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A M E R I C A N C O L L E G E O F
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Lung Cancer in Women*

Emerging Differences in Epidemiology, Biology, and Therapy

Leno Thomas, MD; L. Austin Doyle, MD; and Martin J. Edelman, MD

Lung cancer is the major cause of cancer-related death in both men and women in the United States. Emerging evidence indicates that there are differences in the pathogenesis and possibly increased susceptibility to lung cancer in women. In addition, considerable data support small, but important differences favoring women in terms of response to therapy and long-term survival after the diagnosis of lung cancer, regardless of histology or stage. These differences in both biology and outcome will be important considerations in the design of future trials of screening and therapy for lung cancer. (CHEST 2005; 128:370–381)

Key words: DNA repair; estrogen receptor; human papilloma virus; non-small cell lung cancer; sex; small cell lung cancer

Abbreviations: BAC = bronchiolalveolar carcinoma; CI = confidence interval; DRC = DNA repair capacity; ED = extensive-stage disease; ELCWP = European Lung Cancer Working Party; ER = estrogen receptor; ETS = environmental tobacco smoke; HPV = human papilloma virus; HRT = hormone replacement therapy; IDEAL = IRESSA Dose Evaluation in Advanced Lung; LD = limited disease; NSCLC = non-small cell lung cancer; OR = odds ratio; PCR = polymerase chain reaction; RR = relative risk; SCLC = small cell lung cancer; SWOG = Southwest Oncology Group

Learning Objectives: 1. Identify major differences between men and women diagnosed with lung cancer as it relates to biological and natural history as this disease progresses. 2. State the different responses to the therapeutic interventions between men and women diagnosed with lung cancer.

Lung cancer is now the leading cause of cancer mortality in both men and women in the United States. It is estimated that in 2004 lung cancer incidence will reach 173,700, accounting for 13% of all new cancer cases and 29% of cancer deaths.¹ There has been a fourfold increase in lung cancer in women over the past 30 years (Fig 1), and it is estimated that this rise will not plateau until after 2010. This increase in lung cancer in women has been referred to as a “contemporary epidemic.”²

The rise in lung cancer-related mortality among women accompanied by a decrease among men has significantly altered the male/female ratio in this disease. While much of this altered epidemiology can be attributed to changing patterns of tobacco use, it

is becoming increasingly apparent that the relative risks (RRs) of specific types of lung cancer, the relationship between smoking and lung cancer, as well as the response to therapy may not be the same for both sexes. There are several differences between lung cancer in men and women that are of growing importance and may impact on diagnosis, treatment, and outcome (Table 1).

RISK FACTORS

Smoking

Smoking is the overwhelming cause for lung cancer in both men and women; 85 to 90% of patients with lung cancer are current or former tobacco smokers. Smokers are 22 times more likely to die from lung cancer than nonsmokers.³ Although smoking is a risk factor for all histologic types of lung cancer, the association is stronger for small cell, squamous cell, and large cell carcinoma than for adenocarcinoma.

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Women began smoking in significant numbers in the 1940s, with a peak incidence in the 1970s. Currently, 22% of women are smokers.⁴ While the

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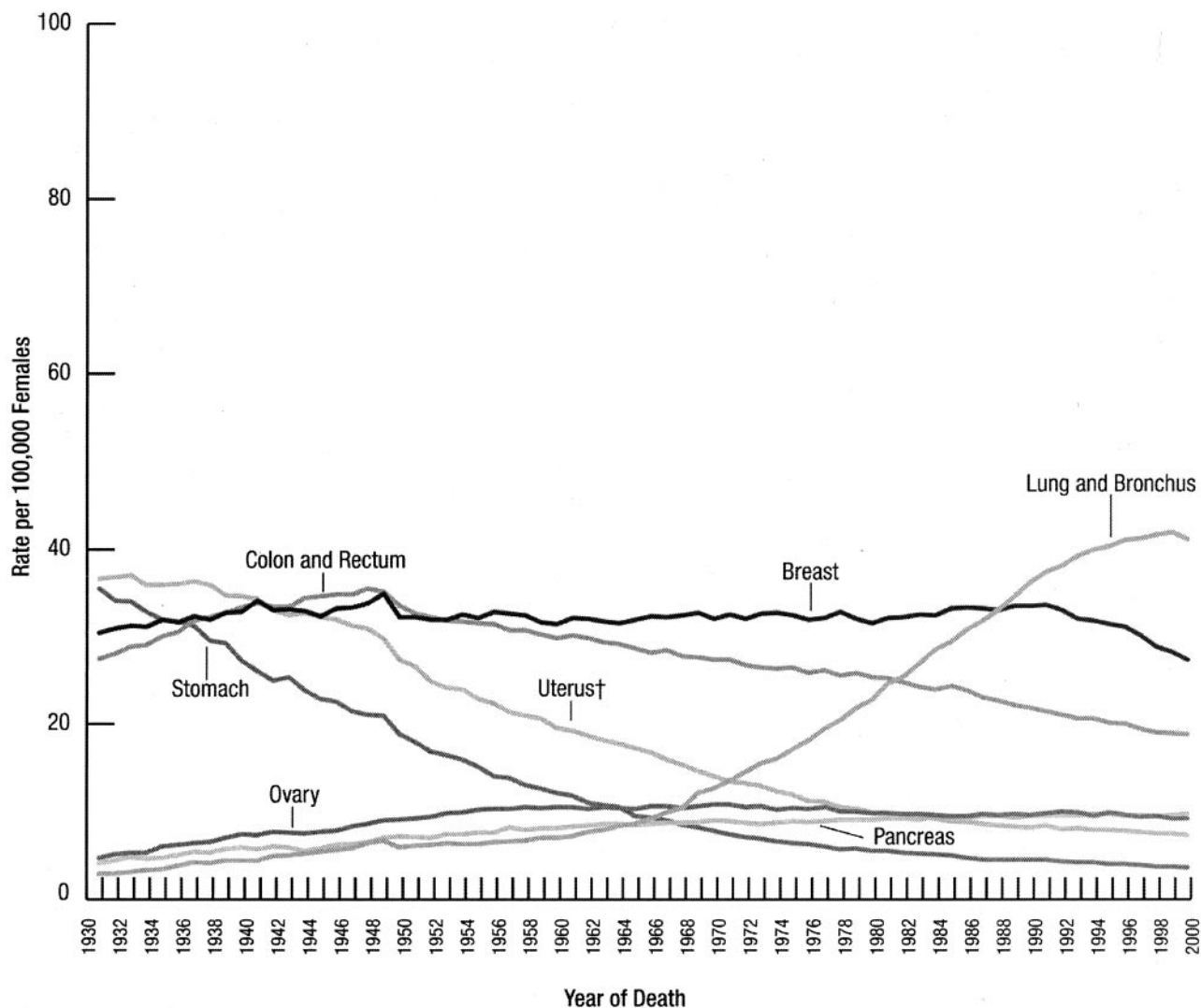


FIGURE 1. Lung cancer deaths in women. Reprinted with permission from Ahmedin et al.¹

death rate from smoking-related disease for men has leveled off, women's rates continue to rise, both as a delayed effect of past smoking and a lower rate of smoking cessation. There is considerable controversy over the RR for lung cancer in women vs men at any given level of tobacco exposure. A hospital-based, prospective, case-con-

trol study by Zang and Wynder⁵ found that women had a 1.2- to 1.7-fold higher risk for lung cancer than men.⁵ CT screening of an at-risk population (*ie*, > 10 pack-years) yields an increased risk of lung cancer for women compared to men (odds ratio [OR], 2.7) after adjusting for age and smoking history.⁶ Bain et al,⁷ however, recently ana-

Table 1—Sex Differences in Lung Cancer

Characteristics	Sex Differences
Risk	Women may be at greater risk for lung cancer than men
Molecular variables	Different metabolism of tobacco-related carcinogens Possible association with HPV infection Women have relatively less DRC Increased frequency of K-ras
Response to therapy	Women have increased response rates to cisplatin-based chemotherapy compared with men
Outcome	Women have better outcome stage for stage than men

lyzed cohort data from the Nurses Health Study of women and the Health Professionals Follow-up Study of men and failed to find a difference in risk. In addition, they reviewed six other cohort studies that also failed to demonstrate a difference.⁷ At this time, the question remains unanswered. Despite this uncertainty regarding the RR of lung cancer between males and females, there is considerable evidence that the biology of the disease differs between the sexes.

Environmental Tobacco Smoke

Environmental tobacco smoke (ETS) accounts for approximately 3,000 lung cancer deaths each year in the United States among nonsmokers, primarily women. A nonsmoking woman has a 24% greater risk of lung cancer if she lives with a smoker.⁸ Urinary levels of nicotine, cotinine, 4-(methylnitrosamino)-1-(3-pyridyl)-butanol (NNK), a tobacco-specific carcinogen, and its glucuronide (NNAL-Gluc) were elevated in nonsmoking women exposed to ETS compared to those who were not exposed.⁹ A population-based, case-control study¹⁰ in central Florida among nonsmoking women demonstrated an elevated risk of lung cancer (or 2.4; 95% confidence interval [CI], 1.1 to 5.4) in women who were exposed to ≥ 22 years of ETS. Nonsmoking women with spouses who used tobacco had a 30% increased risk of lung cancer, with a higher risk in those women with increased levels of exposure in a multicenter case control study ($p = 0.03$).¹¹

Family History

Patients with lung cancer have a higher number of relatives with lung cancer than control subjects.¹²⁻¹⁴ The simplest explanation of this phenomenon is the clustering of cigarette smokers within families. While undoubtedly true, there is also an increased risk of lung cancer regardless of family smoking history. This finding suggests that genetic and perhaps other shared environmental factors may be present in this population.¹⁵ A US population-based, case-control study estimated the familial risk for lung cancer by restricting the analysis to nonsmokers.¹⁶ Cases were significantly more likely than controls to have a family history of aerodigestive cancers (OR, 2.78) and a trend toward an excess of lung cancer (OR, 4.14; $p = 0.07$). Previous studies for example in nonsmokers also demonstrated an increased risk in nonsmoking women, and this risk was found to be greater for adenocarcinoma of the lung.^{12,17} Schwartz et al¹² demonstrated a similar trend in nonsmokers in general; in particular, the risk was found to be greater in women (ORs, 1.7 vs 0.5,

respectively) than in men, and again adenocarcinoma was the predominant tissue type.

Diet

Other factors including diet pose a potential risk for the development of lung cancer. A prospective study¹⁸ examined the relationship between smoking, dietary antioxidants, and lung cancer risk. Women who consumed five or more carrots per week had an RR of 0.4 (95% CI, 0.2 to 0.8) compared with the risk for women who had not consumed carrots.¹⁸ Two prospective US cohorts lend further support to this observation.¹⁹ A 10-year follow-up of a cohort of men in the Health Professionals Follow-up Study and a 12-year follow-up period of a cohort of women in the Nurses Health Study found that new lung cancers were diagnosed in 275 of 46,924 men and 519 of 77,283 women. The risk of lung cancer was significantly reduced in those who had consumed a variety of carotenoids for a maximum protective period of 4 to 8 years even after adjusting for residual confounding from smoking (RR, 0.68; 95% CI, 0.49 to 0.94 for the highest compared with the lowest total carotenoid intake). Of note, the association was stronger in women than in men. Among female never-smokers, a significant 63% lower risk was noted.²⁰

A hospital-based, case-control study demonstrated that fruit intake and the use of soy in Chinese women provided a protective effect against lung cancer.²¹ The same protective effect was observed with the consumption of green tea in a population-based, case-control study.²²

Possible Association With Human Papilloma Virus Infection

Human papilloma virus (HPV) infection is a well-recognized event in the pathogenesis of cervical cancer. The most frequently implicated HPV viruses are types 6 and 11, which are associated with intraepithelial neoplasia, and types 16 and 18, which are associated with invasive cervical carcinoma. HPV DNA utilizing polymerase chain reaction (PCR) and *in situ* hybridization was detected in the tumors of 49% of women with lung cancer who also had a history of high-grade cervical intraepithelial neoplasia (grade III).²³

A Taiwanese study²⁴ revealed the presence of HPV DNA (types 16 and 18) in the cancer cells of nonsmoking women with lung cancer. Interestingly, HPV infection seems to be most associated with squamous lung cancer. Yousem et al²⁵ demonstrated the occurrence of HPV 6/11, 16/18, and 31/33/35 serotypes in squamous metaplasia of the bronchus, but no association was found in adenocarcinoma or small cell carcinoma. Japanese studies^{26,27} have detected HPV DNA (serotypes 6, 11, 16, and 18) in

well-differentiated squamous cell carcinoma and in adenocarcinoma cells that were adjacent to squamous cell carcinoma.

There is far from universal agreement that HPV is an etiologic agent in lung cancer.²⁸⁻³⁰ An analysis of paraffin-embedded tissue from 32 squamous bronchial carcinomas and 15 cervical cancers utilizing both *in situ* hybridization and PCR techniques was negative for HPV in the lung cancer cases, while 12 of the 15 cervical cases were positive.³⁰ It is also quite possible that an association of HPV in lung cancer reflects the coexistence of increased and earlier smoking behavior with more frequent sexual contacts.

PATHOBIOLOGY

The development of lung cancer is the end result of a complex interplay of factors including carcinogen exposure, metabolism, and genetics. Tobacco smoke, recognized to be the foremost risk factor for lung cancer, contains more than a hundred diverse mutagens and carcinogens, including polycyclic aromatic hydrocarbons, N-nitro amines, and aromatic amines. The initiating activity remains for an extended period after the cessation of smoking.

Two classes of enzymes play a crucial role in the metabolism of tobacco-related carcinogens: the phase I and II detoxifying enzymes. While phase I enzymes (*ie*, cytochrome P450, monooxygenases) activate carcinogens to reactive intermediates, their action is balanced by phase II enzymes, which serve to convert these same reactive intermediates (*ie*, reactive oxygen species) to inactive conjugates that are more water soluble and hence excreted more readily. Polymorphisms have been found to alter the metabolic activity of detoxification enzymes. Those active metabolites that are not detoxified bind to DNA forming DNA adducts. Women have higher levels of these DNA adducts when compared to men.^{31,32} The higher DNA adduct levels were also found to be associated with the expression of the cytochrome P4501A1 (CYP1A1) gene, an aryl hydrocarbon hydroxylase enzyme. This enhanced enzyme inducibility causes bioactivation of benzopyrene, a polycyclic aromatic hydrocarbon that is found in cigarette smoke.³³ When noncancerous lung tissue from 159 patients with lung cancer was evaluated, both male and female smokers had much higher levels of DNA adducts compared with nonsmokers. Despite substantially fewer pack-years of smoking (22.9 vs 35.0, $p = 9.4 \times 10^{-5}$) and younger age (56.2 years vs 62.2 years, $p = .034$), women smokers had substantially higher levels of adducts (15.39 vs 12.08 per 10^8 DNA bases, $p = 0.047$). Increased adduct

levels correlated with CYP1A1 levels, as measured by quantitative reverse transcriptase-PCR and normalized to the expression of GAPDH, which were substantially higher in female than male subjects (494 ± 334 CYP1A1 mRNA/ 10^6 GAPDH mRNA vs 210 ± 208 , $p = 0.016$).³²

Dresler et al³⁴ confirmed the risk of high CYP1A1 expression to the development of lung cancer in women vs men (OR, 4.98 vs 1.37). In addition, the expression of the glutathione S-transferase M1 (GSTM1) gene was also evaluated. GSTM1 has the ability to inactivate highly reactive intermediates that are carcinogenic; hence, reduced expression of this gene could lead to an increased risk for smoking-related cancers including lung cancer.³⁵ While non-expression (null phenotype) did not increase risk by itself, a null phenotype combined with high CYP1A1 expression raised the risk ratio for lung cancer in women as opposed to men (OR, 6.54 vs 2.36), despite the fact that women in this study had a far less significant smoking history than men. The GSTM1 null phenotype was also associated with an increased risk of lung cancer in nonsmoking women with ETS. The OR was 2.6 for women with ETS exposure and GSTM1 null, compared to those expressing GSTM1. This risk increased with increasing exposure to ETS.³⁶ It is important to be cautious in interpreting and generalizing these findings beyond the study populations given the wide ethnic and racial differences in hepatic enzyme phenotypes.³⁷

MOLECULAR ABNORMALITIES

Many genetic and epigenetic alterations of tumor suppressor genes have been demonstrated in lung cancer. The most frequent genetic alterations found are in p53 (in 90% of small cell lung cancers [SCLCs] 40 to 70% of non-small cell lung cancers [NSCLCs]) and in oncogenes such as K-ras. The p53 pathway has long been recognized as playing a key role in cell cycle regulation by causing arrest in both the G1 and G2 phases in cell division in response to DNA damage. This arrest allows for DNA repair or apoptosis. P53 mutation leads to abrogation of this arrest and perpetuation of DNA damage and consequent inhibition of the normal apoptotic mechanism. Smoking has been found to induce p53 mutation via the formation of DNA adducts. Women have been found to have higher levels of pulmonary DNA adducts per pack-year than men.³⁸

Of the Ras family of proto-oncogenes, K-ras is the most frequently affected gene. As in the p53 gene mutation, the formation of DNA adducts secondary to the effects of smoking appears to play a pivotal role.³⁹ Women are three times more likely to carry

the K-ras mutation than men.^{40,41} In most studies,^{42,43} Ras mutations are predominantly associated with adenocarcinoma. Data regarding whether K-ras is an adverse prognostic variable are conflicting.^{44–50}

Growth Factor Receptors

Certain growth factors have been shown to stimulate the growth of both normal and neoplastic cells in the lung. A receptor for the autocrine growth factor, gastrin releasing peptide receptor (GRPR), has been identified in both small cell lung cancer and NSCLC.^{51,52} The GRPR gene is on the X chromosome and escapes X-inactivation. It is expressed more frequently in female nonsmokers (than male) and is activated earlier in response to tobacco exposure.⁵³

ERBB2 (HER-2/neu) is one of four receptor-type tyrosine kinases that form a heterodimer with other members of the ERB-B class and mediates cell growth and survival. HER 2/neu has been found to be overexpressed in 25 to 30% of invasive breast cancers and is associated with a more aggressive clinical course. Its incidence in NSCLC varies from 27 to 63%.⁵⁴ In advanced NSCLC, one study⁵⁵ found inferior survival for patients with high serum levels of HER-2/neu compared to patients with lower levels (median, 7.1 months vs 10.9 months; $p = 0.004$). Previously, several surgical series^{56,57} found that overexpression of HER-2/neu is associated with a poorer prognosis and survival. HER-2/neu is most commonly expressed in adenocarcinoma, the most common subtype in women.⁵⁸ Despite these observations, treatment with trastuzamb (a monoclonal antibody to Her2/neu) in addition to standard chemotherapy failed to improve outcome.⁵⁹

DNA Repair Capacity

An emerging literature implicates differences in DNA repair capacity (DRC) in both the pathogenesis of lung cancer and response to therapy. A complex family of proteins exists to remove damaged DNA segments or to repair mismatched nucleotides. Deficiencies in this process are unequivocally mutagenic and carcinogenic. Wei et al⁶⁰ evaluated the repair of tobacco carcinogen-induced DNA adducts and lung cancer risk. Lymphocytes were obtained from newly diagnosed lung cancer patients ($n = 316$) or from age-, sex-, and smoking status-matched control subjects ($n = 316$). Cells were cultured and transfected with a plasmid containing a reporter gene that would not be expressed if the plasmid DNA was damaged. Lymphocytes were then exposed to the known tobacco-derived carcinogen, benzo(a)pyrene diol epoxide. Younger patients (< 60 years old), those with a family history of lung cancer,

and female patients had a lower DRC and a higher lung cancer risk.⁶⁰ These results were confirmed in a much larger case-control study with 764 lung cancer patients and 677 control subjects.⁶¹

Paradoxically, this relative deficiency in DRC may relate to the observation that women have better responses and survival when treated with platinum-based chemotherapy. Platinum agents act through the formation of DNA adducts resulting in cycle arrest and apoptosis. Repair of these adducts is one mechanism of resistance to platinum agents. Recent studies have demonstrated that diminished DRC (as a result of less ERCC1, a DNA repair enzyme) is associated with improved outcome in stage IV NSCLC treated with cisplatin-based chemotherapy.⁶²

Hormonal Influences

The most obvious biological differences between the male and female are hormonal. An estrogen-driven environment is a recognized factor in the pathogenesis of breast, endometrial, and ovarian cancers. With the increasing rates of lung cancer in women and their increased susceptibility to the detrimental effects of tobacco smoke compared to men, the role of female steroid sex hormones has been hypothesized to be a factor in lung carcinogenesis. Estrogen receptors are abundantly expressed in normal lung tissue and in lung tumor cell lines at the messenger RNA level.⁶³ Stabile⁶⁴ has demonstrated that the most common estrogen receptor (ER) expressed in lung cancer is a variant of ER α (most likely as a result of alternative splicing) which contrasts to the abundant expression of the classic estrogen receptor, ER α in hormone sensitive breast cancers. The novel ER ER β was also expressed and was found to be a mixture of full-length and alternative splicing. β -Estradiol has a proliferative effect on normal lung fibroblasts and lung cancer cell lines *in vitro*. There was a 17-fold increase in cellular proliferation in lung cancer-derived cell line as opposed to only a 3.8-fold increase when normal lung fibroblasts were incubated with β -estradiol. This finding suggests an increased responsiveness of malignant clones to estrogen.

The exact role of estrogens in lung cancer is not clear, but they may act as direct carcinogens via the formation of DNA adducts.^{65,66} Other mechanisms include a possible indirect role in the activation of several growth factor genes, such as transforming growth factor- α , epidermal growth factor, and insulin-like growth factor-1, all of which in turn have been known to mediate cell division in lung neoplasms.⁶⁷

Previous data have been conflicting regarding the prognostic value of ER receptors. Expression of the

ER-related protein p29 was inversely related to survival in women, whereas a positive trend was noted in men.⁶⁸ Yang⁶⁹ observed that the 5-year survival rates for ER-negative patients was higher than for ER-positive patients (72.5% vs 8.8%, respectively).

Hormone replacement therapy (HRT) in women is very controversial. Adami et al⁷⁰ showed an increased risk (RR, 1.26) of lung cancer in women receiving HRT. Taioloi and Wynder⁷¹ showed that the use of HRT and its interaction with smoking leads to an increased risk of lung cancer in women (ORs, 1.7 and 32.4 in nonsmokers and smokers, respectively), while early menopause was associated with a decreased risk (OR, 0.3) of adenocarcinoma in women. It appears that the higher circulating levels of estrogen in women when compared to men, coupled with their lower rate of DNA repair, make women particularly susceptible to the carcinogenic influence of tobacco smoke. Soy phytoestrogens have been shown to compete with endogenous estradiol for ERs and have been shown to have a protective effect against lung cancer.⁷²

There are data that HRT may actually exert a protective effect. A case-control study from Texas of 499 women with lung cancer and 519 age-, ethnicity-, and smoking-matched control subjects found that HRT was associated with a reduced risk of lung cancer in current smokers (OR, 0.59; 95% CI, 0.38 to 0.92). However, this reduced risk was not seen in never-smokers or former smokers.⁷³

Moore et al⁷⁴ analyzed the Surveillance, Epidemiology, and End Results Database to evaluate the

influence of menopausal status on outcomes in lung cancer. Utilizing an average menopausal age of 51 years, they classified 14,676 women entered in the database into premenopausal and postmenopausal groups. In addition to comparisons between the two groups, there were also comparisons against men from similar age groups. Several intriguing differences emerged between the groups. Premenopausal women tended to present with more extensive disease and adenocarcinoma than postmenopausal women. They underwent more extensive surgical procedures (pneumonectomies, vs lobectomies) at every stage of disease ($p < 0.0001$) and were more likely to receive radiotherapy (58% vs 48%, $p < 0.0001$). While premenopausal women and younger men had similar mortality (after adjustments for covariates), postmenopausal women had fewer lung cancer-related deaths compared with older men.

The authors acknowledge that a major limitation of this study is the potentially confounding effects of age. However, the different death rates for postmenopausal women as opposed to older men seems to confirm a sex-specific effect.

THERAPEUTIC IMPLICATIONS

Although the incidence of lung cancer is higher in women than in men and continues to rise, women have superior responses to therapy. This appears to be true regardless of stage, therapeutic modality, or histology (Tables 2, 3). In the mid-1970s, Edmonson

Table 2—Treatment Results by Sex in NSCLC*

Author/Institution	Year	Study Years	No.	Female Gender,		Modality	MST		HR	P Value	
				%	Stage		Female	Male			
O'Connell et al ⁸⁵ /MSKCC	1986	1978–1986	378	30	III-IV	Chemotherapy†	12.4	8.8	0.71	0.001	
Mitsudomi et al ⁷⁸ /Kyushu University	1989	1974–1988	492	27	I-IV	Surgery	60	38	0.63	0.00036	
Sorenson/Finsen Institute	1989	1981–1985	259	46	III-IV	Chemotherapy‡	6.8	6.8	1.0	0.5	
Ferguson et al ⁸⁰ /University of Chicago§	1990	1974–1989	299	45	I-IV	All modalities	12.1	9.1	0.75	0.044	
			(adenocarcinoma)	244	24		11.1	7.1	0.64	0.08	
			(squamous)	192	29	III-IV	Chemotherapy†	14.6	9.1	0.62	0.02
Shinkai/National Cancer Institute Japan	1992	1982–1989	192	29	III-IV	Chemotherapy†	14.6	9.1	0.62	0.02	
Albain et al ⁹⁰ /SWOG	1991	1974–1988	2,531	23	III-IV	Chemotherapy	NS	NS	0.77	< 0.00005	
Paesmans et al ⁸⁹ /ELCWP	1995	1980–1991	1,052	10	III-IV	Chemotherapy†	NS	NS	0.70	0.03	
									(RR)		

*HR = hazard ratio, expressed as ratio of risk of patients with the favorable variable to the unfavorable variable. NS = not significant.

MS = median survival time. Staging has been converted to current staging.

†Platinum-based therapy.

‡Nonplatinum chemotherapy.

§Both platinum and nonplatinum therapy.

||A total of 772 patients with diverse histologies (including SCLC) were evaluated.

Table 3—Treatment Results by Gender: SCLC

Author/Institution	Year	Study Years	Female Gender,		Stage	Modality	MST		HR	P Value
			No.	%			Female	Male		
Johnson et al ⁸⁸ /Navy-National Cancer Institute	1988	1973–1986	378	28	LD and ED	Chemotherapy, chemotherapy/thoracic radiotherapy	13	10	0.77	0.002
Albain et al ⁹⁰ /SWOG	1990	1976–1988	1,363	32	LD	Chemotherapy/thoracic radiotherapy	NS	NS	0.77 (RR)	0.0001
			1,217	28	ED	Chemotherapy	NA	NA	0.91 (RR)	0.35
Paesmans et al ⁸⁹ /ELCWP	2000	1982–1993	763	11	LD and ED	Chemotherapy	11.1	10.2	0.91*	0.16*

*By Cox multivariate analysis, the role of gender was significant with a HR of 0.71 ($p = 0.02$). MST = median survival time.

et al⁷⁵ noted that “survival was better for ambulatory patients and women survived longer than men” regarding outcome of chemotherapy-treated patients with adenocarcinoma or inoperable small cell carcinoma of the lung. The Surveillance, Epidemiology, and End Results Database (31,226 patients) of lung cancer has been analyzed for prognostic factors and has identified the following as favorable prognostic factors: low-stage disease, surgical therapy, age < 50 years, and female sex.⁷⁶ A Polish population-based study⁷⁷ of 20,561 cases of lung cancer between 1995 to 1998 revealed that female patients had a better prognosis than males regardless of the modality of therapy, with an RR of death of 1, compared to 1.21 ($p = 0.001$) in male patients by univariate analysis. It was also noted in this series that women patients were younger (age < 50 years: 23.3% vs 12%, $p < 0.001$), and were more likely to have adenocarcinoma (21.6% vs 9.6%, $p < 0.001$) and SCLC (26.6% vs 19.9%, $p < 0.001$). More women were nonsmokers compared to men (18.8% vs 2.4%, $p < 0.001$). A multivariate analysis of absolute survival in this series showed that the RR of death was significantly higher for men (1.15; $p = 0.001$).

NSCLC

In localized (*ie*, stage I, II) NSCLC, women will experience superior survival after either surgical resection or radiation as single modalities. A Japanese study⁷⁸ of resected NSCLC noted that women have a significantly longer survival rate than men ($p = 0.0036$), although on multivariate analysis the difference was significant only in stage III disease ($p = 0.0234$). Minami et al⁷⁹ evaluated the results of 1,242 consecutive operative interventions for lung cancer and noted that complete resection was achieved less often in women than in men (79.6% vs 85.2%). However, women who underwent a complete resection survived longer (5-year and 10-year survival rates were 69% and 51%, respectively) than their male counterparts. Women < 60 years of age

did not show a significantly longer survival than men, but women > 60 years old survived significantly longer.⁷⁹

Ferguson et al⁸⁰ evaluated the outcomes of 451 patients who underwent surgical resection for localized lung cancer between from 1980 to 1998 with an emphasis on sex-associated differences. There was an overall superiority in median survival favoring women vs men (41.8 months vs 26.9 months, respectively). This gender gap was particularly pronounced in stage I disease (109.8 months vs 50.3 months, $p = 0.0008$). However, in a Cox proportional hazards model, this advantage did not reach significance when other factors including age and FEV₁ were considered.⁸⁰

Female sex has also been associated with superior outcome in patients treated with radiotherapy as well. Werner-Wasik et al⁸¹ reviewed 1,999 patients treated in nine Radiation Therapy Oncology Group trials between 1983 and 1994 with thoracic radiation with or without chemotherapy (cisplatin-based). Women had a significantly better outcome than men, 11.4 months vs 9.9 months, respectively.

Female sex was also noted to be an independent positive prognostic factor after trimodality therapy (chemotherapy, radiotherapy, and surgery). The Southwest Oncology Group (SWOG)⁸² evaluated concurrent cisplatin/etoposide plus chest radiation followed by surgery for stages IIIA and IIIB NSCLC. A univariate analysis of prestudy factors revealed that the two best predictors of survival were substage and sex. The survival time for women was 21 months, vs 12 months for men ($p = 0.08$).

A similar survival advantage for women is present in advanced-disease patients treated with chemotherapy. Albain et al⁸³ reviewed the 2,531 patients enrolled in 13 SWOG trials of therapeutic interventions in “extensive stage nonsmall cell lung cancer” conducted between 1974 and 1987. Female sex was a strong independently favorable factor for survival with a risk ratio of 0.77.⁸³ The median survival ratio

for females/males was 5.7/4.8, with 1-year survival rates of 19% vs 14% ($p \leq 0.01$ for survival comparisons within each category). Almost identical results were noted by the European Lung Cancer Working Party (ELCWP) in a review of 1,052 patients with locally advanced or metastatic NSCLC treated with cisplatin-based chemotherapy from 1980 to 1991.⁸⁴ Among 23 pretreatment variables evaluated, female sex emerged as one of eight significantly associated with superior survival. An RR of 0.7 ($p = 0.03$) was noted in multivariate analysis. In an analysis of 378 by O'Connell et al,⁸⁵ patients, Karnofsky performance scale > 80 , normal lactate dehydrogenase (LDH) level, 0–1 nonosseous metastases, and female gender were noted to have improved overall survival.

A randomized trial of postoperative therapy by the Eastern Cooperative Oncology Group⁸⁶ also shows a trend toward better outcomes for women compared to men (median survival of all men; 35 months; for women, 41 months; $p = 0.12$). Multivariate analyses demonstrated significantly improved survival for women with nonsquamous histology ($p < 0.01$).

Preliminary results of an analysis of 91 patients (21 female) with curatively resected NSCLC demonstrated that several prognostic markers appeared to be sex specific.⁸⁷ High levels of ERCC1, Her2, and RXR β predicted for better survival in women, but not in men. In men, low cyclooxygenase-2 expression and high ornithine decarboxylase expression predicted for better survival, but were not predictive in women. This study is limited by its small numbers and will require validation. However, it serves to further emphasize the potential importance of gender in analyzing both outcomes results as well as potential predictive and prognostic markers.

SCLC

In SCLC, women similarly will experience superior outcomes. The NCI-Navy Medical Oncology Branch analyzed the results of four consecutive prospective trials and found that women had superior survival compared with men.⁸⁸ This advantage was most pronounced for patients surviving > 2.5 years, implying that the chance of cure is higher in women than in men. This difference was independent of other factors analyzed.

The ELCWP analyzed 763 patients with a minimum follow-up of 5 years and demonstrated that female patients had a better objective response (80%, vs 69% for male) in a univariate analysis, but the comparison was not statistically significant ($p = 0.16$). In a multivariate analysis, women did better than men (OR, 1.82 for female patients; 95%

CI, 1.00 to 3.34; $p = 0.05$). However, there were relatively few women (10%) analyzed in this series.⁸⁹

A total of 2,580 patients enrolled on 10 SWOG SCLC trials including both limited disease (LD) and extensive-stage disease (ED) were analyzed for prognostic indicators. In the six SWOG LD trials, good performance status (0 to 1), age < 70 years, normal LDH level, and female sex ($p = < 0.001$ for all these variables; median survival in females, 24.4 months, vs 17.7 months in men) were significant favorable independent predictors and therefore predicted for the best outcome.⁹⁰ In the SWOG ED trials,⁹⁰ the most favorable prognostic factors were good performance status and normal LDH level. There was a nonsignificant trend toward superior survival in females.

Bronchiolalveolar Carcinoma

There is emerging evidence that bronchiolalveolar carcinoma (BAC) represents a distinct clinicopathologic entity. Though currently considered as a subset of adenocarcinoma (with the formal terminology of “adenocarcinoma with bronchioalveolar features”), there are clear differences. True BAC as defined by the World Health Organization/International Association for the Study of Lung Cancer is characterized by a lepidic growth pattern and lack of invasiveness and distant metastases.⁹¹ The actual diagnosis can only be made with a completely resected surgical specimen, and this has resulted in some confusion as most patients with advanced disease are diagnosed based on biopsy specimens. Biologically, it is characterized by a distinct pattern of gene expression.⁹² Clinically, there is relatively frequent occurrence in younger, female nonsmokers. The disease tends to progress more indolently than other NSCLC, though it also appears to be less sensitive to conventional platinum based therapies.⁹³ Interestingly, BAC appears to be the subset of NSCLC with the greatest responsiveness to gefitinib or erlotinib, the tyrosine kinase inhibitor of epidermal growth factor receptor signaling. Two large phase II trials of gefitinib monotherapy, the IRESSA Dose Evaluation in Advanced Lung Cancer (IDEAL) 1 and IDEAL 2 studies^{94,95} evaluated the agent in pretreated NSCLC. Retrospective subset analysis demonstrated that female sex, adenocarcinoma (in particular, bronchiolalveolar histology), and nonsmoking status were predictors of response.^{95,96} In the IDEAL 2 study,⁹⁵ 50% of women experienced symptomatic response, vs 31% of men ($p = 0.006$). Radiographic regression was also seen in 19% of women, vs only 3% of men ($p = 0.001$). The results of these studies, both in

terms of the activity of gefitinib in general as well as predictive factors of response, should be viewed with caution as neither trial was randomized and the factors analyzed were retrospectively selected. Similar results have been obtained with erlotinib, a chemically similar agent recently approved for the second- and third-line therapy of advanced NSCLC.⁹⁷

OTHER ISSUES

Smoking Cessation

Smoking is the most predominant risk factor for all the different tissue types of lung cancer. It has long been known that the risk of lung cancer declines after smoking cessation. The risk after a patient stops smoking appears to be related to the level of consumption. In those persons who have smoked 1 to 20 cigarettes per day, the risk decreases to 1.6 at 15 years after smoking cessation. In those who had smoked > 21 cigarettes per day, the risk for lung cancer at 15 years after quitting smoking remains fourfold that of a never-smoker. Among all previous smokers, there was a consistent decline in the combined ORs for all histologic types of lung cancer. In ex-smokers, women had a greater risk reduction for squamous cell and SCLC when compared to men.⁹⁸ Between 1 year and 4 years of cessation, there was a 19% reduction in the risk of SCLC, and the lowest risk reduction (12%) was for adenocarcinoma. After > 10 years of smoking cessation, there was 65% risk reduction for SCLC, while the reduction in risk for adenocarcinoma was only 47%. Of note, in this study, it was noted that women had a greater reduction in the risk of SCLC and squamous cell cancer compared to men. With adenocarcinomas, however, this difference was not significant.

CONCLUSION AND OUTLOOK

Lung cancer is the major cause of cancer-related death in women. It is possible that women are inherently more susceptible to lung cancer, although that issue is far from settled. There are, however, very clear differences in the biology, natural history, and response to therapy between men and women with this disease. An emerging literature provides a biological basis for these differences, but this understanding is quite tentative. Most of the literature on this topic is retrospective and subject to various biases. Prospective evaluations of these differences, particularly as they apply to clinical practice, are required. Furthermore, as new therapeutic interventions are evaluated, the potential for differential

response based on sex must be prospectively considered in trial design. Studies or arms of randomized studies with imbalances in terms of sex may lead to false conclusions. Given the superior prognosis for women in most clinical trials, future studies should stratify for the variable of sex. For current clinical practice, there is only one clear area for which sex enters into the equation in patient management. The value of the epidermal growth factor receptor tyrosine kinase inhibitors (gefitinib, erlotinib) are clearly most pronounced in never-smoking females. The level of activity may warrant initial use of these agents in this group as opposed to standard therapy. However, even in this situation, this approach will require confirmation from prospective clinical trials. Tragically, for both men and women, this disease is largely preventable through smoking cessation.

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Lung Cancer in Women*

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