Jill Smith, a 58-year-old waitress in a local bar, comes to the clinic complaining of shortness of breath and a persistent cough for the last month. She reports she has lost 10 lbs recently, even though her eating habits (including a high meat intake and few green vegetables) haven’t changed.

Mrs. Smith states that she doesn’t smoke; she tried smoking one cigarette when she was 16. “That was enough for me,” she says. “I couldn’t stop coughing. I don’t get why people smoke. I was so glad my husband stopped smoking 6 months ago.”

Based on a complete history and physical examination, the practitioner orders a chest X-ray, which reveals a lung mass. Mrs. Smith subsequently is diagnosed with lung cancer. “I don’t understand it,” she says. “I’m not a smoker. How can this be?”

Like Mrs. Smith’s nurse, you might be surprised to encounter a patient who has lung cancer yet never smoked. Although lung can-
Environmental factors linked to lung cancer

Environmental tobacco smoke (ETS, also called secondhand smoke) is classified as a known human carcinogen by the U.S. Environmental Protection Agency, U.S. National Toxicology Program, U.S. Surgeon General, and International Agency for Research on Cancer. ETS causes more than 7,300 lung cancer deaths in U.S. non-smokers each year. Clean indoor air laws may decrease that total significantly.

Radon, an inert gas and known respiratory carcinogen, is the second leading cause of lung cancer, responsible for 2,900 deaths annually in never-smokers. It was first discovered in underground uranium miners; epidemiologic studies of miners and the general population confirmed a causal relationship between radon and lung cancer in never-smokers. The risk of developing lung cancer depends largely on the radon concentrations to which the person was exposed; it’s estimated at approximately 34%.

The World Health Organization recognizes many other environmental carcinogens that are toxic to the lungs, including asbestos, crystalline silica (found in sand, stone, rock, concrete, brick, block, and mortar), polycyclic aromatic hydrocarbons (particles from volcanoes, forest fires, burning coal, aerosolized oils caused by cooking, and automobile exhaust), and certain heavy metals (such as mercury, benzene, and arsenic).

Risk factors

In never-smokers like Mrs. Smith, NSCLC incidence has increased steadily since 1990. One U.S. study found a twofold increase in NSCLC from 2001 to 2013; a United Kingdom study found lung cancer rates in never-smokers rose from 13% to 28% over a 6-year period.

Reasons for the increase remain speculative. Some experts believe that thanks to relentless education campaigns on the harmful effects of smoking, fewer Americans are smoking today, reflected in the all-time lowest smoking rates since 1965. Although more lung cancers seem to be occurring in never-smokers, scientists aren't sure if the LCINS rate is falsely elevated due to the sharp decline in smoking or if it’s truly higher than before. Some experts propose that exposure to environmental tobacco smoke (ETS), radon, air pollution, diet, and genetic factors may contribute to higher lung cancer rates in never-smokers.

Environmental exposures

The link between ETS and lung cancer was established in 1981 when a large prospective study (n = 91,540) found that nonsmoking Japanese wives of heavy smokers had a higher risk of developing lung cancer than nonsmoking wives of nonsmoking men. Since then, dozens of studies have confirmed this connection. (See Environmental factors linked to lung cancer.)

Genetic alterations

Certain genetic mutations are much more common in never-smokers with lung cancer than in smokers with lung cancer. (See Genetic alterations in never-smokers.)

Diet

A diet high in red meat, processed meats, high-fat foods, and butter significantly increases lung cancer risk in never-smokers. On the other hand, a diet high in vegetables, fruit, and fish has been shown to decrease lung cancer risk in never-smokers. Alcohol consumption and body mass index don’t affect risk.

Familial predisposition

Growing evidence indicates a family history of lung cancer increases a person’s lung cancer risk. A classic study by Tokuhta and Lilienfeld (1963) reported a 2.5-fold higher lung cancer risk in individuals who had a first-degree relative with a history of lung cancer. More recent epidemiologic studies confirm this risk level. Risk increases even more in people whose relatives were diagnosed with lung cancer before age 40 or who had multiple family members with lung cancer.

Age

As with all cancers, lung cancer risk increases with age. In never-
smokers, the average age at diagnosis is controversial. Some studies report lung cancer is more likely in persons older than 65; others report just the opposite. One reason for the opposing data is that just 2% to 3% of patients with lung cancer are younger than 40, so obtaining a cohort large enough to study is challenging.

**Gender**

Research repeatedly has shown that LCINS is more common in women than men. Although this may result from women's greater susceptibility to risk factors, it also may reflect the fact that twice as many women as men are never-smokers. Due to this higher proportion of female never-smokers, evidence suggests hormones, specifically estrogen, may play a role in lung carcinogenesis by stimulating NSCLC cell proliferation. Two estrogen receptors, ERα and ERβ, are expressed in lung tissue. ERβ is more commonly expressed and correlated with improved survival; ERα is a poor prognostic indicator for lung cancer. Hormone replacement therapy and hormonal contraceptives remain controversial in reducing lung cancer risk.

**Geographic factors**

Asia has a higher proportion of never-smokers with lung cancer than the United States. Among Asian females with the disease, 80% are never-smokers, compared to 10% or 15% of Western women. This most likely reflects a higher prevalence of smoking in Asian countries than in Western countries.

**Clinical presentation**

The patient may present to the primary healthcare provider with complaints of a cough or another sign or symptom that suggests an infection. Clinicians should always consider lung cancer as a differential diagnosis, even in never-smokers.

In both smokers and never-smokers, lung cancer signs and symptoms vary with tumor location and disease extent. Some patients lack symptoms and are diagnosed incidentally from a routine chest X-ray. Unfortunately, most are diagnosed late and have signs and symptoms of advanced disease. These manifestations may stem from:

- the tumor itself, which may cause cough, shortness of breath, wheezing, hemoptysis, chest pain, weight loss, hoarseness, and fatigue
- metastasis, which can lead to blurred vision, headaches, and pain
- paraneoplastic syndrome, which may cause hypercalcemia, confusion, nausea, vomiting, constipation, excessive thirst or urination, fatigue, seizures, coma, and syndrome of inappropriate antidiuretic hormone secretion.

Because never-smokers lack a history of smoking, many are misdiagnosed and treated for upper respiratory infection or allergies. Prompt, accurate identification of signs and symptoms is crucial for promoting a timely diagnosis and improving both outcome and quality of life.

**Treatment**

Treatment is based on cancer stage, which hinges on assessment of the tumor, whether it has metastasized, and the status of regional lymph nodes. (See Lung cancer staging.)

Treatment of curable lung cancer (stages I, II, or III) may involve surgery, radiation, chemotherapy, or a combination. Incurable or metastatic lung cancer (stage IV) warrants chemotherapy, targeted therapy, or immunotherapy.

If a genetic mutation goes undetected but the tumor expresses more than 50% of the programmed cell death ligand 1 (PD-L1) receptor, the patient should receive the immunotherapy agent pembrolizumab as first-line treatment. Patients with neither genetic mutations nor PD-L1 expression typically receive standard treatment with I.V. chemotherapy, consisting of cisplatin or carboplatin in combination with pemetrexed or a taxane (paclitaxel or docetaxel) and, in some cases, bevacizumab (an angiogenesis inhibitor). Bevacizumab is contraindicated in patients with a history of a thromboembolic event, hemoptysis, or untreated brain metastases.

**Genetic alterations in never-smokers**

Genetic alterations that control cancer-cell initiation and maintenance include epidermal growth factor receptor (EGFR) mutation and echinoderm microtubule-associated protein-like 4 anaplastic lymphoma kinase (EML4-ALK) translocation. Approximately 50% of never-smokers have one of these alterations, compared to just 10% of smokers who have either.

Discovery of these alterations has defined lung cancer in never-smokers as a distinct disease entity. What's more, it has changed the treatment landscape and quality of life for patients, because it means they can receive molecularly targeted therapy. Ideally, those with either genetic mutation should receive first-line treatment with an oral therapy (erlotinib or gefitinib, or alternatively, crizotinib). These drugs specifically target the genetic alteration, thus halting cancer progression.
A study of nearly 1,800 people in a 10-minute online test, 74% said they were biased against people with lung cancer. In a perception that lung cancer is preventable and therefore self-inflicted makes never-smokers feel they’re being blamed for their illness. In a study of nearly 1,800 people in a 10-minute online test, 74% said they were biased against people with lung cancer. Lung cancer stigma can lead to anxiety, depression, and isolation, which affects the patient’s health and quality of life.

Nurses’ role
Nurses can play a key role in improving patient outcomes by screening and identifying patients—not just those at high risk for lung cancer but also those with few or no risk factors. Recognizing signs and symptoms regardless of smoking status and expediting the initial workup through appropriate diagnostic tests and referrals help ensure a prompt diagnosis and may improve prognosis.

When assessing a patient for pos-

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**Lung cancer staging**

Lung cancer is staged using the TNM system from the American Joint Committee on Cancer.

- **T** denotes size of the primary tumor.
- **N** indicates regional lymph node status.
- **M** denotes whether the cancer has metastasized.

The TNM results are combined to produce a stage group. This classification system helps clinicians plan the patient’s treatment and evaluate its results, helps establish prognosis, and promotes information exchange among treatment centers.

**T = Tumor**

<table>
<thead>
<tr>
<th>TX</th>
<th>Primary tumor can’t be assessed; or tumor is proven from malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy</th>
</tr>
</thead>
<tbody>
<tr>
<td>T0</td>
<td>No evidence of primary tumor</td>
</tr>
<tr>
<td>Tis</td>
<td>Carcinoma in situ</td>
</tr>
<tr>
<td>T1</td>
<td>Tumor 3 cm or less in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than lobar bronchus (for example, not in the main bronchus)¹</td>
</tr>
<tr>
<td>T1a</td>
<td>Tumor 2 cm or less in greatest dimension</td>
</tr>
<tr>
<td>T1b</td>
<td>Tumor more than 2 cm but 3 cm or less in greatest dimension⁴</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor more than 3 cm but 7 cm or less or tumor with any of the following features (T2 tumors with these features are classified T2a if 5 cm or less): involves main bronchus, 2 cm or more distal to carina; invades visceral pleura (PL1 or PL2); associated with atelectasis or obstructive pneumonitis that extends to hilar region but doesn’t involve entire lung</td>
</tr>
<tr>
<td>T2a</td>
<td>Tumor more than 3 cm but 5 cm or less in greatest dimension</td>
</tr>
<tr>
<td>T2b</td>
<td>Tumor more than 5 cm but 7 cm or less in greatest dimension</td>
</tr>
<tr>
<td>T3</td>
<td>Tumor more than 7 cm or one that directly invades any of the following: parietal pleural (PL3), chest wall (including superior sulcus tumors), diaphragm, phrenic nerve, mediastinal pleura, parietal pericardium; or tumor in main bronchus less than 2 cm distal to carina¹ but without involvement of carina; or associated atelectasis or obstructive pneumonitis of entire lung or separate tumor nodule(s) in same lobe</td>
</tr>
<tr>
<td>T4</td>
<td>Tumor of any size that invades any of the following: mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, carina, separate tumor nodule(s) in different ipsilateral lobe</td>
</tr>
</tbody>
</table>

**N = Regional lymph nodes**

| NX | Regional lymph nodes can’t be assessed |
| N0 | No regional node metastasis |
| N1 | Metastasis in ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension |
| N2 | Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s) |
| N3 | Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph nodes |

**M = Metastasis**

| M0 | No distant metastasis |
| M1 | Distant metastasis |
| M1a | Separate tumor nodule(s) in a contralateral lobe; tumor with pleural nodules or malignant pleural (or pericardial) effusion² |
| M1b | Distant metastasis (in extrathoracic organs) |

**Cancer stage groups**

Clinicians combine TNM results to determine the stage group. Most cancers have four stages (stage I to IV). Some cancers, including lung cancer, have five stages (stage 0 to IV).

- Stage 0: Tis, N0, M0
- Stage IA: T1a/T1b, N0, M0
- Stage IB: T2a, N0, M0
- Stage IIA: T1a/T1b, N1, M0 or T2a, N1, M0, or T2b, N0, M0
- Stage IIB: Any T, N1, M0 or T3, N0, M0
- Stage IIIA: T1 to T2, N2, M0 or T3, N1/N2, M0 or T4, N0/N1, M0
- Stage IIIB: Any T, N3, M0 or T4, N2, M0
- Stage IV: Any T, any N, M1a or any T, any N, M1b

¹ The uncommon superficial spreading tumor of any size with its invasive component limited to the bronchial wall, which may extend proximally to the main bronchus, is also classified as T1a.

² Most pleural (and pericardial) effusions with lung cancer are due to tumor. In a few patients, however, multiple cytopathologic examinations of pleural (pericardial) fluid are negative for tumor, and the fluid is nonbloody and is not an exudate. Where these elements and clinical judgment dictate that the effusion is not related to the tumor, the effusion should be excluded as a staging element and the patient should be classified as M0.

sible lung cancer, be sure to take a thorough medical history, family history, environmental exposure history, and social history. These may reveal risk factors that clinicians might otherwise overlook. The National Comprehensive Cancer Network (NCCN) and the U.S. Preventive Services Task Force (USPSTF) have developed evidence-based screening guidelines. USPSTF recommends annual lung cancer screening with low-dose computed tomography in adults ages 55 to 80 who have a 30 pack-year smoking history and currently smoke or have stopped smoking within the past 15 years; NCCN recommends such screening for people ages 55 to 74. However, screening guidelines for never-smokers don’t exist.

**Patient education**

Educate patients about lung cancer risk factors besides smoking. Like Mrs. Smith, never-smokers who are diagnosed with lung cancer may ask, “Why me?” or “How did this happen?” Teaching them that lung cancer isn’t just a disease of smokers and exploring their medical and exposure histories in detail can offer insight into why and how they got lung cancer. As needed, initiate referrals for counseling to help mitigate the anger, guilt, and stigma they may be experiencing.

**Early diagnosis is key**

LCINS is a rapidly growing disease that’s not fully understood. Unless detected early, it carries a poor prognosis. Screening methods for LCINS haven’t been identified, so healthcare providers must be vigilant and recognize that people with no smoking history are still at risk for lung cancer. Research aimed at understanding this growing-at-risk population needs to be a top priority.

Mrs. Smith is diagnosed with stage IIB cancer. She undergoes surgery followed by radiation treatment. Six months later, she is able to return to her job and her usual activities.

Visit AmericanNurseToday.com/?p=24914 for a complete list of selected references.

Victoria Sherry is an oncology nurse practitioner at the Abramson Cancer Center of the Hospital of the University of Pennsylvania in Philadelphia. *(Note: Names in the clinical scenario are fictitious.)*

**Selected references**


U.S. Environmental Protection Agency. Health risk of radon. Updated September 22, 2016. epa.gov/radon/health-risk-radon


Please mark the correct answer online.

1. Which statement about the incidence of lung cancer in never-smokers (LCINS) is correct?
   a. About half of lung cancer cases occur in never-smokers.
   b. About 10% of lung cancer cases occur in never-smokers.
   c. The incidence of LCINS is falling.
   d. The incidence of LCINS is rising.

2. John Bennett, a 67-year-old man who smoked only a few cigarettes as a teen, has been diagnosed with lung cancer. Which type of lung cancer does he most likely have?
   a. Small-cell adenocarcinoma
   b. Non-small-cell (NSC) adenocarcinoma
   c. Small-cell squamous cell carcinoma
   d. NSC squamous cell carcinoma

3. The second leading cause of lung cancer is:
   a. smoking.
   b. radon.
   c. asbestos.
   d. mercury.

4. Which of the following is not an environmental cause of lung cancer?
   a. Secondhand tobacco smoke
   b. Polycyclic aromatic hydrocarbons
   c. Crystalline silica
   d. Certain light metals

5. Which statement about LCINS in women is correct?
   a. Expression of ERβ in lung tissue is a poor prognostic indicator.
   b. Women are less likely than men to be never-smokers.
   c. Estrogen may play a role in lung carcinogenesis.
   d. LCINS is significantly less common in women than men.

6. Which of Mr. Bennett’s dietary habits may have put him at increased risk for lung cancer?
   a. Drinking one glass of wine twice a week
   b. Drinking two beers each week
   c. Eating a diet high in fruit and vegetables
   d. Eating a diet high in red meat

7. Genetic alterations found in some never-smokers include:
   a. epidermal growth factor receptor mutation.
   b. subdermal growth factor receptor mutation.
   c. fat-like 4 anaplastic lymphoma kinase translocation.
   d. protein-like 4 anaplastic lymphoma kinase transmutation.

8. Which of the following statements about the clinical presentation of patients with LCINS is correct?
   a. Patients may be misdiagnosed and treated for upper respiratory infection.
   b. Presenting signs and symptoms typically lead to an early diagnosis.
   c. Patients rarely are diagnosed based on results of a routine chest X-ray.
   d. Presenting signs and symptoms don’t vary with location of the tumor.

9. Mr. Bennett’s tumor is 2 cm in its greatest diameter; metastasis is found in the ipsilateral peribronchial lymph nodes and two pleural nodules are present. The correct TNM classification is:
   a. T2a, N1, M1
   b. T2a, N2, M1a
   c. T1a, N2, M1b
   d. T1a, N1, M1a

10. Another patient with lung cancer has a TNM of T2b, N1, M0. What is the correct cancer stage group?
    a. Stage IIA
    b. Stage IIB
    c. Stage IIIA
    d. Stage IIIB

11. The TNM for a female patient with lung cancer is T2a, N3, M0. What is the correct cancer stage group?
    a. Stage IIA
    b. Stage IIB
    c. Stage IIIA
    d. Stage IIIB

12. Because Mr. Bennett’s tumor expresses 60% of the programmed cell death ligand 1 (PD-L1) receptor, his physician prescribes:
    a. bevacizumab.
    b. cisplatin.
    c. pembrolizumab.
    d. paclitaxel.

13. If Mr. Bennett did not have a genetic mutation or PD-L1 expression but did have a history of hemoptysis, he most likely would receive:
    a. cisplatin.
    b. bevacizumab.
    c. carbonate.
    d. pembrolizumab.

14. Which of the following should you keep in mind when providing education and support to Mr. Bennett?
    a. Referrals for psychological support usually aren’t needed.
    b. Patients typically accept their diagnosis.
    c. Many people are biased against those with lung cancer.
    d. The U.S. Preventive Services Task Force has never-smoker guidelines.