathological staging requires biopsy of tumors and involved lymph node tissue.\textsuperscript{19} When a suspicious nodule is identified in a LD-CT lung screening examination, follow-up imaging with positron emission tomography-computed tomography (PET-CT) allows preoperative staging to reduce the rate of unnecessary or futile surgeries.\textsuperscript{19} CT and PET-CT have become routine staging modalities in lung cancer and are used in follow-up after initial LD-CT detection of suspicious nodules (see Figure 3).\textsuperscript{20}

The tumor, node, and metastasis (TNM) cancer staging system widely is used to classify cancer to reflect the degree of local tumor invasion and a cancer’s spread. \textit{T} refers to the size and invasiveness or position of the primary tumor; \textit{N} refers to spread from its tissue of origin to local-regional lymph nodes; and \textit{M} refers to the cancer’s spread to distant organs. This system was based on a model of tumor progression and spread that assumed locally advanced tumors eventually spread to local-regional lymph nodes and then spread to distant organs.\textsuperscript{20} However, so-called “skip metastasis” is increasingly recognized, with cases reported of metastatic tumors in the brain (M1) but not in local-regional lymph nodes (N0).\textsuperscript{20}

The International Association for the Study of Lung Cancer recently proposed changes to the 7th edition of TNM staging for lung cancers (TNM-7) based on analysis of data from an international database.\textsuperscript{20} TNM-7 better accommodates skip metastases than the previous system. However, TNM-7 does not offer guidelines for...
tumor measurement in CT scans because it is based on data obtained between 1990 and 2000 from axial image measurements rather than from contemporary multi-planar reconstructions (see Box 1). 20

**Screening**

Cancer screening is a form of secondary prevention meant to detect tumors before they are large and symptomatic when they can be treated effectively to prolong patients’ lives. Generally, when lung cancers are detected at early stages of development, they can be treated with surgery or surgery plus chemotherapy. 24 When surgery is not possible, tumor control is sometimes achieved with radiation therapy, but this rarely yields a durable cure. 24

There are 3 types of cancer screening: population screening, selective screening, and case-finding screening. The ultimate goal of all 3 types of screening is to reduce disease-specific mortality rates. Population screening is undertaken with large numbers of asymptomatic people at different levels of risk in an effort to identify those individuals who are at high risk of cancer. Population screening for lung cancer is not practiced. Selective screening involves testing those individuals already known to be at significantly higher risk than the general population, such as heavy tobacco smokers. Case-finding screening is a prediagnostic endeavor undertaken when cancer is suspected because of the presence of disease symptoms, such as shortness of breath or bloody sputum. Case-finding screening more frequently is described as diagnostic imaging rather than screening.

Screening tests should be effective and cost-effective, with a high sensitivity (ie, few false-negative results) and specificity (ie, few false-positive results). However, all screening modalities have strengths and weaknesses, and none is 100% sensitive and specific.

The true cost of prevention by CT screening is unclear. Estimated costs involved in preventing one lung cancer death using CT screening have varied from $2500 to $240 000, probably reflecting variations in data sources, populations, and study methodology. 5,21 Nevertheless, cancer types in which patients

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**Box 1**

**TNM-7 Lung Tumor Classification**

- T1a: primary tumor ≤ 2 cm in diameter
- T1b: > 2 and ≤ 3 cm
- T2a: > 3 and ≤ 5 cm
- T2b: > 5 and ≤ 7 cm
- T3: > 7 cm or with central invasion or with additional nodules in the same pulmonary lobe as the primary tumor
- T4: nodules in the same lung as the primary tumor
- M1a: T4 with pleural dissemination or nodule in the contralateral lung from the primary tumor
- M1b: distant metastasis (primary lung tumor and tumors in other organs, such as bone)

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**Figure 3.** Axial computed tomography (CT), positron emission tomography (PET), and PET-CT images obtained in 58-year-old man with non–small cell lung cancer of right middle lung lobe. A. At CT, a pulmonary metastasis (arrow) was detected in the right upper lobe, and the diagnosis was verified at radiologic follow-up. B. PET scan was negative for pulmonary metastases. C. Diagnosis of the pulmonary metastasis depicted on PET-CT images was based on the CT data. Reprinted with permission from the Radiological Society of North America. Antoch G, Stattaus J, Nemat AT, et al. Non-small cell lung cancer: dual-modality PET/CT in preoperative staging. Radiology. 2003;229(2):526-533.
frequently are diagnosed at advanced stages are excellent choices for the development of screening tests that detect the cancers at earlier tumor stages when cure might be possible.

In lung cancer screening, the goal is to identify dense nodules, which often are solitary and likely to be tumors, while minimizing radiation dose to the patient. Unnecessary exposures to ionizing radiation always should be avoided in keeping with the ALARA (as low as reasonably achievable) principle. LD-CT lung cancer screening offers relatively low radiation doses, and individuals who are eligible for such screenings are typically aged older than 50 years, so the long-term cancer risks posed by the LD-CT examination should be relatively minor compared with the risk for younger patient populations. Latency periods for radiation-associated cancers tend to be long and a greater concern for children and young adults than for older adults. However, radiation concerns for LD-CT screening are not negligible. A 2004 analysis estimated that LD-CT radiation doses associated with lung cancer screening would increase lung cancer risk by up to 5.5%. This means the mortality benefits of screening would have to exceed 5.5% “considerably” to outweigh radiation risks. Radiation dose also depends on quality control practices observed for each CT scanner.

Despite a clear need for earlier detection of lung cancers, selective screening using chest radiography and LD-CT has been controversial for many years. Until recently, there was unclear evidence that such screening improves patients’ chances of survival. Further, false-positive results lead to unnecessary interventions, including surgical biopsies, which entail nontrivial risks of morbidity and mortality.

Several early randomized trials of lung cancer screening with chest radiography, with or without sputum cytology, were discouraging, reinforcing widespread doubts about the value or promise of lung cancer screening. However, among other arguments in favor of screening, proponents argued that lung screening affords an opportunity for early detection of other diseases such as cardiovascular disease, coronary and aortic calcification, lymphadenopathy, and COPD. Although some patients might enjoy health benefits from the discovery and treatment of incidental findings, for others, incidental findings result in no health benefit but entail diagnostic procedures or other interventions accompanied by morbidity risks and harm to patients’ quality of life (e.g., increased anxiety).

The National Lung Screening Trial

Following early studies that strongly suggested LD-CT selective screening offers greater sensitivity than chest radiography in detecting small pulmonary nodules and that LD-CT might improve patient survival rates, a large multicenter trial was initiated in 2002. The randomized, controlled National Lung Screening Trial (NLST) was supported with funding from the National Cancer Institute (NCI). NLST was designed to compare the outcomes of patients at high risk for lung cancer who are screened with chest radiography against outcomes among those screened with LD-CT.

Between 2002 and 2004, 53,454 current or former heavy smokers were enrolled in the study and randomly assigned to a group undergoing annual chest radiography screening or to a group undergoing annual LD-CT screening between 2002 and 2007. Smoking history was defined by pack-years, or the number of packs of cigarettes the individual smoked per day multiplied by how many years the person smoked. For example, 1 pack year is equal to smoking 1 pack per day for 1 year, or 2 packs per day for half a year. Patients were screened each year for 3 years, and all lung cancer diagnoses and lung cancer deaths for both study groups were totaled through 2009.

Eligibility criteria for patients enrolling in the study were:
- Aged 55 to 74 years.
- Current smokers with 30 pack-years or more of cigarette use.
- Former smokers with at least 30 pack-years who had quit no longer than 15 years before enrollment.

Exclusion criteria included prior cancer diagnoses, a chest CT scan within the past 18 months, hemoptysis, or unexplained weight loss exceeding 15 lb over the preceding year.

LD-CT scans in the NLST were obtained with patients in a supine position with their arms elevated above their heads, at maximal breath hold, with scan
times of 24 seconds or less. CT parameters for the study were:
- 120 to 140 kVp.  
- 20 to 80 mAs.  
- Pitch of 1.25 to 2.0.  
- Collimation at 2.55 mm or more.  

In 72% of cases, LD-CT screen-positive findings were followed up with diagnostic procedures, including imaging follow-up (57.9%), bronchoscopy (3.8%), needle biopsy (1.8%), and surgery (4%).  

In 2010, the NLST’s independent review board determined that the primary study endpoint had been achieved. A statistically significant 20.3% relative reduction in lung cancer mortality was identified among study participants who underwent LD-CT screening, compared with those who underwent chest radiography screening.  

A 6.7% relative reduction in overall mortality, from all causes, also was noted among patients in the LD-CT group. Positive screen rates were 24.2% for LD-CT and 6.9% for chest radiography. A total of 7.5% of LD-CT group participants were found to have “significant nonlung-related abnormality” such as cardiovascular disease.  

The results “provided compelling evidence of the efficacy of lung cancer screening using low-dose helical computed tomography,” the authors concluded. “LD-CT detected more than twice the number of early-stage lung cancers” with “minimal” LD-CT screening-associated complications. The main concern with LD-CT, the authors reported, was a very high (96.4%) false-positive rate and the resulting potential for overdiagnosis and overtreatment of ultimately benign lesions. The chest radiography screening false-positive rate was 94.5%.  

A subsequent analysis of NLST data concluded that properly implemented annual LD-CT screening of current and former smokers aged 55 to 74 years with at least 30 pack-years of cigarette use would delay or prevent an estimated 12,250 lung cancer deaths each year in the United States.  

Other authors argued that the study underestimated the true benefits of LD-CT selective screening for lung cancer. Had screening continued beyond the 3-year mark, additional cancers would have been detected, and had cancer deaths been tracked beyond 2009, additional control (chest radiography) group patient deaths would have been recorded, argued David Yankelevitz, MD, and James P Smith, MD.  

A subsequent systematic review that included data from the NLST and 2 other randomized trials of patients aged 55 to 74 years with history of 30 pack-years or more noted that of the 3 studies analyzed, only the NLST found a survival benefit associated with LD-CT screening. The review, commissioned by the American Cancer Society (ACS), American Society of Clinical Oncology, American College of Chest Physicians, and National Comprehensive Cancer Network (NCCN), and published in the Journal of the American Medical Association (JAMA), concluded that when data from all 3 studies were considered, LD-CT screening retained a lung cancer–specific survival benefit but not an overall survival benefit.  

The review’s authors emphasized that considerable uncertainty remains about potential harms associated with screening, including effects to patients’ quality of life. The review yielded little evidence that LD-CT screening would benefit populations other than heavy smokers. Across all 3 studies, 20% of participants each year had positive results requiring follow-up, but only 1% were diagnosed with lung cancer. “There was marked heterogeneity in this finding and in the frequency of follow up investigations,” the authors noted. Major complication rates were 33 per 10,000 among patients screened with LD-CT and 10 per 10,000 among those screened with chest radiography. The NLST was the only study of the 3 included in the review that had reported complication rates. The NLST noted 8 deaths per 10,000 individuals within 2 months of undergoing diagnostic procedures such as biopsy or bronchoscopy following screening by LD-CT, compared with 5 per 10,000 among those screened with chest radiography.  

Radiation doses varied between CT scanners used in the NLST, reflecting different models and generations of CT scanners, and scanner settings. Screening and follow-up diagnostic imaging in the NLST exposed LD-CT screening group patients to an estimated average radiation dose of 8 mSv, which the authors of the JAMA review calculated would result in 1 additional cancer death per 2500 patients screened. The ACS’s lung cancer screening guidelines note that patients at low risk of lung cancer and patients undergoing follow-up imaging
because of ambiguous or false-positive screening results could receive unnecessary irradiation.\textsuperscript{29}

With publication of the NLST findings and endorsement of practice guidelines by professional bodies, demand for lung cancer screening is expected to rise, and increased interest in establishing new CT screening centers has been reported.\textsuperscript{30} Demand also is likely to increase if public reimbursement or private insurance programs begin covering the costs of LD-CT lung cancer screening. However, it is unclear whether the benefits found in the NLST would be replicated in small, stand-alone screening center patient populations. The authors of the systematic review noted that the 3 studies they analyzed had been conducted primarily at large NCI-designated cancer centers with multidisciplinary teams and experienced diagnostic experts.\textsuperscript{31}

In light of the \textit{JAMA} review, researchers likely will continue to debate the merits of LD-CT lung screening because benefits were limited and potential risks were difficult to quantify. Other authors argued that the \textit{JAMA} reviewers’ conclusions were overly conservative because the NLST findings underestimated case-fatality reductions associated with LD-CT screening.\textsuperscript{32}

A subsequent database analysis of records for more than 25,000 patients found that the prevalence of benign findings following surgery for suspected lung tumors was 9.1% overall, nationwide.\textsuperscript{33} The authors cautioned that nationwide false-positive rates masked dramatic geographic variation, although the underlying cause of this geographic variation is unknown. Specifically, prevalence of benign disease following lung surgery varies widely by state and resulted in a 2.1% mortality rate.\textsuperscript{34} False-positive (benign) findings represented only 1.3% of lung surgery outcomes in Vermont but 25% of surgeries in Hawaii, for example.\textsuperscript{35}

Several randomized clinical trials in the United Kingdom and Europe, such as the Danish Randomized Lung Cancer CT Screening Trial and the UK Lung Screen trial, are being conducted. Results of these trials are not expected in the near future.\textsuperscript{26,30}

**Screening Guidelines**

Based on the NLST findings and the subsequent systematic review published in \textit{JAMA}, professional bodies have developed practice guidelines for LD-CT lung cancer screening. The American Society of Clinical Oncology and American College of Chest Physicians jointly endorsed guidelines published along with the \textit{JAMA} systematic review.\textsuperscript{36}

The ACS has issued guidelines recommending that clinicians discuss LD-CT screening only with patients meeting the NLST criteria, clearly communicating both the potential benefits, risks, and uncertainties associated with the procedure.\textsuperscript{29} All the screening guidelines emphasize that screening should not be viewed as an alternative to smoking cessation.\textsuperscript{29} ACS recommendations prioritize smoking cessation counseling for current smokers.\textsuperscript{37} Screening provides an opportunity for raising the importance of quitting smoking with patients, regardless of what the screening results might indicate about patients’ health.\textsuperscript{37}

In summer 2013, the U.S. Preventive Services Task Force (USPSTF) issued draft recommendations that determined people aged 55 to 80 years who have smoking histories of more than 30 pack-years should have LD-CT screening examinations.\textsuperscript{38,39} The task force determined that LD-CT benefits outweighed the risks for the recommended screening group. The draft recommendations updated 2004 guidelines from the USPSTF that did not recommend LD-CT lung screening.\textsuperscript{29}

Based on NCCN findings, chest radiography should not be used for lung cancer screening.\textsuperscript{29} Physicians should initiate discussions about screening only with patients meeting the selection criteria described below to identify patients for whom they believe the potential benefits of early detection of lung cancer justify the potential risks of screening.\textsuperscript{29} Patients who wish to avoid testing because of the high rate of false-positive screening results or who wish to avoid the relatively small risk of complications resulting from false-positive rates should be told that they face higher risk of death from lung cancer than from screening complications, and they should be encouraged to quit smoking.\textsuperscript{29}

The NLST LD-CT screening protocol should be followed annually, once initiated, until a patient reaches 74 years of age. Patients should undergo screening at institutions with multidisciplinary teams and LD-CT and lung-cancer diagnostic expertise.\textsuperscript{29}

The NCCN, a consortium of 21 U.S. cancer centers, and the American Association of Thoracic Surgeons have endorsed guidelines that include modifications of
patient selection criteria from NLST eligibility factors. The latter organization removed distinctions between current and former smokers, emphasizing criteria based on patient age and total tobacco consumption.\textsuperscript{40} The screening process starts with a discussion between the patient and clinician. Patients should be informed that research (NLST) suggests that initial positive screening results require follow-up examinations and in most cases do not result in a lung cancer diagnosis.\textsuperscript{29} According to the ACS guidelines, follow-up usually requires only additional imaging.\textsuperscript{29} Clinicians have a responsibility to help patients determine their out-of-pocket expenses for screening tests; few, if any, insurers currently cover the costs of LD-CT lung cancer screening.\textsuperscript{29}

**Patient Selection Criteria**

The ACS, American College of Chest Physicians, and American Society of Clinical Oncology all have endorsed the NLST eligibility criteria as appropriate selection criteria for screening. The NCCN and American Association for Thoracic Surgery, however, have developed practice guidelines that expand patient selection criteria recommendations.

The NCCN has endorsed practice guidelines recommending LD-CT lung screening not only for patients meeting the eligibility criteria for the NLST, for example, but also individuals aged 50 years or older with a 20 pack-year or longer history of smoking plus at least 1 additional risk factor from this list\textsuperscript{39}:

- History of any cancer.
- History of lung disease.
- Family history of lung cancer.
- Radon exposure.
- Occupational inhalation exposures to carcinogens.

The NCCN reported that its reviewers did not achieve unanimous consensus on the inclusion of this second category of patients who should be considered candidates for LD-CT screening.\textsuperscript{41}

Similarly, the American Association for Thoracic Surgery recommends screening be discussed with patients who meet the NLST eligibility criteria, plus patients aged 50 years or older with at least a 20 pack-year smoking history and who have either a history of lung cancer at least 5 years prior to screening or 1 or more additional risk factors from this list\textsuperscript{40}:

- History of COPD.
- Environmental or occupational exposures to lung carcinogens.
- Any prior cancer or thoracic radiation exposure.
- Genetic risk factors for lung cancer.
- Family history of lung cancer.

As the U.S. Patient Protection and Affordable Care Act and the Health Information Technology for Economic and Clinical Health (HITECH) Act are implemented, electronic medical records likely will allow automated identification of patients with whom lung cancer screening should be raised during physician visits.\textsuperscript{28} The HITECH Act requires clinicians to screen the smoking status of more than 50% of patients aged older than 13 years.\textsuperscript{59}

The American Association for Thoracic Surgery guidelines’ expanded patient selection criteria have been strongly endorsed by some authors who have noted that cancer mortality “increases exponentially” after age 50 years and calculated that including smokers with less-heavy pack-year histories will improve screening detection of up to 15% of additional lung cancer cases.\textsuperscript{40} People with genetic lung cancer risk factors and a medical history of COPD are many times more likely to develop lung cancer than others.\textsuperscript{42}

Risk-prediction models might well yield better patient selection for screening than criteria based on the NLST’s eligibility criteria. A modified version of the 2011 lung cancer risk prediction model from the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial has been developed and validated.\textsuperscript{43} This PLCO(M2012) model includes age, level of education, body mass index, family history of lung cancer, COPD, smoking status and duration of smoking, pack-year history, time since quitting, and chest radiography during the previous 3 years.\textsuperscript{43} The authors of the study, which was published in February 2013, reported that using these selection criteria for screening instead of the NLST eligibility criteria should lead to more effective patient selection for screening.\textsuperscript{43} Using data from the PLCO trial, this model selected for screening 81 more patients who had been diagnosed with lung cancer than did the NLST selection criteria, yielding a sensitivity of 83% compared with NLST’ criteria sensitivity of 71% and 41% fewer missed lung cancers.\textsuperscript{43}
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Screening as Educational Intervention Opportunity

Antitobacco education campaigns have been the most important factor in reducing lung cancer mortality rates, averting an estimated 70,000 lung cancer deaths in the year 2000 alone.44,45 Larry Kessler, MD, of the University of Washington Health Sciences Center in Seattle, stated that a 20% reduction in mortality is not a reason to ignore the importance of primary prevention. Clinicians should persist in trying to help patients stop smoking, and public campaigns directed at reducing smoking should continue.46 Kessler and others argue that screening and antismoking campaigns are compatible and should be pursued together in a coordinated fashion.44 Patients should be made aware that smoking leaves them at increased risk not only for lung cancer but also for numerous other cancers and chronic diseases.

Lung cancer screenings appear to present an opportunity to remind patients of the importance of smoking cessation and a window for empowering them with information about local resources. Patients should be encouraged to stop smoking at the LD-CT examination, and they should be told that regardless of the results of their screening examination, quitting smoking can benefit their health and quality of life. Patients should be provided easy-to-understand brochures or other smoking cessation literature along with phone numbers for local assistance programs (see Box 2).4 A 2012 review of 9 studies found that screening participants have increased motivation to quit smoking.37

Screening Procedure and Parameters

Patient Preparation

Patients are screened in the supine position with arms elevated above their heads.30 Patients should be told that the goal of the LD-CT lung screening examination is to acquire the entire scan in 1 breath hold, and they should be instructed to hold their breath at maximal inhalation.22 Breath holds typically last 24 seconds or less and may require practice. This should not be a problem for most patients if a CT scanner with 4 or more detector arrays is used.22 Breath-hold acquisition is necessary to avoid respiratory motion artifacts in the resulting images. Caudocranial scanning direction also can help avoid respiratory motion artifacts in patients who are unable to achieve 1 breath hold during scan acquisitions.22

Scanning Parameters and Reconstruction

Minimizing radiation dose while achieving sufficiently high-quality images requires a crucial balance. LD-CT scans expose patients to lower doses of radiation but are more prone to image noise than conventional chest CT scans.22 Lower mA yields a lower dose but more image noise, for example. Tissue contrast between lung parenchyma and lung nodules allows significant radiation dose reductions, but improper settings can increase radiation dose unnecessarily or, conversely, impair image quality and reduce the likelihood of nodule detection.22 Therefore, LD-CT lung screening must involve careful planning and acquisition. Generally speaking, lower radiation doses involve lower tube current and voltage settings, but the roles of voltage in LD-CT lung screening image quality and radiation dose have not yet been well studied.22

Nodule detection is impaired at tube currents below 20 mA and screening LD-CT in the NLST was, in most cases, performed at 20 to 40 mA.22,30,31 Tube voltages of 120 to 140 kVp typically are used in LD-CT screening.22 Thin-section axial images with slice thicknesses less than or equal to 2 mm are used, with 10% slice overlap.22 Low-pass smoothing filter algorithms typically are not used in LD-CT screening image reconstruction because details of fine pulmonary anatomy can be obscured.22 High-resolution (bone) algorithms should not be employed as the only image reconstruction technique because they can complicate detection of small nodules and might cause noncalcified nodules to appear calcified.22

High-resolution reconstruction might improve nodule size assessments compared with standard algorithms; depending on radiologist preference, both high-resolution and standard reconstruction can be used,

Box 2

Smoking Cessation Resources4

- National Cancer Institute hotline – (877) 44U-QUIT [(877) 448-7848]
- American Lung Association – www.lung.org/stop-smoking
yielding 2 image sets. Improved nodule-detection sensitivity might be achieved with axial maximum intensity projection image reformatting at 8-mm thickness and 3-mm intervals.

**Screening Image Interpretation**

Images are reviewed on a CT workstation or remote computer screen. Rapid scrolling between adjacent images allows detection of blood vessels that might be mistaken for pulmonary nodules in cross-section. Axial image viewing on lung windows typically involves a low-level setting of 600 Hounsfield units (HU) and a wide-width setting of 1600 HU.

LD-CT screening interpretation usually includes determining nodule size, consistency, and density, as well as growth rate measured as nodule diameter doubling time. 

The definition of a positive screening result is evolving and should be reappraised regularly to minimize potential harm from unnecessary diagnostic follow-up, according to the authors of a recent cohort study. The retrospective study suggests that a threshold definition of 7- to 8-mm nodules for positive findings in baseline screening images deserves additional prospective study.

Both false-negative and false-positive findings can lead to harmful outcomes for the patient. In a Japanese study of 10-mm slice thickness LD-CT screening-missed lung tumors (false negatives), 20 of 32 missed lesions resulted from imaging detection failures. Importantly, however, the remaining false-negative results were attributed to reader-interpretation errors, which included misdiagnosing tumors as evidence of tuberculosis infection or other inflammatory condition. False-negative results occurred in patients with complex lung diseases, including emphysema and pulmonary fibrosis. Almost all of the missed tumors appeared as “ground-glass” nodules—rather than solid ones—or mimicked pulmonary vasculature.

Lung abnormalities other than tumors or nodules frequently are encountered in screening images of heavy smokers. Examples include emphysema and interstitial lung diseases such as occupational or smoking-associated respiratory bronchiolitis. These pathologies could appear as centrilobar micronodules or cysts, thickened bronchial walls, or in cases of interstitial pneumonitis, patchy or diffuse ground-glass opacities. Mediastinal windows (ie, 40 HU level with 400 HU width) and bone windows (300 HU level at 2000 HU width) improve the likelihood of incidental findings. Bone windows can be useful for identifying metastatic bone tumors. CT frontal projection scout views also are useful for detecting lung abnormalities. Comparisons of screening images with previous CT lung scans on a patient can hasten identification of suspicious nodules, especially those that have grown larger during the interval between the previous imaging and the screening examination.

**Computer-Aided Diagnosis**

Computer-aided diagnosis (CAD) of LD-CT lung screen data sets is under development and might prove clinically useful. CAD software has been shown in pilot studies to detect most tumors missed by human visual inspection alone. As noted above, CT datasets with 10-mm slice thickness can yield relatively high failures to detect (false-negative reports) from visual inspection alone. Visual detection of suspected tumors using CT data reconstructed at 1- to 1.5-mm slice thickness is even more challenging, partly because the larger sets of images can cause reviewer fatigue. CAD might be more sensitive in detecting centrally located nodules, but radiologists appear to be better at detecting peripheral ones. CAD plus radiologist review might yield 90% or better sensitivity in detecting lesions exceeding 4 mm in diameter.

Unfortunately, CAD programs yield up to 20 false positives per CT scan, usually involving misidentification of lung vasculature, precluding CAD’s routine clinical use now. When CAD programs are incorporated, it will be essential that human reviewers not rely on CAD nodule detections or relax the vigilance of their visual searches of screening images.

**Follow-up**

Follow-up procedures prompted by positive findings in screening images include imaging with screening LD-CT protocols or conventional chest CT—or for nodules with diameters measuring 7 to 10 mm, contrast-enhanced CT or PET-CT. Follow-up imaging
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should be informed by a detailed patient history and physical examination; if lung cancer still is suspected, a 2-projection chest radiograph and CT scan of the thorax and upper abdomen is indicated. If CT suggests localized malignancy, PET-CT is undertaken to confirm that there is no metastasis or lymphadenopathic enlargement of nodes indicating lymph node involvement.

Invasive tissue-biopsy staging procedures are not recommended if mediastinal lymph nodes are normal size on CT scans and negative on PET-CT images, and if imaging-based staging indicates the nodule, if malignant, would be stage 1a (T1N0M0) (see Figure 4). Depending on the level of suspicion that a nodule is malignant, follow-up also might include more invasive procedures such as diagnostic bronchoscopy, surgery, or fine-needle percutaneous biopsy (eg, in patients with palpable lymphadenopathy). Lymph node biopsy is recommended if tumors are stage T2 or if mediastinal lymph nodes appear abnormal on either CT scans or PET-CT images. Magnetic resonance imaging can exclude the possibility of metastatic tumors in the brain.

Noncalcified nodules measuring less than 10 mm in diameter that do not grow after 2 years of LD-CT lung screening usually are benign, but follow-up to monitor such nodules for as long as 7 years is considered reasonable.

In the NLST, positive screens prompted follow-ups consistent with local practice by the participating cancer centers. A positive finding in a patient’s first screening requires more immediate follow-up than positive findings in subsequent annual screenings because frequently no previous imaging exists with which to compare a suspect nodule and to determine whether it is new or has grown. The NCCN definition of nodule growth involves 1 or more of the following conditions:

- An increase in nodule diameter of 2 mm or more for those nodules measuring 15 mm or less in the baseline image, or a 2 mm increase in the solid portion of a partially solid nodule.
- A 15% or more increase in mean diameter for nodules measuring 15 mm or more, compared with the baseline image.

High rates of false-positive findings can lead to over-diagnosis or the detection of subclinical lesions that would never have become symptomatic or diagnosed had a patient not been screened. Estimations of over-diagnosis rates in the NLST patient populations are not yet possible, but follow-up protocols can reduce the risk of harm to patients from false-positive results. The NLST yielded a 2.7% rate of invasive procedures resulting from false-positive findings. However, follow-up procedure complications for patients with false-positive findings were low (0.06%).

Nevertheless, given the high rate of false-positive findings noted in the NLST, follow-up protocols have been recommended for LD-CT screening to minimize unjustified invasive or irradiating procedures. In the NLST study protocol, intermediate or positive findings should prompt diagnostic tests, follow-up LD-CT, or serial CT follow-up at 3-, 6-, 12-, or 24-month intervals, depending on the size of the nodule. If serial or follow-up imaging reveals a change in nodule size, follow-up imaging intervals may be decreased or definitive diagnostic procedures such as biopsy might be performed.

Surveillance

If diagnosis is confirmed and surgery, radiation therapy, or other treatment is undertaken for early-stage or localized lung tumors, post-treatment monitoring with serial CT scans after treatment is common. This surveillance can detect lung injuries (eg, from radiation therapy52), local tumor recurrence, or the development of new primary (metachronous) tumors.

Metachronous tumors occur in the absence of lymph node involvement and have a distinct histology from the primary tumor, or they occur after a disease-free period of 2 years or more. Metachronous tumors also might originate from carcinoma in situ or emerge in a different lung or a different lobe of the lung in which the treated primary tumor occurred. A metachronous tumor also can be distinctly different at the chromosomal level from the primary tumor.53

Other surveillance methods include chest radiography, PET, and bronchoscopy.53 (According to the ACS guidelines, follow-up usually requires only additional radiological imaging.29) Early detection of tumor recurrence before symptoms emerge might prolong patients’ lives or improve their quality of life; therefore, surveillance is a common practice. A recent retrospective cohort study of 1294 patients at Memorial Sloan-Kettering Cancer Center in New York found that nearly all metachronous tumors were detected using LD-CT.44 Nevertheless, the overall empirical evidence for these hypothetical benefits has not been well established.53

Surgery can miss tissue-harboring cancer cells or micrometastases, particularly when surgical margins around the tumor are small; up to 24% of NSCLC patients have locoregional tumor recurrence after curative surgery.52

Other factors can increase the risk of tumor recurrence. Diabetes nearly doubles local recurrence risk. (The increased hazard ratio from diabetes is 1.81, or 81%.53) Continued smoking has been identified in some, but not all, studies of local tumor recurrence risks.53

Posttreatment CT surveillance leads to 4.4% of surgically treated patients undergoing an additional resection because of incomplete removal of tumor tissue.53 It is unclear, however, whether more frequent posttreatment monitoring imaging examinations ultimately improve patients’ survival times.53

Conformal radiation therapy and stereotactic body radiation therapy frequently prompt posttreatment monitoring with CT. These increasingly common forms of radiation therapy maximize radiation doses to tumor tissues while minimizing irradiation of healthy, nontarget tissue.52 Radiation injuries to lung tissue still can occur within radiation portals, however.52 Serial CT or other imaging after radiation therapy can show acute radiation pneumonitis, which appears as ground-glass opacities and consolidation. Subsequent or late-phase radiation fibrosis 6 to 12 months after therapy is complete could develop and appears radiologically as consolidation and losses in parenchymal volumes.52 PET-CT imaging allows the use of anatomic CT scan information and physiologic PET information to differentiate radiation injuries to lung parenchyma from persisting or recurring tumors.52

Conclusion

Lung cancer remains the leading cancer killer of men and women, and primary prevention and screening are key to reducing the number of lives lost and maximizing patients’ life spans after initial diagnosis. Screening should not be undertaken as a stand-alone secondary prevention effort against cancer; it should be seen as an opportunity to incorporate primary and secondary prevention by incorporating smoking cessation interventions into the screening process.37

As selection criteria and correlations between screening scan variables and diagnostic outcomes become better understood, improved criteria regarding which patients to screen and which screens should be considered positive likely will evolve. For example, mean lung density might turn out to be an independent predictor of whether nodules found in screening scans are malignant.55 New molecular biomarkers might improve the utility of sputum analysis for the noninvasive detection of early-stage lung cancers, and other biomarker tests might improve risk prediction and patient selection for LD-CT lung cancer screening in the future.56,57

New Mexico–based medical writer and health care journalist Bryant Furlow, BA, is a regular contributor to Radiologic Technology, The Lancet Oncology, and The Lancet Respiratory Medicine.
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Read the preceding Directed Reading and choose the answer that is most correct based on the article.

1. Primary and secondary prevention strategies for lung cancer include:
   1. screening.
   2. smoking cessation education.
   3. radon testing.

   a. 1 and 2
   b. 1 and 3
   c. 2 and 3
   d. 1, 2, and 3

2. Which of the following statements is false regarding low-dose computed tomography (LD-CT) lung cancer screening?
   a. Not every patient benefits from LD-CT screening.
   b. Some patients have unnecessary follow-up procedures because of false-positive results.
   c. Research shows that screening the population at large can prolong and save lives.
   d. Lung cancer screening presents an opportunity for patient education.

3. Smoking ultimately contributes to the deaths of half of smokers who do not quit smoking before developing a smoking-related disease.
   a. true
   b. false

4. _______ have markedly higher lung cancer incidence and mortality rates than people of other ethnicities.
   a. Hispanics
   b. Blacks
   c. Whites
   d. American Indians

5. The “Hispanic paradox” of lower non–small cell lung cancer rates and better outcomes than those seen in other ethnic groups might in part reflect:
   a. socioeconomics.
   b. educational attainment.
   c. lower smoking rates.
   d. healthy immigrants.
6. Which of the following inhalation exposures are clearly risk factors for lung cancer?
   a. asbestos
   b. radon
   c. marijuana
   d. 1 and 2

7. Female smokers’ lung tissue cells usually express higher levels of lung cancer–relevant genetic factor ______ than do men’s lung cells.
   a. ERBB1
   b. CDNK2A
   c. K-RAS
   d. CYPIA1

8. Cellular division rates and apoptosis can become disorganized, yielding premalignant or precursor lesions called:
   a. genetic carcinoma.
   b. carcinoma in situ.
   c. hyperplastic dysplasia.
   d. neuroendocrine tumors.

9. The most common histological types of non–small cell lung cancer are:
   a. squamous cell carcinoma.
   b. large cell carcinoma.
   c. adenocarcinoma.
   d. 1, 2, and 3

10. ______ cancer screening is undertaken with large numbers of asymptomatic people to identify those at high risk for disease.
    a. Selective
    b. Population
    c. Case-finding
    d. Diagnostic

11. Case-finding screening is a prediagnostic endeavor.
    a. true
    b. false

12. Eligibility criteria for participation in the National Lung Screening Trial (NLST) included:
    a. age 50 years or younger.
    b. occupational asbestos exposure.
    c. secondhand smoker.
    d. former smoker with 30 or more pack-years.

13. NLST CT scan parameters included:
    a. 110 to 120 kVp.
    b. 20 to 80 mAs.
    c. 1.5 to 2.0 pitch.
    d. collimation at 1.5 mm or less.

14. LD-CT group participants in the NLST were found to have significant nonlung-related abnormalities such as:
    a. cardiovascular disease.
    b. breast cancer.
    c. nodal disease.
    d. oropharyngeal carcinomas.

15. The main concern with LD-CT that was reported in the NLST was:
    a. a high false-positive rate.
    b. respiratory motion artifacts.
    c. screening-associated complications.
    d. poor detection of early-stage tumors.
16. A subsequent analysis of the NLST data concluded that properly implemented annual LD-CT lung screening would delay or prevent:
   a. lung cancer mortality.
   b. overall mortality.
   c. tumor recurrence.
   d. cardiovascular disease.

17. Publication of the NLST findings likely will result in:
   a. guidelines recommending chest radiography for lung cancer screening.
   b. continued monitoring of CT radiation dose for patients undergoing lung cancer screening.
   c. a decrease in the use of LD-CT for lung cancer screening.
   d. an increase in demand for lung cancer screening.

18. Analysis of records for more than 25,000 patients found that false-positive (benign) findings represented only 1.3% of lung surgery outcomes in Vermont but ______ % of surgeries in Hawaii.
   a. 5
   b. 15
   c. 25
   d. 35

19. National Comprehensive Cancer Network practice guidelines recommend LD-CT lung screening for patients who meet NLST criteria and who are aged 50 years or older with:
   a. at least a 20 pack-year history of smoking plus history of any cancer.
   b. at least a 30 pack-year history of smoking plus history of lung disease.
   c. history of lung disease and radon exposure.
   d. history of any cancer and occupational inhalation of carcinogens.

20. Which professional body has developed screening guidelines that include genetic risk factors among patient selection criteria?
   a. American Medical Association
   b. American Lung Association
   c. American Association for Thoracic Surgery
   d. American Cancer Society

21. Pulmonary nodule detection is impaired at tube currents below ______ mA.
   a. 20
   b. 40
   c. 60
   d. 80

22. High-resolution (bone) algorithms should not be employed as the only image reconstruction technique because they can complicate detection of small nodules.
   a. true
   b. false

23. In a study of false-negative findings on LD-CT lung screening, nearly all of the missed tumors appeared as ______ nodules.
   a. solid
   b. ground-glass
   c. fluid-filled
   d. calcified

24. Recent evidence suggests that computer-aided detection yields up to ______ false positives per CT scan, largely because of misidentified lung vasculature.
   a. 5
   b. 10
   c. 15
   d. 20
25. Lymph node biopsy is recommended if tumors are stage ______ or if mediastinal lymph nodes appear abnormal on either CT scans or positron emission tomography–CT scans.
   a. T1a
   b. T1b
   c. T2
   d. T3

26. In the NLST, ______ % of participants who had LD-CT lung screening underwent invasive procedures following false-positive findings.
   a. 1.7
   b. 2.7
   c. 3.7
   d. 4.7

27. In the NLST study protocol, intermediate or positive findings should prompt which types of follow-up?
   1. diagnostic tests
   2. LD-CT
   3. serial CT
   a. 1 and 2
   b. 1 and 3
   c. 2 and 3
   d. 1, 2, and 3

28. Metachronous tumors occur:
   1. in the absence of lymph node involvement.
   2. after a disease-free period of 2 years.
   3. only in the same lung as the primary tumor.
   a. 1 and 2
   b. 1 and 3
   c. 2 and 3
   d. 1, 2, and 3

29. Tumor recurrence risk factors include:
   1. comorbid diabetes.
   2. Hispanic ethnicity.
   3. small surgical margins.
   a. 1 and 2
   b. 1 and 3
   c. 2 and 3
   d. 1, 2, and 3

30. CT lung monitoring after radiation therapy can show:
   a. acute radiation pneumonitis.
   b. cardiovascular disease.
   c. chronic obstructive pulmonary disease.
   d. metastatic disease.