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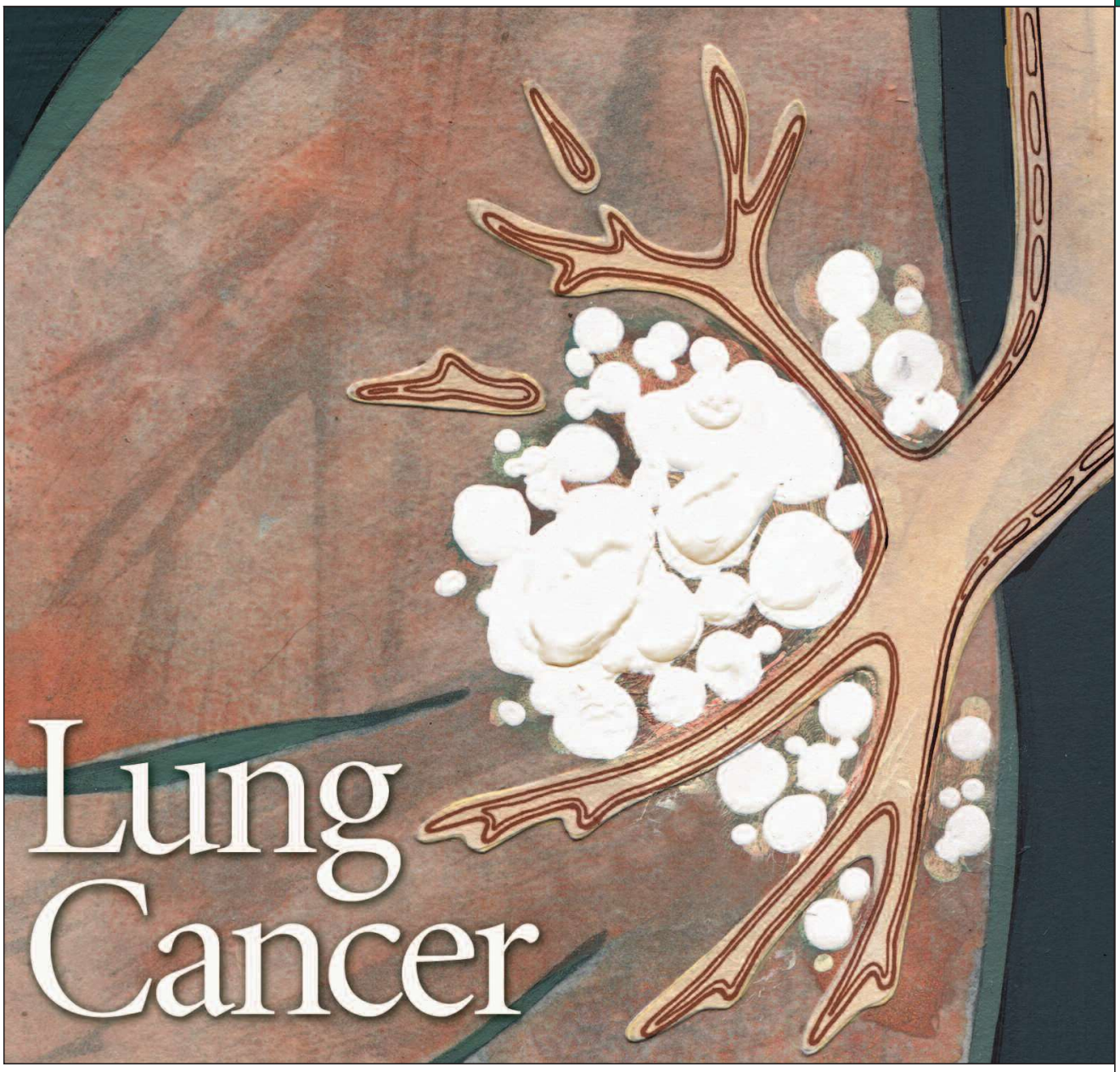

Illustration by Craig Kiefer

Diagnosis in Primary Care

Brooke M. Simon, RN, BSN, MSN

Lung cancer is currently the most fatal malignancy in the world.[1] More individuals die from lung cancer than breast, colorectal, and prostate cancers combined.[2] And because of poor survival rates, the incidence of lung cancer mimics its mortality rates.[3] The 5-year survival rate for lung cancer remains a grim 14%, and 90% of lung cancer patients eventually succumb to the disease.[3,4]

Early detection of lung cancer in the primary care setting is a challenge in the absence of mass screening guidelines. According to the U.S. Preventive Services Task Force (USPSTF), there is insufficient evidence to either refute or recommend screening for lung cancer in asymptomatic patients (including the use of chest X-ray, sputum cytology, and low-dose computerized tomography [CT]).[5] Lung cancer is challenging to treat unless found in its early stage—the majority of patients do not exhibit symptoms until the cancer has metastasized.[6] This is crucial to the excessive mortality rate of lung cancer.

Nurse practitioners should be knowledgeable about risk factors, pathophysiology, and presenting symptoms. Familiarity with current evidence-based research regarding the roles of genetics and estrogen in the development of this dis-

ease must be emphasized. This is essential to ensure timely and appropriate decisions regarding follow-up and management of care for those at risk for lung cancer.

Pathophysiology of Lung Cancer

Based on histologic characteristics, lung cancer is usually separated into two classes: non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). Non-small cell lung cancer comprises adenocarcinoma, squamous cell carcinoma, and large cell carcinoma. Small cell lung cancer is aggressive and tends to proliferate more quickly.[7] Twenty percent of lung cancers are classified as SCLC.[8]

In healthy lungs, inflammation and injury are resolved through apoptosis, or the "programmed" death of needless cells.[9] This process is often abnormal in lung cancer tissue and results in inhibited cellular repair and destructive tumor development.[10]

Since a majority of lung cancers are caused by exposure to tobacco smoke, the pathophysiology is often linked to this habit. Tobacco inhalation, which leads to the induction of neutrophils within the airways, contributes to inflammation in the lungs and an increase in cytokine production, attracting more neutrophils to the airways.[11] Smokers have a decreased ability to clear neutrophils from pulmonary circulation, have increased rigidity of neutrophils in peripheral circulation, and usually have the presence of noncompliant neutrophils.[11] Smoking also leads to oxidative stress caused by oxidants in cigarette smoke and the excessive number of inflammatory cells in the lung.[11]

Cigarettes contain more than 100 carcinogens that can cause mutation in the DNA of lung cells.

Carcinogens

Cigarettes contain more than 100 carcinogens that can cause mutation in the DNA of lung cells.[12] Following exposure to cigarette smoke, the carcinogens polycyclic aromatic hydrocarbons, N-nitrosos compounds, and nitrosamines become activated and create DNA adducts, which lead to metaplasia of lung cells. Genetic mutations and the inactivation of epigenetic genes subsequently lead to abnormal cell growth. Instability of the genes further advances the carcinogenesis, resulting in loss of both apoptosis and the ability to control cellular proliferation. Resultant tissue invasion occurs from this unstoppable cellular growth. These transformed cells become autonomous as they no longer depend on growth factors to proliferate. Angiogenesis, or the formation of new blood vessels, occurs and invasive lung cancer develops.[13]

Carcinogenesis associated with smoking leads to genetic alterations of oncogenes, such as K-ras, and mutated tumor suppressor genes, such as the p53 mutation. The p53 pathway is responsible for cellular apoptosis; a mutation in this pathway has been positively correlated with exposure to tobacco smoke.[12] Radon exposure causes damage to lung tissue via the emission of alpha particles, which are particles that radiate from decaying radon.[3] These particles cause cellular damage and the resulting conversion to lung cancer.[14]

The pathophysiology of lung cancer in nonsmokers is undetermined. Adenocarcinoma, which is more evident in women, is the prevalent malignancy seen in nonsmokers.[1] Estrogen has been noted as a trigger for lung cancer in nonsmokers (see Sidebar: "Gender Differences in Lung Cancer").[15]

Risk Factors

Tobacco Smoke

Cigarette smoking accounts for approximately 87% of all cases of lung cancer.[16] Tobacco smoke contains more than 4,000 chemicals, and the inhalation of these volatile particles leads to a series of changes in the lung tissue.[11] The presence of carcinogens, inflammation, and the resultant oxidative stress contribute to the development of invasive lung cancer.[13]

A dose-response relationship exists between the risk of acquiring lung cancer and the age at which smoking began, the number of cigarettes smoked daily, and the extent of inhalation.[17] The earlier an individual begins smoking, the greater his risk of lung cancer later in life.[1] Smokers of nonfiltered or hand-rolled cigarettes have a higher lifetime lung cancer risk.[1] A lifelong smoker is 20 to 40 times more likely to have lung cancer than a nonsmoker.[1]

Secondhand Smoke

Of the 4,000 chemicals evident in secondhand smoke, at least 60 are suspected or known to cause cancer.[18] Secondhand smoke is divided into two categories: mainstream smoke, which is the smoke exhaled by the smoker, and sidestream smoke, which is released into the air from the burning cigarette.[17] Nicotine, carcinogens, and other toxins are present in both; however, sidestream smoke appears to have higher concentrations of these carcinogens.[17]

A meta-analysis of 43 research studies indicated that nonsmokers exposed to secondhand smoke were at increased risk for lung cancer.[19] This association was observed in 84% of the studies, with nine studies declaring statistical significance.[19]

Those subjected to secondhand smoke in the home for

Gender Differences in Lung Cancer

Between 1990 and 2003, a 60% increase was seen in the number of lung cancer cases among U.S. women; yet, the number of cases evident in U.S. men remained constant.[15] The mortality rate has increased by 197% in men and by more than 612% in women since 1950.[42] This astonishing increase in women has been called a "contemporary epidemic."[15] In the United States, one-quarter of all adult women are current smokers—these statistics generate questions as to whether women are more susceptible to lung cancer.[15] Given a comparable smoking history, are women more predisposed to carcinomas of the lung than men? Are female nonsmokers more likely to develop lung cancer?

The most extensive population-based research study to date is the National Surveillance, Epidemiology and End Results (SEER) database supported by the National Cancer Institute. Findings from the SEER study revealed that the median age of diagnosis of lung cancer for men and women was 66 years.[42]

The SEER study found that younger women were diagnosed with lung cancer more often than their male counterparts. This suggests an inherent susceptibility to the carcinogens of tobacco smoke.[42] A classic study from 1993 found that given the same 40-pack-year smoking history, the odds ratio was 27.9 in women and 9.6 in men regarding probability of developing lung cancer.[43] In those who never smoked, women are 2.5 times more likely than men to get lung cancer.[44]

The Estrogen Effect

Endogenous estrogen affects lung cancer etiology by influencing the metabolism of the carcinoma and promoting cellular proliferation.[44] Adenocarcinomas, common among women with lung cancer, typically exhibit more estrogen receptors than other types of tumors.[44]

Estrogen receptors are found in healthy lung tissue and in lung carcinomas.[12] Estrogen may function as a carcinogen by forming DNA adducts that result in p53 mutations, or it may indirectly activate growth factors by causing cellular division and proliferation.[12] Women have higher levels of DNA adducts than men, which make them more likely to experience p53 mutations.[12] It may also induce the CYP1A1 gene and subsequently increase the metabolism of the carcinogens.[44]

Exogenous estrogen, present in estrogen replacement therapy (ERT), could also increase the risk of lung cancer. One study found that ERT was positively correlated with adenocarcinoma of the lung with an odds ratio of 1.7.[45] A relationship between smoking, ERT, and the development of adenocarcinoma was established with a large odds ratio of 32.4[45]; however, Kreuzer et al. found that women who were prescribed ERT were at a lower risk for developing the disease.[46] The Kreuzer study, however, did not consider the amount of tobacco exposure; subjects were identified as "ever smokers" or "never smokers."[44]

30 years or more are at a 20% to 30% increased risk of developing lung cancer.[17,18] Nonsmokers exposed to secondhand smoke in a work environment have a 16% to 19% increased risk.[17]

Exposure to secondhand smoke before 18 years of age may be correlated with increased risk; early exposure may potentiate the effects of exposure to secondhand smoke in adulthood.[20,21] Childhood exposure to passive smoke was associated with a 1.8-fold increased risk of developing lung cancer.[21] This study also found that children may be more susceptible to the effects of secondhand smoke than adults. Children have an increased ventilation rate when compared with adults, and inhale greater amounts of secondhand smoke.[22] A smaller case-controlled study of 58 nonsmokers with lung cancer found an association between childhood exposure to tobacco smoke and the development of lung cancer in adulthood (95% confidence interval, odds ratio 3.9%).[23] However, a meta-analysis of 11 studies on lung cancer development in adulthood and childhood exposure to tobacco smoke did not find an association.[24] A definitive association between childhood exposure and the development of lung cancer has yet to be resolved.

Environmental and Occupational Exposure

According to the U.S. Environmental Protection Agency, exposure to indoor radon, a naturally occurring gas formed by the decay of radium 226, is the second major risk factor for lung cancer.[14,25] It is found in the soil beneath homes and buildings and diffuses into the air via foundation cracks, insulation gaps, drains, pipes, or walls.[26]

High levels of inhaled radon have been associated with the development of lung cancer, and 12% of all lung cancer deaths are caused by radon exposure.[3] It is estimated to be present at unsafe levels in one out of 15 homes.[26] Residing in a radon-contaminated home for many years can almost triple the risk of lung cancer development.[27]

Occupational exposure to carcinogens, such as asbestos, accounts for 5% of lung cancer cases in the United States.[3] Other environmental risk factors include exposure to chromium, nickel, silica, cadmium, and beryllium.[3] Inorganic arsenic consumption via contaminated drinking water has been associated with lung cancer.[28] Exposure to radon, asbestos, and arsenic each has a synergistic effect with smoking cigarettes and significantly increases the risk of lung cancer.[1]

Wood smoke contains similar carcinogens as found in tobacco smoke.[29] In a study of 62 individuals diagnosed with lung cancer, exposure to wood smoke was correlated with the development of lung neoplasm.[29] Some 38.7% of patients with lung cancer were nonsmokers who had a history of continuous exposure to wood smoke for at least 10 years.[29]

A past medical history of lung inflammation or injury

is another risk factor. Tuberculosis and pneumonia may scar lung tissue, increasing the odds for the development of adenocarcinoma.[27] Childhood pneumonia, chronic bronchitis, asthma, and chronic obstructive pulmonary disease have been correlated with increased risk of lung cancer, especially in nonsmoking women.[30]

Radiation therapy to the chest may increase the chance for lung cancer if patients are smokers.[27] For example, those who have received radiation therapy to treat Hodgkin's disease or breast cancer are at increased risk for developing lung cancer. Smokers who receive radiation therapy to the chest to treat other cancers must be educated about the risk for lung cancer development and should be referred to smoking cessation programs.

Presenting Signs and Symptoms

Ten percent of lung cancers are asymptomatic, although the majority will present with symptoms in the primary care setting.[31] Specific presentation of symptoms depends on tumor size, location, airway compromise, the presence of metastasis, and systemic involvement.[7] Certain indicators are also present in smokers who do not have lung cancer or among those suffering from a benign upper respiratory infection.

The chief complaint in patients with lung cancer is a persistent cough.[7] Yet, cough is a common complaint in smokers who do not have lung cancer or as an adverse effect of certain medications. The NP should investigate a complaint of cough in a chronic smoker through a detailed history. Any cough that lasts for several months or changes in nature is a red flag for bronchogenic carcinoma.[32] Hemoptysis is often a mild occurrence; frequently, hemoptysis and enlarged supraclavicular lymph nodes accompany a persistent cough.[14,32]

Ten percent of lung cancers are asymptomatic, although the majority will present with symptoms in the primary care setting.

Patients may report constant, dull, poorly localized chest pain.[4] Pain might be pleuritic if the tumor involves the pleura or if a pleural effusion is present.[14] Shoulder pain, in addition to chest pain, is associated with a worse prognosis as the cancer may have metastasized.[31]

Dyspnea is often gradual in onset.[32] Lung disease typically presents with dyspnea on exertion, with rapid, shallow respirations and no easing with position changes.[32] Other symptoms that often accompany dyspnea include wheezing, stridor, respiratory tract infections, and pneumonia.[31] An airway obstruction by a lung tumor could be a possible source of pneumonia.[14]

At diagnosis, weight loss, nausea, vomiting, anorexia, weakness, fatigue, and alterations in taste perception may be evident.[33] As a cluster, these symptoms have high internal validity in describing initial symptomatology of lung cancer patients.[33]

Depending on the tumor location or rate of metastasis, patients might also present with hoarseness and dysphagia.[7] Clubbing of the fingernails can be seen with any form of lung cancer, although it is rarely seen in SCLC.[4]

Metastatic Disease

Lung cancer that has metastasized will present in a different manner. The most likely sites for distant spread include the liver, adrenal glands, bones, and brain.[14] Liver metastasis could present as jaundice and abdominal pain.[14] A patient with metastasis to the brain might report headaches, seizures, or alterations in mental capacity.[14] Bone involvement may cause generalized, extreme pain.[14] Night sweats and fever are also suggestive of systemic disease.[34] The constitutional symptoms of weight loss and fatigue suggest metastasis and should heighten level of suspicion.[14]

Lung Cancer Screening

Currently, no mass screening guidelines are recommended for early detection of lung cancer. The USPSTF reported there is insufficient evidence in favor of or against the use of tools for the detection of lung cancer in asymptomatic patients. The American Cancer Society also does not advocate screening for at-risk individuals.[16] Providers should inform patients of at-risk status, discuss advantages and disadvantages of lung cancer screening, and encourage patients to participate in clinical trials to establish efficacy.[35]

There are several reasons why chest X-ray, spiral CT, and sputum analysis are not recommended. Chest X-rays expose patients to a small amount of radiation and do not detect masses smaller than 1 cm.[36] The specificity of chest X-rays was estimated to be 89%, while the sensitivity was 50%.[36]

Mahadevia et al.[47] found that CT was not cost-effective or sufficiently beneficial. Barriers include patient noncompliance, extreme follow-up testing or medical procedures caused by false-positive results, substandard quality of life following diagnosis, and overdiagnosis bias. A CT scan uses approximately 15 times the amount of radiation found in a chest X-ray.[36] Benign lung nodules are frequently de-

Lung Health Assessment Questionnaire

The following assessment form has been given to you to determine if you have any known risk factors for, and/or symptoms suggestive of, the development of lung cancer. Please take a few moments to complete this questionnaire.

Smoke Exposure

- Do you currently smoke cigarettes?
  ❍ Yes ❍ No
  If yes, how many packs per day?
  _____
- Do you inhale when you smoke?
  ❍ Yes ❍ No
- At what age did you begin smoking?_____
- Do you smoke nonfiltered or hand-rolled cigarettes?
  ❍ Yes ❍ No
- If you no longer smoke, at what age did you quit?_____
- Do you currently smoke cigars?
  ❍ Yes ❍ No
- Do you currently smoke a pipe?
  ❍ Yes ❍ No
- Do you have a history of exposure to wood smoke?
  ❍ Yes ❍ No

Passive Smoke Exposure

- Do you live with someone who smokes?
  ❍ Yes ❍ No
  If yes, for how many total years?
  _____
- Were you exposed to cigarette smoke as a child?
  ❍ Yes ❍ No
  If yes, for how many total years?
  _____
- Are you exposed to cigarette smoke at work?
  ❍ Yes ❍ No
  If yes, for how many total years?
  _____

Environmental Exposure

- Do you have any known exposure to radon?
  ❍ Yes ❍ No
- Do you have any known exposure to asbestos?
  ❍ Yes ❍ No

Occupational Exposure

- Do you work, or have you worked in the past, in any of the following job settings:

  Underground mines
  ❍ Yes ❍ No

  Asbestos textile factories
  ❍ Yes ❍ No

  Hot smelting plants
  ❍ Yes ❍ No

  Vineyards
  ❍ Yes ❍ No

  Fur companies
  ❍ Yes ❍ No

  Cadmium battery factories
  ❍ Yes ❍ No

  Roofing
  ❍ Yes ❍ No

  Chimney sweeping
  ❍ Yes ❍ No

  Road paving
  ❍ Yes ❍ No

  Exposure to diesel engine fumes
  ❍ Yes ❍ No

  Aluminum manufacturing
  ❍ Yes ❍ No

  Coke production
  ❍ Yes ❍ No

  Bartender or restaurant server
  ❍ Yes ❍ No

Family History

- Do you have a first-degree relative with cancer?
  ❍ Yes ❍ No
  If yes, what type of cancer?
  _____

Past Medical History

- Do you have a history of any of the following:

  Childhood pneumonia?
  ❍ Yes ❍ No

  Tuberculosis?
  ❍ Yes ❍ No

  Chronic bronchitis?
  ❍ Yes ❍ No

  Chronic obstructive pulmonary disease?
  ❍ Yes ❍ No

  Asthma?
  ❍ Yes ❍ No

- Have you ever been diagnosed with cancer?
  ❍ Yes ❍ No
  If so, what type of cancer?
  _____
- Have you had radiation therapy to your chest or back?
  ❍ Yes ❍ No

Lung Symptoms

Please check any of the following symptoms that you have experienced in the last 12 months:

- ❍ Hoarseness
- ❍ Nagging cough
- ❍ Changes in your pattern of cough
- ❍ Cough that produces blood-tinged or rust-colored sputum
- ❍ Repeated episodes of pneumonia or bronchitis
- ❍ Pain in your chest, shoulder, or arm
- ❍ Shortness of breath or difficulty breathing
- ❍ Wheezing
- ❍ Swelling of your face or arms
- ❍ Fatigue
- ❍ Weakness
- ❍ Change in taste
- ❍ Loss of appetite
- ❍ Difficulty eating or swallowing
- ❍ Loss of weight (without trying to lose weight)
  - If yes to the above, how much weight have you lost?_____
- ❍ Night sweats
- ❍ Pain in your bones

tected by CT scanning and contribute to a high rate of false-positives, patient anxiety, and unnecessary invasive procedures that could lead to death.[37]

If an irregularity is detected through the use of sputum cytology, additional screening tools are needed for a definitive diagnosis.[36]

Effective Screening Tools

The search for effective screening tools is ongoing. One promising method analyzes buccal mucosal scrapings. The nuclei of cells were obtained from scrapings of 150 confirmed lung cancer cases and 990 high-risk negative cases. These were evaluated for early changes in DNA; automated method yielded 66% sensitivity and 70% specificity, and may prove useful in determining which patients should undergo CT scan. This approach is fast and inexpensive, not only for those at high risk for lung cancer, but for the mainstream population as well.[38]

The NCI is conducting an immense randomized controlled trial, the National Lung Screening Trial, to examine the value of chest X-ray and spiral CT in early detection. More than 50,000 smokers and previous heavy smokers in more than 30 locations have been enrolled.[40] Subjects are randomized to receive an annual chest X-ray or CT scan for 3 consecutive years.[36] Results comparing the two study arms are expected in 2009.[40]

Patient Education

Nurse practitioners have the ability to influence the welfare of patients by encouraging smoking cessation.[40] The Agency for Health Research and Quality has delineated guidelines for the promotion of smoking cessation and suggests the "Five A's":[41]

- Ask about the use of tobacco
- Advise smokers to quit
- Assess patients' motivation levels regarding quitting
- Assist patients in devising a cessation plan
- Arrange for follow-up after the cessation date has been set

Discussion about the advantages of smoking cessation requires only minutes, yet the benefits are invaluable.[41] But this five-step plan is only the beginning—once the patient decides to stop smoking, a thorough treatment plan must address nicotine addiction and support continued behavior modification.

Encourage absolute cessation over smoking a low-yield cigarette. Individuals often compensate for decreased levels of nicotine in low-yield cigarettes by smoking more, inhaling deeper, or taking additional puffs, which increase exposure to carcinogens.[1]

Patients should avoid secondhand smoke and avoid exposing children to the effects of passive tobacco smoke. Nurse practitioners are encouraged to advocate the rights of nonsmokers through legislation aimed at decreasing passive smoke exposure in the occupational or social settings.

Secondary Prevention

In the absence of mass screening guidelines, it is imperative that the NP recognize clinical signs of the disease and its risk factors. A Lung Health Assessment Questionnaire could ascertain patients at high risk for the development of lung cancer or who have symptoms suggestive of this disease (see Figure: "Lung Health Assessment Questionnaire").

Monitor patients susceptible to occupational risk factors. In particular, those who work in underground mines, asbestos textile factories, hot smelting plants, vineyards, fur companies, and cadmium battery factories.[28] Employees exposed to polycyclic aromatic hydrocarbons in the form of roofing, chimney sweeping, road paving, diesel engine fumes, aluminum manufacturing, and coke production are also at increased risk for lung cancer.[28] Bartenders and restaurant servers are at risk for lung cancer caused by extensive passive smoke exposure.[22] NP

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AUTHOR DISCLOSURE

The author has disclosed that she has no significant relationship or financial relations with any commercial companies mentioned in this continuing education activity.

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