Epidemiology of Lung Cancer in Women: Risk Factors, Survival, and Screening

Seth Kligerman[1]
Charles White

OBJECTIVE. Lung cancer remains the leading cause of cancer mortality in both men and women. Tobacco use causes the vast majority of lung cancer in women but does not explain all cases, because about one in five women who develop lung cancer have never smoked.

CONCLUSION. Environmental exposures, genetic predisposition, hormonal factors, and viral infection may all play a role in lung cancer in women. A better understanding may provide an avenue to more effective screening, diagnosis, and therapy.

Lung cancer has been the leading cause of malignancy in women since 1987, when it surpassed breast cancer. In 2010, it was estimated that over 116,000 men and 105,000 women would be diagnosed with lung cancer in the United States [1]. Lung cancer is responsible for over 71,000 deaths per year in women. This number exceeds the mortality associated with both breast cancer (39,840 deaths) and colon cancer (24,790 deaths) combined, which are the second and third leading causes of cancer-related mortality in women, respectively [1]. Age-adjusted lung cancer incidence in women has more than doubled since 1975, while mortality has increased over 600% since 1950 [2]. It was not until 2003 that lung cancer mortality in women decreased for the first time since the 1930s, a trend that began among male smokers in the 1980s [3] (Fig. 1). There are multiple explanations for the dramatic increase in lung cancer mortality, but the primary cause remains tobacco, which rapidly gained social acceptance among women after World War II [4]. However, environmental exposures, genetic mutations, hormonal factors, and certain infections have also been implicated in the development of lung cancer in women and may help to explain why approximately 20% of women who develop lung cancer have never smoked [5].

Tobacco Use

Cigarette smoking remains the most common cause of lung cancer among both men and women, with 85–90% of all patients with lung cancer admitting to a current or prior smoking history [6]. However, tobacco use is implicated not only in the development of lung cancer, but also is considered a causative factor in the development of cancers of the oral cavity, pharynx, larynx, esophagus, stomach, bladder, pancreas, liver, kidney, and cervix. Overall, tobacco is responsible for approximately 30% of all cancer deaths in the United States [4].

Although male smokers still outnumber female smokers, the sex gap has continued to narrow in the United States since World War II. Today, approximately 23.1% of men and 18.3% of women in the United States are current cigarette smokers [7]. Although these numbers remain high, they represent a substantial decrease from 1965, when over one-third of women in the United States smoked cigarettes [8]. This nearly 50% decline is linked in part to the 1964 report by the Surgeon General, which affirmed directly that tobacco use was a cause of lung cancer and that smokers had a 70% increase in mortality compared with nonsmokers [9]. Most women start smoking during or before high school, and in 1999, 36.5% of female students reported using tobacco [10]. More recently, this number has significantly decreased to 18.7% [11]. Although the trend toward decreased smoking is promising, the deleterious long-term effects of smoking have yet to be realized in a large percentage of women because of the lengthy lag time between the onset of smoking and the development of lung cancer.

Smoking remains one of the most important causes of preventable death in the United

Keywords: cigarette smoking, lung cancer, risk factors, screening, women

DOI:10.2214/AJR.10.5412

Received July 26, 2010; accepted after revision October 10, 2010.

[1]Both authors: Department of Diagnostic Radiology and Nuclear Medicine, University of Maryland, 22 S. Greene St., Baltimore, MD 21201. Address correspondence to S. Kligerman (skligerman@umm.edu).

CME
This article is available for CME credit.
See www.arrs.org for more information.

AJR 2011; 196:287–295

0361–803X/11/1962–287

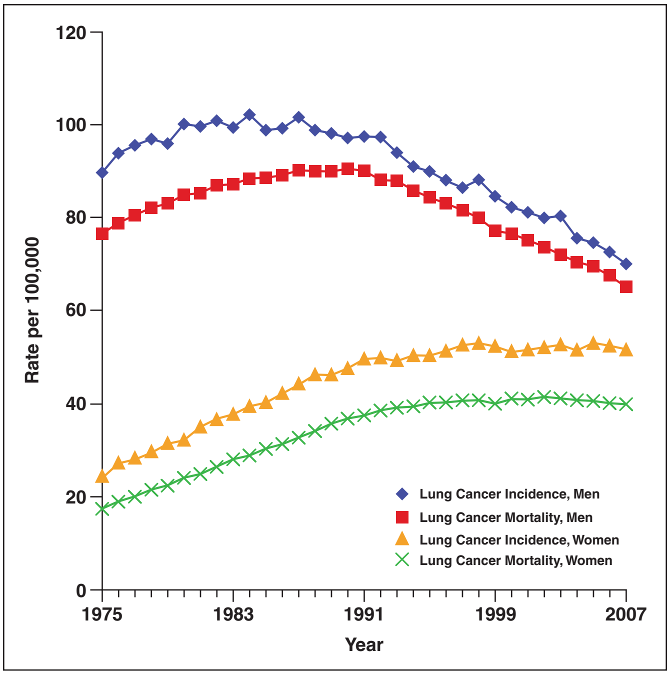


Fig. 1—Age-adjusted lung cancer incidence and mortality in men and women from 1975 to 2007.

States and throughout the world. Second only to high blood pressure, tobacco use is a leading risk for mortality worldwide and causes approximately 5.1 million deaths per year, accounting for 8.7% of all global deaths [12]. Global estimates are that smoking causes 71% of lung cancers, 42% of chronic respiratory diseases, and 10% of cardiovascular diseases. Worldwide, the number of male smokers outnumbers female smokers, given the relatively low percentage of women in poor countries who smoke. However, tobacco is responsible for 6% of female deaths, and the rate of tobacco use among young women in low-income countries has soared in recent years, suggesting that this percentage will only increase [13–16]. Despite this trend, smoking-related mortality currently affects the developed world disproportionately. In high-income countries, such as the United States, tobacco use is directly responsible for 17.9% of all deaths, and only in high-income countries does tobacco use surpass high blood pressure as the leading risk factor for early death [12] (Table 1). In addition to mortality, tobacco use is the leading cause of healthy life-years lost in the high-income countries.

Genetic and Molecular Susceptibility to Carcinogenic Effects of Smoking

Tobacco exposure is well established as the leading cause of lung cancer in both men and women, but there is disagreement among investigators as to whether women who smoke are more likely to develop lung cancer than their male counterparts. In women with a 40 pack-year smoking history, Risch et al. [17] reported an odds ratio of developing lung cancer of 27.9, compared with women nonsmokers. In contrast, the odds ratio for smoking to nonsmoking men was only 9.60. In 1996, Zang and Wynder [18] showed a significantly increased risk (odds ratio, 1.7) of lung cancer in women compared with men across all levels of cigarette usage. The International Early Lung Cancer Action Program Investigators [19] reported similar findings in 2006, showing an odds ratio of 1.9 in the prevalence of lung cancer in women compared with men with comparable smoking histories. However, not all researchers agree on this increased susceptibility. Bain et al. [20] evaluated lung cancer incidence in over 80,000 men and women smokers and reported no significant difference in lung cancer risk between men and women. A smaller study reported an odds ratio of 19.7 in men with a long smoking history compared with nonsmoking men and an odds ratio of 15 among women [21].

The reasons for this potential increased risk in women smokers have been widely studied, and various genetic and molecular differences between men and women have been recognized. Women have an increased expression of the CYP1A1 gene, which codes for an enzyme that metabolizes polycyclic hydrocarbons in tobacco smoke [22, 23]. This increased expression leads to increased formation of DNA-forming adducts, which are pieces of DNA chemically bound to a carcinogenic compound, and may represent the first stage in carcinogenesis [24]. In addition, the glutathione S-transferase M1 enzyme competes with enzymes encoded by the CYP1A1 gene, inhibiting the formation of reactive oxygen species and helping to convert toxic intermediates into inactive compounds. This enzyme is absent in 40–60% of the population and its absence may represent an underlying susceptibility to lung cancer development [25]. Although this enzyme is often absent in both men and women, Tang et al. [26] looked at the development of lung cancer in smokers with the glutathione *S*-transferase M1 mutation and reported an odds ratio in female smokers that was twice that of comparable male smokers with the same mutation. This finding suggests that women with this mutation are at greater risk for developing lung cancer.

Mutations in the tumor protein 53 tumor suppressor gene occur in 50% of patients with non-small-cell lung cancer and 70% of patients with small-cell lung cancer [27]. Specific transversions in the tumor suppressor gene p53 were found in 36% of female smokers with lung cancer, compared with 27% of male smokers with lung cancer [27]. This same mutation in nonsmokers with lung cancer was present in only 13% of women but still present in 31% of men, suggesting a higher degree of tobacco-related molecular damage in women smokers.

Gastrin-releasing peptide receptor is a gene located on the X chromosome and escapes X-chromosome inactivation in women [22]. Tobacco use is associated with activation of this gene, which leads to proliferation of bronchial cells and has been linked to the development of lung cancer. The highest frequency of expression of this gene is seen in smoking women, followed by nonsmoking women, smoking men, and nonsmoking men, respectively [28]. Mutations in the K-ras oncogene are also linked to the development of adenocarcinomas, predominantly in smokers. There is debate as to whether this mutation occurs more frequently in smoking women, with the majority of studies showing no difference between the sexes [29–31].

Additional Risk Factors

Radon

Although smoking causes most cases of lung cancer in both men and women, it is not the sole cause. Twenty-two percent of women

TABLE 1: Ten Leading Worldwide Risk Factors for Death, by Income Group

Rank of Risk Factor	World Total	High-Income Countries	Middle-Income Countries	Low-Income Countries
1	High blood pressure (12.8)	**Tobacco use (17.9)**	High blood pressure (17.2)	Childhood underweight (7.8)
2	**Tobacco use (8.7)**	High blood pressure (16.8)	**Tobacco use (10.8)**	High blood pressure (7.5)
3	High blood glucose (5.8)	Overweight and obesity (8.4)	Overweight and obesity (6.7)	Unsafe sex (6.6)
4	Physical inactivity (5.5)	Physical inactivity (7.7)	Physical inactivity (6.6)	Unsafe water, sanitation (6.1)
5	Overweight and obesity (4.8)	High blood glucose (7)	Alcohol use (6.4)	High blood glucose (4.9)
6	High cholesterol (4.5)	High cholesterol (5.8)	High blood glucose (6.3)	Indoor smoke from solid fuels (4.8)
7	Unsafe sex (4)	Poor diet (2.5)	High cholesterol (5.2)	**Tobacco use (3.9)**
8	Alcohol use (3.8)	Urban outdoor air pollution (2.5)	Poor diet (3.9)	Physical inactivity (3.8)
9	Childhood underweight (3.8)	Alcohol use (1.6)	Indoor smoke from solid fuels (2.8)	Suboptimal breastfeeding (3.7)
10	Indoor smoke from solid fuels (3.3)	Occupational risks (1.1)	Urban outdoor air pollution (2.8)	High cholesterol (3.4)

Note—Countries are grouped by gross national income per capita per year, with low income equal to $825 or less, middle income equal to $826–$10,065, and high income equal to $10,066 or more. Data in parentheses denote percentage of preventable deaths. Boldface type highlights the ranking of tobacco as a cause of preventable death relative to other risk factors.

and 2.9% of men in Western countries who develop lung cancer are lifetime nonsmokers, and female nonsmokers are more likely to develop lung cancer than nonsmoking men [5, 32, 33]. Various environmental and occupational factors have been directly linked to the development of lung cancer. Exposure to ionizing radiation from radon is the second leading cause of lung cancer mortality in the United States. The Environmental Protection Agency calculates that radon is responsible for approximately 21,000 lung cancer deaths per year, and 2,900 of these deaths occur in patients who were never smokers [34]. In a risk analysis study that assessed 413 women with lung cancer and prolonged radon exposure in Iowa, the risk of development of lung cancer was directly proportional to the amount of radon exposure [35]. Moreover, smoking and radon exposure are believed to be synergistic in lung cancer development.

Secondhand Smoke and Environmental Exposures

The health risks of secondhand smoke exposure have been widely reported and are associated with an increased incidence of lung cancer, emphysema, asthma, and upper respiratory tract infections. It is estimated that approximately 3,400 people in the United States die each year from lung cancer due to secondhand smoke exposure, making it the third leading cause of lung cancer [16]. Globally, women and children constitute the majority of those exposed to secondhand smoke [36]. In a large meta-analysis by Hackshaw et al. [37], nonsmoking women who live with smoking men were shown to have a 24% increased risk for the development of lung cancer compared with nonsmoking women who were not exposed to secondhand smoke. Additionally, lung cancer development was directly associated with both the time course of exposure and the amount of tobacco smoked by the spouse. Exposure to asbestos, arsenic, cadmium, nickel, metal dusts, polycyclic aromatic hydrocarbons, and vinyl chloride are also implicated in the development of lung cancer but account for only a small number of cases among women in the United States.

Smoking is relatively uncommon among women in developing countries in Asia, but lung cancer is not rare because many women are exposed to environmental factors that are associated with lung cancer [38]. Multiple studies have suggested that the prolonged inhalation of cooking fumes from high temperature oils in poorly ventilated rooms is a cause of the high rate of lung cancer in nonsmoking women in China and Taiwan [39–41]. Inhalation of fumes from cooking with hot oils leads to increased levels of acrolein, crotonaldehyde, and benzene, which are all potent carcinogens [42]. The indoor burning of coal and biomass in poorly ventilated areas for both heating and cooking has also been linked with the development of lung cancer in nonsmoking women in low-income countries [43].

Genetic and Molecular Susceptibility Not Related to Tobacco Use

Patients with a family history of lung cancer have an increased incidence of lung cancer, even in nonsmoking families [44, 45]. It has been shown that nonsmoking women in nonsmoking families with a history of lung cancer have a greater risk in the development of lung cancer compared with nonsmoking men with a similar family history [33]. One study performed on sets of twins with lung cancer showed a similar prevalence of lung cancer in male dizygotic twins compared with monozygotic twins, favoring an environmental link, such as smoking, over a genetic cause. However, 75% of the sets of female twins with lung cancer evaluated were monozygotic, suggesting a genetic pattern [46].

One potential cause for this increased susceptibility lies within epidermal growth factor receptor (EGFR). Although mutations in tumor protein 53, gastrin-releasing peptide receptor, and K-ras are seen predominantly in smokers, lung cancers with mutations in EGFR occur almost exclusively in nonsmokers. This mutation rarely occurs in squamous or large-cell carcinomas but is found in 10% of adenocarcinomas [47]. Within the adenocarcinoma subgroup, this mutation is present in only 6% of solid tumors but in 26% of bronchioloalveolar carcinomas. In addition, it is significantly more common in women and thus may help to explain why women, especially nonsmoking women, are two to four times as likely to develop the bronchioloalveolar subtype of adenocarcinoma compared with nonsmoking men [23, 47]. It is interesting to note that mutations in EGFR and K-ras are mutually exclusive, because both of these genes are on the same locus.

On a molecular level, impaired DNA repair capacity (DRC) has been explored as a possible cause in the development of many different types of cancer. DRC, which can be quantified through various assays, is decreased in women with lung cancer compared with both men with lung cancer and healthy female control subjects [48, 49]. These decreased levels of DRC are very similar in both female smokers and nonsmokers with lung cancer, suggesting that this factor is independent of the carcinogenic effects of tobacco [48–50].

Hormonal Factors

Hormonal factors have been widely studied as a possible factor in the development of lung cancer in both smoking and nonsmoking women. These investigations have shown conflicting results. Although some authors have suggested that there is a potential protective effect of increased or prolonged estrogen exposure, others have found an increase in lung cancer related to estrogen exposure [51–53]. Another study found no difference between length and degree of estrogen exposure and the development of lung cancer but suggested that female smokers with lung cancer who were receiving hormone replacement therapy had increased mortality compared with nonsmokers with lung cancer who were receiving hormone replacement therapy [54]. The estrogen receptors (ERs) ERα and ERβ have also been implicated as a possible link to lung cancer in women. ERβ, which is found in both healthy lung and lung tumors, is expressed to a similar extent in both men and women. In contrast, ERα, which is not normally present in lung tissue, can be overexpressed in adenocarcinoma of the lung in women [55]. However, the rates of expression vary widely, ranging from 7% to 97%, and some studies have found similar overexpression in both men and women [23, 53]. In an in vitro study evaluating both male and female adenocarcinoma cell lines, ER expression was similar between the sexes. However, although estradiol had no effect on the adenocarcinoma cells from the male lines, estradiol stimulated the growth of adenocarcinoma cells in the female lines [53]. Such a result points toward varying biologic responses of the same cell type between men and women and may explain some of the differences between lung cancer development and growth between the sexes.

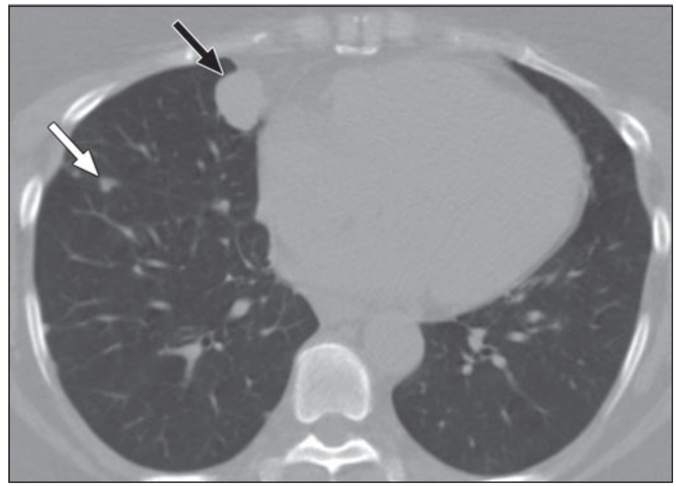


Fig. 2—52-year-old nonsmoking woman. Axial CT image shows rounded 2.2-cm soft-tissue nodule in right middle lobe (*black arrow*) with associated fissural nodules (*white arrow*). Biopsy of nodule showed adenocarcinoma, and thoracoscopy confirmed pleural metastases. Adenocarcinoma is most common type of lung cancer in both women and men in United States.

Infections

Certain infections have also been suggested as a cause of lung cancer. Human papillomavirus (HPV) is widely recognized as a leading cause of cervical cancer, and some studies point to an increased incidence of HPV in lung tumors. A large meta-analysis reported a 24.5% worldwide incidence of HPV in lung cancer [56]. The rates of HPV-positive lung cancer cases were highest in Asian nations, where rates exceed 78% in some studies. A 2001 study from Taiwan showed a high rate of HPV-positive lung cancers in nonsmoking women, five times that in nonsmoking men and significantly higher than in nonsmoking women in the control arm [57]. HPV-positive tumors in this study were of various cell types and, contrary to most prior studies, were more likely to be adenocarcinoma of the lung than squamous cell carcinoma. These findings suggest a strong link between the development of lung cancer in nonsmoking women and HPV infection in Asia. However, in the United States, HPV infection rates in tumors have been much lower, ranging from 0% to 12.7%, and in most cases, the HPV-positive tumors were squamous cell carcinoma, not adenocarcinoma [56, 58].

Histology

Because of the potential environmental, genetic, molecular, hormonal, and infectious factors that affect the development of lung cancer in women, it is expected that lung cancer histology rates would vary between the two sexes. Adenocarcinoma is now the dominant cell type in both men and women in the United States [3, 59] (Fig. 2 and Table 2). However, both women smokers and nonsmokers have a greater chance of developing a lung adenocarcinoma compared with their male counterparts. Women, especially nonsmoking women, are two to four times as likely to develop the bronchioloalveolar subtype of adenocarcinoma compared with men [6] (Fig. 3). Currently, adenocarcinoma of the lung constitutes 41.4% of lung cancers in women and 34.1% of lung cancers in men, whereas squamous cell

TABLE 2: Five-Year Relative Survival Rate Percentages, by Sex, Histologic Diagnosis, and Stage

	Total Percentage of Cases		Total[a]		Stage I[a]		Stage II[a]		Stage III[a]		Stage IV[a]	
Histologic Diagnosis	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women
Adenocarcinoma	34.1	41.4	17.1	23.7	59.2	67.7	30.8	37.8	9.1	11.4	1.9	2.5
Squamous cell carcinoma	23.3	15.6	16.3	18	50.5	52.8	35.3	34.7	10	9.8	1.6	2.6
Large-cell carcinoma	3.5	3	11.4	13.1	49.4	51.1	32.9	34.6	9.6	9.4	1.6	1.9
Small-cell carcinoma	13	14.8	5.1	7.1	29.4	33.4	18.9	19.7	7.9	9	1.2	1.8
Other	26.1	25.2	11.7	18.4	46.6	46.7	32	35.1	7.6	8.9	1.4	1.9

[a]Data are 5-year relative survival rate (%).

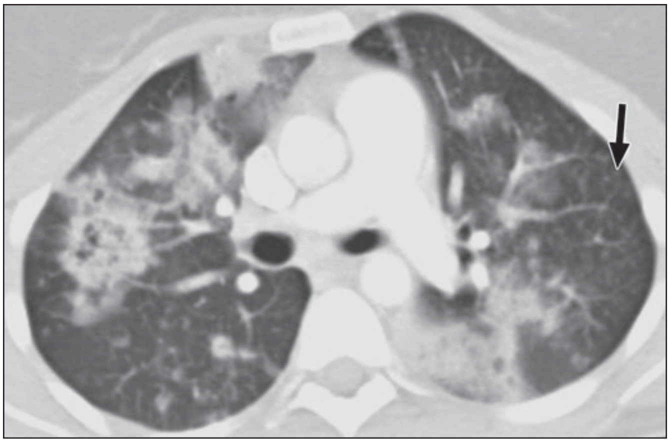


Fig. 3—40-year-old nonsmoking woman. Axial CT image shows multiple areas of consolidation with numerous centrilobular nodules (*arrow*). Patient was treated for pneumonia but areas of consolidation and nodules persisted. Bronchoscopy revealed bronchioloalveolar carcinoma, which is two to four times as common in women as men.

carcinoma accounts for 15.6% and 23.3% of lung cancer cases in women and men, respectively [3] (Fig. 4). The incidence of small-cell carcinoma, which is highly associated with smoking, is similar between the two sexes, accounting for 14.8% and 13% of cases among women and men, respectively [3] (Fig. 5 and Table 2).

Survival

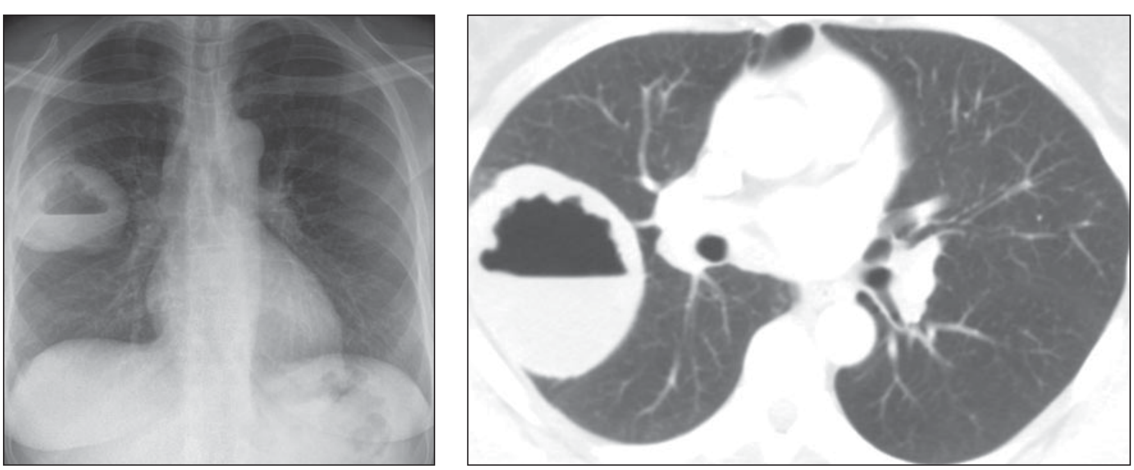
One distinct advantage that women have regarding lung cancer prognosis is improved survival compared with men. Although survival continues to decrease in both sexes as overall stage increases, women have improved 5-year relative survival rates across all ages with comparable stages [59] (Table 3). Women also have improved 5-year relative survival rates across nearly all stages with similar histologies, a benefit that is most pronounced in those with adenocarcinoma [3, 59] (Table 2). This improved survival is not the result of an age bias because the median age at diagnosis, which is similar in both smokers and nonsmokers alike, is 70 years in men and 71 years in women [3, 33]. In addition, because relative survival rates are adjusted for normal life expectancy, the difference between the sexes cannot be explained by the increased average life expectancy of women (80.2 years) compared with men (75.1 years) [60]. The stages at presentation are nearly identical between men and women, so a stage bias cannot explain the differences in survival [3, 59]. Nonsmokers have improved lung cancer survival compared with smokers [61], and the increased incidence of nonsmoking women with lung cancer could explain some of this difference in survival. However, men continue to have a higher death rate than women do, in both smoking and nonsmoking populations alike [43].

One explanation for the improved survival is that many of these studies did not differentiate between adenocarcinomas and the bronchioloalveolar subtype of adenocarcinoma, which is much more common among women. The improved survival in those with the bronchioloalveolar subtype may play a part in the large gap seen in survival between men and women with adenocarcinoma [62]. This reason alone cannot explain the difference because women have improved survival even for tumors that are highly associated with smoking, such as squamous cell carcinoma and small-cell carcinoma [59] (Table 2). Overall, it is unclear why such a discrepancy exists but it again suggests that lung cancer is not a biologically identical disease in men and women. Even with this benefit, lung cancer survival remains dismal because most cancers are discovered after symptoms arise and patients commonly have advanced disease. Today, the 5-year survival rate in women with lung cancer is 19%, only slightly better than the 15.9% 5-year survival rate in women from 1975 to 1977 [3]. Given the incidence and mortality associated with lung cancer, research has been directed toward the search for a powerful screening tool similar to mammography for breast cancer and colonoscopy for colon cancer.

Screening

Numerous national and international lung cancer screening trials have been reported or are currently under way. The utility of radiography and sputum cytology has been examined but has yet to show a clinical benefit [63]. In the case of radiography, less than optimistic results may be due to the limited ability of radiography to detect small subtle lung cancers. Newer technologies, such as dual-energy radiography and bone removal software, both of which allow subtraction imaging, as well as computer-aided detection, have improved detection rates of small lung nodules but have not been studied in the setting of lung cancer screening [64, 65].

Most current screening trials have used low-dose CT to evaluate for lung cancer. Al-



A B

Fig. 4—47-year-old woman who has smoked one pack of cigarettes per day since she was 7 years old.
A, Posteroanterior chest radiograph shows large cavitary mass in right midlung.
B, Axial CT shows air-fluid level in thick-walled right upper lobe cavitary mass. Biopsy confirmed squamous cell carcinoma, which is second most common lung cancer among women.

TABLE 3: Age Distribution Percentage at Time of Diagnosis and Associated 5-Year Relative Survival Rate Percentage

Age at Diagnosis (y)	Total				Stage I				Stage II				Stage III				Stage IV			
	Men		Women		Men		Women		Men		Women		Men		Women		Men		Women	
	Age Distribution	Relative Survival Rate	Age Distribution	Relative Survival Rate	Age Distribution	Relative Survival Rate	Age Distribution	Relative Survival Rate	Age Distribution	Relative Survival Rate	Age Distribution	Relative Survival Rate	Age Distribution	Relative Survival Rate	Age Distribution	Relative Survival Rate	Age Distribution	Relative Survival Rate	Age Distribution	Relative Survival Rate
< 45	2.9	22.8	3.4	26.2	1.6	67.1	2.1	71.9	2.1	47.6	2.6	58.5	2.8	14.7	3	14.9	3.5	2.4	3.9	2.5
45–54	10.8	15.1	10.8	23.5	7.9	62.6	9.5	69.3	12.3	43	12.9	41.3	10.8	12.4	10.2	14.8	13	1.8	12.8	3.3
55–64	25.5	15.1	23.6	21.3	24.4	58.3	23.5	65.6	27	35.2	27.7	39.1	25.3	10.7	22.5	12.9	28	1.6	25.9	2.3
65–74	36.9	13.4	35.6	18.4	41.7	52.4	39.6	59.7	40.5	27.9	38.2	31.2	36.2	8.1	35.5	9.3	35.6	1.5	34.1	2
≥ 75	23.9	9.8	26.6	12.7	24.4	40.7	25.3	50.3	18.1	21.7	18.6	29.1	24.9	4	28.8	4.8	19.9	0.9	23.3	1.3

Note—All data are percentages.

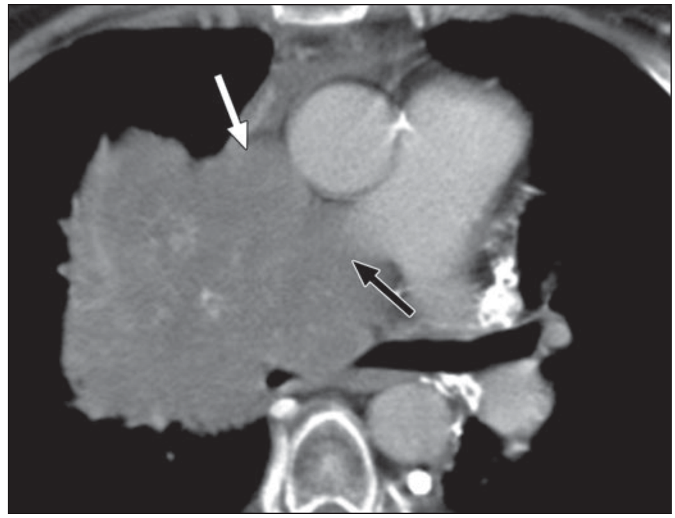


Fig. 5—40-year-old woman who smokes two packs of cigarettes per day. Axial CT image shows very large mass invading mediastinum with obstruction of superior vena cava (*white arrow*) and right pulmonary artery (*black arrow*). Small-cell carcinoma, which is highly associated with smoking, was found on biopsy.

though the number of male participants outnumbered female participants in most studies, large trials performed at the Mayo Clinic and in Japan showed a higher rate of lung cancer detection in women compared with men [66, 67]. Although the Mayo Clinic study only enrolled patients with a smoking history of 20 pack-years or longer, the Japanese study enrolled both smokers and nonsmokers alike. Interestingly, all 12 women in the Japanese trial who had lung cancers detected by CT were lifelong nonsmokers. Although these trials have led to the detection of many early-stage lung cancers in both men and women alike, no published study to date has shown a decrease in late-stage disease compared with a nonscreened population or proof of mortality benefit [66, 68, 69].

One shortcoming of the utilization of CT for lung cancer screening is that false-positive results are common and can lead to added morbidity and mortality by requiring subsequent invasive interventions, including bronchoscopy, percutaneous biopsy, thoracoscopy, and thoracotomy. In the Mayo Clinic CT Screening Trial, false-positive nodule rates were high, affecting 69% of participants [66]. In the National Lung Screening Trial sponsored by the National Cancer Institute, false-positive results were reported in 21% of patients after one screening CT scan and 33% of patients after the second screening CT scan [70]. Although most of these false-positive results could be accurately triaged with further imaging, unnecessary invasive procedures were performed in 7% of patients with a false-positive result. However, it should be noted that this study did not use a standardized protocol for addressing positive incidental findings, which may have contributed to the high rate of invasive procedures. In the future, if lung cancer screening were to be performed on a national scale, it would be imperative to establish a set of standardized guidelines for the workup of incidental findings to help prevent potentially unnecessary interventions.

An additional consideration is the growing concern about ionizing radiation exposure from CT scans, which has been discussed in the medical literature and lay press in the past few years. On the basis of current utilization rates, Brenner and Hall [71] calculated that 1.5–2% of all cancers in the United States are caused by CT. A more recent article estimated that the totality of CT examinations performed in the United States in 2007 would lead to an additional 27,000 cases of cancer [72]. Approximately 6,800 of these additional cancer cases were attributed to CT scans of the chest, and of these, 78% were thought likely to occur in women because of the additional risk of breast cancer as well as the assignment of higher risk coefficients for lung cancer development in women. It is important to note that both articles derived their data from studies performed during very large brief exposures, such as that from atomic bomb survivors, Chernobyl, and patients who underwent therapeutic medical irradiation. No study to date has decisively shown that low-level radiation doses from diagnostic medical irradiation are responsible for the development of cancer. Although the utilization of low-dose CT protocols can help reduce radiation exposure, the dose would still be higher than that received in other screening studies such as mammography.

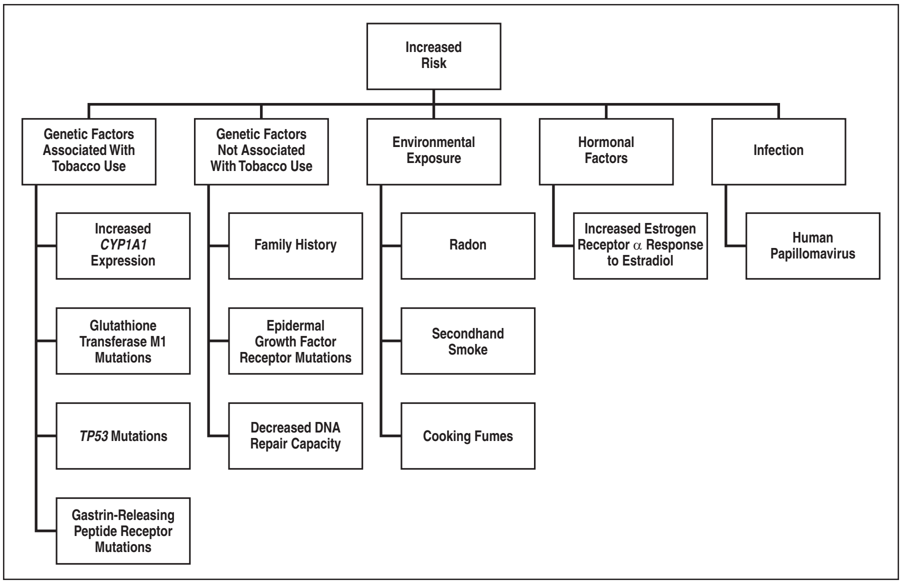


Fig. 6—Summary of potential increased risks for development of lung cancer in women.

Given these shortcomings, the use of low-dose CT is not currently recommended by most national advisory committees. This may soon change as recently released information from the National Lung Screening Trial has stated a 20% mortality benefit in former and current heavy smokers undergoing low-dose screening chest CT compared with those undergoing standard chest radiography [73]. However, it should be recognized that a significant percentage of women who ultimately develop lung cancer may not be screened if CT screening is limited to those with a smoking history. Therefore, if CT screening is adopted at some point in the future, different screening protocols between the sexes may have to be adopted to best account for sex-related differences in the development of lung cancer.

In conclusion, lung cancer remains the leading cause of cancer mortality in both men and women. Tobacco use causes the vast majority of lung cancers in women. Many studies have suggested that women have an increased susceptibility to the carcinogenic effect of tobacco smoke, but smoking does not explain all cases, because about one in five women who develop lung cancer are lifelong nonsmokers. In addition, the incidence of lung cancer in never-smoking women is much higher than that seen in never-smoking men. Environmental exposures, genetic constitution, hormonal factors, and viral infection may each have a role to play in lung cancer development in women (Fig. 6). A better understanding of the particular causes of lung cancer in women may provide an avenue to more effective screening, diagnosis, and therapy.

References

1. American Cancer Society. *2010 Cancer facts and figures.* Atlanta, GA: American Cancer Society, 2010
2. Women and smoking: a report of the Surgeon General. Executive summary. *MMWR Recomm Rep* 2002; 51:i–iv, 1–13
3. Altekruse SF, Kosary CL, Krapcho M, et al., eds. SEER Cancer Statistics Review, 1975–2007. Bethesda, MD: National Cancer Institute. Available at http://seer.cancer.gov/csr/1975_2007. Based on November 2009 SEER data submission. Posted to the SEER Website 2010
4. Jemal A, Thun MJ, Ries LA, et al. Annual report to the nation on the status of cancer, 1975-2005, featuring trends in lung cancer, tobacco use, and tobacco control. *J Natl Cancer Inst* 2008; 100: 1672–1694
5. Siegfried JM. Women and lung cancer: does oestrogen play a role? *Lancet Oncol* 2001; 2:506–513
6. Patel JD, Bach PB, Kris MG. Lung cancer in US women: a contemporary epidemic. *JAMA* 2004; 291:1763–1768
7. Lloyd-Jones D, Adams RJ, Brown TM, et al. American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics—2010 update: a report from the American Heart Association. *Circulation* 2010; 121:e46–e215 [Erratum in *Circulation* 2010; 121:e260]
8. Mackay J, Eriksen MP. *The tobacco atlas.* Geneva, Switzerland: Word Health Organization Press, 2002
9. United States Surgeon General's Advisory Committee on Smoking and Health. *Smoking and health report of the Advisory Committee to the Surgeon General of the Public Health Service.* Washington, DC: U.S. Dept. of Health, Education, and Welfare, Public Health Service, 1964
10. Kann L, Kinchen SA, Williams BI, et al. Youth risk behavior surveillance—United States, 1999. *MMWR CDC Surveill Summ* 2000; 49:1–32
11. Eaton DK, Kann L, Kinchen S, et al. Youth risk behavior surveillance—United States, 2007. *MMWR Surveill Summ* 2008; 57:1–131
12. World Health Organization. *Global health risks: mortality and burden of disease attributable to selected major risks.* Geneva, Switzerland: World Health Organization Press, 2009
13. World Health Organization. *Women and health: today's evidence, tomorrow's agenda.* Geneva, Switzerland: World Health Organization Press, 2009
14. Samet JM, Yoon S-Y, World Health Organization, Johns Hopkins University, and Institute for Global Tobacco Control. *Women and the tobacco epidemic: challenges for the 21st century.* Geneva, Switzerland: World Health Organization Press, 2001
15. World Health Organization. *Sifting the evidence: gender and tobacco control.* Geneva, Switzerland: World Health Organization Press, 2007
16. World Health Organization. *WHO Report on the Global Tobacco Epidemic, 2008.* Geneva, Switzerland: World Health Organization Press, 2008
17. Risch HA, Howe GR, Jain M, Burch JD, Holowaty EJ, Miller AB. Are female smokers at higher risk for lung cancer than male smokers? A case-control analysis by histologic type. *Am J Epidemiol* 1993; 138:281–293
18. Zang EA, Wynder EL. Differences in lung cancer risk between men and women: examination of the evidence. *J Natl Cancer Inst* 1996; 88:183–192
19. Henschke CI, Yip R, Miettinen OS. International Early Lung Cancer Action Program Investigators. Women's susceptibility to tobacco carcinogens and survival after diagnosis of lung cancer. *JAMA* 2006; 296:180–184
20. Bain C, Feskanich D, Speizer FE, et al. Lung cancer rates in men and women with comparable histories of smoking. *J Natl Cancer Inst* 2004; 96: 826–834
21. Osann KE, Anton-Culver H, Kurosaki T, Taylor T. Sex differences in lung-cancer risk associated with cigarette smoking. *Int J Cancer* 1993; 54: 44–48
22. Kirsch-Volders M, Bonassi S, Herceg Z, Hirvonen A, Möller L, Phillips DH. Gender-related differences in response to mutagens and carcinogens. *Mutagenesis* 2010; 25:213–221
23. Patel JD. Lung cancer in women. *J Clin Oncol* 2005; 23:3212–3218

24. Thomas L, Doyle LA, Edelman MJ. Lung cancer in women: emerging differences in epidemiology, biology, and therapy. *Chest* 2005; 128:370–381
25. Novello S, Baldini E. Women and lung cancer. *Ann Oncol* 2006; 17[suppl 2]:ii79–ii82
26. Tang DL, Rundle A, Warburton D, et al. Associations between both genetic and environmental biomarkers and lung cancer: evidence of a greater risk of lung cancer in women smokers. *Carcinogenesis* 1998; 19:1949–1953
27. Toyooka S, Tsuda T, Gazdar AF. The TP53 gene, tobacco exposure, and lung cancer. *Hum Mutat* 2003; 21:229–239
28. Shriver SP, Bourdeau HA, Gubish CT, et al. Sex-specific expression of gastrin-releasing peptide receptor: relationship to smoking history and risk of lung cancer. *J Natl Cancer Inst* 2000; 92:24–33
29. Sartori G, Cavazza A, Sgambato A, et al. EGFR and K-ras mutations along the spectrum of pulmonary epithelial tumors of the lung and elaboration of a combined clinicopathologic and molecular scoring system to predict clinical responsiveness to EGFR inhibitors. *Am J Clin Pathol* 2009; 131:478–489
30. Gazdar AF, Thun MJ. Lung cancer, smoke exposure, and sex. *J Clin Oncol* 2007; 25:469–471
31. Nelson HH, Christiani DC, Mark EJ, Wiencke JK, Wain JC, Kelsey KT. Implications and prognostic value of K-ras mutation for early-stage lung cancer in women. *J Natl Cancer Inst* 1999; 91:2032–2038
32. Meguid RA, Hooker CM, Harris J, et al. Long-term survival outcomes by smoking status in surgical and nonsurgical patients with non-small cell lung cancer: comparing never smokers and current smokers. *Chest* 2010; 138:500–509
33. Wakelee HA, Chang ET, Gomez SL, et al. Lung cancer incidence in never smokers. *J Clin Oncol* 2007; 25:472–478
34. Environmental Protection Agency. *EPA assessment of risks from radon in homes*. Washington, DC: United States Environmental Protection Agency, 2003
35. Field RW, Steck DJ, Smith BJ, et al. Residential radon gas exposure and lung cancer: the Iowa Radon Lung Cancer Study. *Am J Epidemiol* 2000; 151:1091–1102
36. Wipfli H, Avila-Tang E, Navas-Acien A, et al. Secondhand smoke exposure among women and children: evidence from 31 countries. *Am J Public Health* 2008; 98:672–679
37. Hackshaw AK, Law MR, Wald NJ. The accumulated evidence on lung cancer and environmental tobacco smoke. *BMJ* 1997; 315:980–988
38. Koo LC, Ho JH. Worldwide epidemiological patterns of lung cancer in nonsmokers. *Int J Epidemiol* 1990; 19[suppl 1]:S14–S23
39. Gao YT, Blot WJ, Zheng W, et al. Lung cancer among Chinese women. *Int J Cancer* 1987; 40:604–609
40. Ko YC, Lee CH, Chen MJ, et al. Risk factors for primary lung cancer among non-smoking women in Taiwan. *Int J Epidemiol* 1997; 26:24–31
41. Seow A, Poh WT, Teh M, et al. Fumes from meat cooking and lung cancer risk in Chinese women. *Cancer Epidemiol Biomarkers Prev* 2000; 9:1215–1221
42. Hecht SS, Seow A, Wang M, et al. Elevated levels of volatile organic carcinogen and toxicant biomarkers in Chinese women who regularly cook at home. *Cancer Epidemiol Biomarkers Prev* 2010; 19:1185–1192
43. Samet JM, Avila-Tang E, Boffetta P, et al. Lung cancer in never smokers: clinical epidemiology and environmental risk factors. *Clin Cancer Res* 2009; 15:5626–5645
44. Matakidou A, Eisen T, Houlston RS. Systematic review of the relationship between family history and lung cancer risk. *Br J Cancer* 2005; 93:825–833
45. Wu AH, Fontham ET, Reynolds P, et al. Family history of cancer and risk of lung cancer among lifetime nonsmoking women in the United States. *Am J Epidemiol* 1996; 143:535–542
46. Lichtenstein P, Holm NV, Verkasalo PK, et al. Environmental and heritable factors in the causation of cancer: analyses of cohorts of twins from Sweden, Denmark, and Finland. *N Engl J Med* 2000; 343:78–85
47. Marchetti A, Martella C, Felicioni L, et al. EGFR mutations in non-small-cell lung cancer: analysis of a large series of cases and development of a rapid and sensitive method for diagnostic screening with potential implications on pharmacologic treatment. *J Clin Oncol* 2005; 23:857–865
48. Wei Q, Cheng L, Amos CI, et al. Repair of tobacco carcinogen-induced DNA adducts and lung cancer risk: a molecular epidemiologic study. *J Natl Cancer Inst* 2000; 92:1764–1772
49. Gorlova OY, Weng SF, Zhang Y, Amos CI, Spitz MR, Wei Q. DNA repair capacity and lung cancer risk in never smokers. *Cancer Epidemiol Biomarkers Prev* 2008; 17:1322–1328
50. Boffetta P. Biomarkers in cancer epidemiology: an integrative approach. *Carcinogenesis* 2010; 31:121–126
51. Weiss JM, Lacey JV Jr, Shu XO, et al. Menstrual and reproductive factors in association with lung cancer in female lifetime nonsmokers. *Am J Epidemiol* 2008; 168:1319–1325
52. Schabath MB, Wu X, Vassilopoulou-Sellin R, Vaporciyan AA, Spitz MR. Hormone replacement therapy and lung cancer risk: a case-control analysis. *Clin Cancer Res* 2004; 10:113–123
53. Dougherty SM, Mazhawidza W, Bohn AR, et al. Gender difference in the activity but not expression of estrogen receptors alpha and beta in human lung adenocarcinoma cells. *Endocr Relat Cancer* 2006; 13:113–134
54. Chlebowski RT, Schwartz AG, Wakelee H, et al. Oestrogen plus progestin and lung cancer in postmenopausal women (Women's Health Initiative trial): a post-hoc analysis of a randomised controlled trial. *Lancet* 2009; 374:1243–1251
55. Stabile LP, Siegfried JM. Estrogen receptor pathways in lung cancer. *Curr Oncol Rep* 2004; 6:259–267
56. Klein F, Amin Kotb WF, Petersen I. Incidence of human papilloma virus in lung cancer. *Lung Cancer* 2009; 65:13–18
57. Cheng YW, Chiou HL, Sheu GT, et al. The association of human papillomavirus 16/18 infection with lung cancer among nonsmoking Taiwanese women. *Cancer Res* 2001; 61:2799–2803
58. Yousem SA, Ohori NP, Sonmez-Alpan E. Occurrence of human papillomavirus DNA in primary lung neoplasms. *Cancer* 1992; 69:693–697
59. Ries LAG, Young JL, Keel GE, Eisner MP, Lin YD, Horner M-J, eds. *SEER survival monograph: Cancer survival among adults: U.S. SEER program, 1988-2001: patient and tumor characteristics*. NIH Publication no. 07-6215. Bethesda, MD: National Cancer Institute, 2007. Available at http://seer.cancer.gov/publications/survival/
60. Arias E. United States life tables, 2006. *Natl Vital Stat Rep* 2010; 58:1–40
61. Kligerman S, Abbott G. A radiologic review of the new TNM classification for lung cancer. *AJR* 2010; 194:562–573
62. Zell JA, Ou SH, Ziogas A, Anton-Culver H. Epidemiology of bronchioloalveolar carcinoma: improvement in survival after release of the 1999 WHO classification of lung tumors. *J Clin Oncol* 2005; 23:8396–8405
63. Humphrey LL, Teutsch S, Johnson M. Lung cancer screening with sputum cytologic examination, chest radiography, and computed tomography: an update for the U.S. Preventive Services Task Force. *Ann Intern Med* 2004; 140:740–753
64. White CS, Flukinger T, Jeudy J, Chen JJ. Use of a computer-aided detection system to detect missed lung cancer at chest radiography. *Radiology* 2009; 252:273–281
65. Balkman JD, Mehandru S, DuPont E, Novak RD, Gilkeson RC. Dual energy subtraction digital radiography improves performance of a next generation computer-aided detection program. *J Thorac Imaging* 2010; 25:41–47
66. Swensen SJ, Jett JR, Hartman TE, et al. CT screening for lung cancer: five-year prospective experience. *Radiology* 2005; 235:259–265
67. Nawa T, Nakagawa T, Kusano S, Kawasaki Y, Sugawara Y, Nakata H. Lung cancer screening using low-dose spiral CT: results of baseline and 1-year follow-up studies. *Chest* 2002; 122:15–20

68. Bach PB, Jett JR, Pastorino U, Tockman MS, Swensen SJ, Begg CB. Computed tomography screening and lung cancer outcomes. *JAMA* 2007; 297:953–961
69. Henschke CI, Yankelevitz DF, Libby DM, Pasmantier MW, Smith JP, Miettinen OS; International Early Lung Cancer Action Program Investigators. Survival of patients with stage I lung cancer detected on CT screening. *N Engl J Med* 2006; 355:1763–1771
70. Croswell JM, Baker SG, Marcus PM, Clapp JD, Kramer BS. Cumulative incidence of false-positive test results in lung cancer screening: a randomized trial. *Ann Intern Med* 2010; 152:505–512; [web]:W176–W180
71. Brenner DJ, Hall EJ. Computed tomography: an increasing source of radiation exposure. *N Engl J Med* 2007; 357:2277–2284
72. Berrington de González A, Mahesh M, Kim KP, et al. Projected cancer risks from computed tomographic scans performed in the United States in 2007. *Arch Intern Med* 2009; 169:2071–2077
73. National Cancer Institute. Lung cancer trial results show mortality benefit with low-dose CT: twenty percent fewer lung cancer deaths seen among those who were screened with low-dose spiral CT than with chest X-ray. Press Release, November 4, 2010. www.cancer.gov/newscenter/pressreleases/NLSTresultsRelease. Accessed November 16, 2010

FOR YOUR INFORMATION

This article is available for CME credit. See www.arrs.org for more information.