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International Early Lung Cancer Action Program Investigators

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Context It has been hypothesized that women are more susceptible to tobacco carcinogens than men, but after diagnosis of lung cancer, they have better survival rates than men.

Objective To add to the evidence on the lung cancer risk of women who smoke and their survival after diagnosis of lung cancer, conditional on other prognostic indicators and compared with men of the same age who smoke.

Design, Setting, and Participants Nonexperimental, etiologic study with prospective collection of data based on baseline computed tomographic screening for lung cancer and follow-up of diagnosed cases of lung cancer in North America in 1993-2005. A total of 7498 women and 9427 men were screened, all of whom were asymptomatic, aged at least 40 years, and had a history of cigarette smoking.

Main Outcome Measures Comparing women with men, the prevalence odds ratio (OR) for screen-detectable lung cancer (conditional on age and smoking history) and the hazard ratio of fatal outcome of lung cancer (conditional on smoking history, disease stage, tumor cell type, and resection).

Results Lung cancer was diagnosed in 156 women and 113 men (rates of 2.1% and 1.2%, respectively).The prevalence OR comparing women with men was 1.9 (95% confidence interval [CI], 1.5-2.5). The hazard ratio of fatal outcome of lung cancer comparing women with men was 0.48 (95% CI, 0.25-0.89).

Conclusion Women appear to have increased susceptibility to tobacco carcinogens but have a lower rate of fatal outcome of lung cancer compared with men.

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In 2006 in the United States, it is estimated that lung cancer will cause 73 020 deaths in women, proportionately only slightly fewer than the estimated 90 470 deaths in men.[1] Lung cancer now accounts for more deaths in women than any other cancer, more even than the second and third cancer killers (breast and colon cancer) combined.

Research to quantify the benefit of computed tomographic (CT) screening for lung cancer in preventing deaths is ongoing. We previously reported on the Early Lung Cancer Action Project (ELCAP) baseline screening study of 2490 high-risk persons, which indicated that women have a higher absolute risk for lung cancer than do men of the same age with the same history of smoking.[2] There have been other studies indicating that women have a higher relative risk of getting lung cancer than men[3-9]; other studies disagree,[10-12] the issue being the smoker vs nonsmoker risk ratio.

Sex differences in rates of survival following diagnosis of lung cancer have also been reported. Women have been reported to have higher survival rates regardless of the stage of the disease at diagnosis,[9,12-21] the most recent evidence in the United States derived from the national Surveillance, Epidemiology, and End Results (SEER) database[9] and a large cohort at the Mayo Clinic.[21]

For editorial comment see p 218.

Since our previous report, screening has continued at the original ELCAP institutions and has markedly expanded the amount of poolable data by institutions collaborating worldwide in the International Early Lung Cancer Action Project (I-ELCAP).[22] In this article, we again address the lung cancer risk of women compared with men, accounting for age and history of smoking, but herein we also compare the rate of fatal outcomes between sexes.

METHODS

In our previous report, we addressed the risk for lung cancer in 1202 women and 1288 men using New York City data undergoing baseline screening at Joan and Sanford I. Weill Medical College of Cornell University in 1993-1999 (series 1).[2] This report is based on a new

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series of 14 435 persons (6296 women and 8139 men) undergoing baseline CT screening for lung cancer in North America in 1999-2005 (series 2), and also on both series combined (7498 women and 9427 men). The comparison of women with men as to fatal outcome of cancer is based on cases from both screening series combined.

All of the screenees were asymptomatic volunteers with no history of cancer (other than nonmelanotic skin cancer) and fit to undergo thoracic surgery, were at least 40 years of age, and were past or current cigarette smokers. All of the participants gave informed consent for baseline and repeat screenings under institutional review board–approved protocols. The cohorts' distributions by age and history of smoking are shown in TABLE 1.

Table 1. Distribution of the 2 Series of Baseline Screenings by Age and History of Smoking

Characteristic	Series 1 (n = 2490) Women	Series 1 (n = 2490) Men	Series 2 (n = 14 435) Women	Series 2 (n = 14 435) Men	Combined (N = 16 925) Women	Combined (N = 16 925) Men
Age, y						
Median	63	64	63	64	63	64
Mean	63	63	63	64	63	64
Pack-years of smoking, No.						
Median	36	42	40	40	39	40
Mean	40	47	42	44	42	45
Age at start of smoking, y						
Median	17	17	17	17	17	17
Mean	18	17	18	17	18	17

Information about smoking history was recorded at the time of the initial CT baseline screening. Participants were asked about the following by an interviewer: the age at which habitual smoking began and whether the habit had continued to the last month; if smoking had continued, the daily number of cigarettes smoked in that month; and if smoking had not continued, the typical number of cigarettes smoked per day and the duration of the smoking history. Pack-years of smoking was calculated as the product of the number of cigarettes smoked per day divided by 20 and the number of years of smoking.

The protocol specified a diagnostic workup following a positive result of the initial low-dose CT, ie, the identification of a specified pattern of noncalcified nodules. Although updated since our prior report, this workup has remained essentially unchanged in its indications for biopsy: demonstration of tumor growth on the CT scan, positive positron emission tomographic scan result, or CT 1 month after the initial scan not showing resolution after antibiotic treatment[23]; for nodules 15 mm or more in diameter, immediate biopsy was an option. A nodule's diameter was calculated as the average of its length and width in the image showing its largest cross-section in the CT scan closest to the time of diagnosis.

The consensus diagnoses by a panel of 5 experts on lung pathology, following the I-ELCAP pathology protocol[24,25] based on the 2004 World Health Organization criteria,[26] are used in this article. For patients undergoing resection, diagnoses were based on the histology of the surgical specimens; for other patients, diagnoses were based on the cytology of the biopsy specimens.

The women vs men incidence density ratio for lung cancer was the ratio of the corresponding prevalence odds ratio (OR) (cancer present vs cancer absent),[27] conditional on age and history of smoking. In logistic regression analysis (unconditional), with the dependent variate an indicator of cancer diagnosed (Y=1 if diagnosed, 0 otherwise), we controlled for possible confounding by age by means of a single quantitative term, there being no apparent actual confounding (Table 1); we also used a single quantitative term for pack-years of smoking, which indicated a slight confounding (Table 1).

All cases of lung cancer diagnosed in the combined series have been followed up. In cases of known death, the date and cause of death were obtained from the patient's physician and/or family members. If the patient died as a result of the lung cancer treatment, it was also considered to be a lung cancer death. Follow-up time from diagnosis onward—to death from lung cancer, last contact, or March 15, 2006, whichever came first—was calculated for each case; it ranged from 1 to 117 months (median, 46 months).

The women vs men incidence density (hazard) ratio of fatal outcome of lung cancer in the combined cohort was addressed as the ratio of the respective risks, conditional on pack-years of smoking, disease stage, tumor cell type, and resection. This was performed using multivariate Cox proportional hazards regression analysis to test the independent effect of patient sex after accounting for pack-years of smoking at time of diagnosis, clinical stage of the disease (I, II+), cell type (adenocarcinoma, other non–small cell, small/large cell), and resection (yes, no).

All statistical analyses were performed using the SAS version 8.2 (SAS Institute Inc, Cary, NC) statistical package.

RESULTS

In the new series of 14 435 baseline screenings, lung cancer was diagnosed in 111 of 6296 women and 93 of 8139 men. Thus, for the crude women vs men prevalence OR, the point estimate was 1.6 (111/[6296 – 111]/[93/(8139 – 93)]; P=.001, 1-sided). TABLE 2 shows the corresponding result from the logistic regression discrimination between the case (N=204) and the noncase (N=14231 [14 435 – 204]) series, and also the result when controlling for age and pack-years of cigarette smoking. The OR for age and smoking was 1.7 (95% confidence interval [CI], 1.3-2.3). Combining the 2 series of baseline screenings, lung cancer was diagnosed in 269 cases

Table 2. Logistic Regression Analysis of 14 435 Baseline Screenings for Lung Cancer, Prevalence Odds Ratio, Women vs Men by Controlled Covariates

Covariates	Coefficient (SE)*	Odds Ratio (95% CI) Estimate	P Value†
None	0.44 (0.14)	1.6 (1.2-2.0)	.002
Age and smoking	0.54 (0.14)	1.7 (1.3-2.3)	<.001

Abbreviation: CI, confidence interval.
*Coefficient of sex indicator: 1 if female, 0 otherwise.
†Two-sided.

Table 3. Distributions of Women and Men With Baseline Diagnosis of Lung Cancer According to Age, History of Smoking at Time of Diagnosis, Clinical Stage I of the Disease, and Resection*

Characteristic	Women (n = 156)	Men (n = 113)
Age, median (range), y	67 (47-84)	68 (49-83)
Pack-years of smoking, median (range), No.	47 (2-125)	64 (9-130)
Stage I disease	139 (89)	90 (80)
Underwent resection	125 (90)	79 (88)

*Data are reported as No. (%) of participants unless otherwise noted.

Table 4. Distributions of Cases of Baseline Diagnosis of Lung Cancer by Tumor Diameter

Tumor Diameter, mm	No. (%) Women (n = 156)	Men (n = 113)
<10	17 (11)	10 (9)
10-20	103 (66)	69 (61)
>20	36 (23)	34 (30)

(156/7498 women and 113/9427 men). The combined women vs men prevalence OR estimate, when controlling for age and pack-years of cigarette smoking, was 1.9 (95% CI, 1.5-2.5).

TABLE 3 shows that women diagnosed as having lung cancer were of a similar age as the men (67 vs 68 years) but had smoked considerably less (47 vs 64 pack-years, respectively). Also, the women were more frequently diagnosed as having clinical stage I disease (89% vs 80%), but when diagnosed as clinical stage I, women underwent resection only slightly more often than men (90% vs 88%). TABLE 4 shows the sex-specific frequency distribution of the diagnosed cases of lung cancer by tumor diameter to be quite similar. TABLE 5 provides the cell type distribution of the diagnosed cases. The proportions of adenocarcinoma among the women and men were 73% (114/156) and 59% (67/113), respectively ($P=.01$, 1-sided).

The incidence density (hazard) ratio of fatal outcome of lung cancer, women vs men, was 0.48 (95% CI, 0.25-0.89) (TABLE 6) when controlling for pack-years of smoking, disease stage, tumor cell type, and resection.

COMMENT

Following up on our previous study,[2] the findings reported herein again indicate that the risk of lung cancer is higher in women who smoke than in men of the same age who smoke the same amount.

The diagnoses were initially derived in the institutions in which the screenees were cared for, but in 222 of the 269 cases, the pathology specimens were independently reviewed by an expert panel of pulmonary pathologists. This panel confirmed all of the 222 cases as representing lung cancer, changing only the cell-type particulars in some of them. The low proportions of squamous and small cell carcinomas among the diagnosed cases were to be expected, as baseline screening less commonly leads to the detection of relatively fast-growing types, and also because there has been a shift to adenocarcinoma in cancer registry data in the United States and elsewhere.[9,13-15,28-31]

The results of our analysis do involve some residual confounding by age and/or smoking, despite the data in Table 1, but this confounding is negative, resulting in a diluted association (Table 2). As for potential confounding by other airborne carcinogens, the exposures presumably are more common and more pronounced among men, with the consequent bias again diluting rather than accentuating the apparent role of sex.

Our results also raise other questions. First, could the pursuit of malignancy diagnosis have been more vigorous with women screenees? We see no reason to presume this: not only was the diagnostic protocol the same for the 2 sexes, but its recommendations were followed equally. Had the reading of the images been biased in favor of more common nodule detection in the women, this would have accentuated the frequency of relatively small tumors among the diagnosed cases in the women (being that relatively small nodules are less readily detectable), but the proportions of tumors under 10 mm in diameter were quite similar for women and men (0.11 [17/156] vs 0.09 [10/113], respectively).

Second, could women more commonly have presented themselves for screening on the prompting not merely of risk, but also the presence of cancer-suggestive symptoms? Again, we see no reason to presume this. Nevertheless, if this was the case, the largest tumors would have been relatively more common in the cases diagnosed in the women (as larger cancers are more likely to be symptomatic). But the proportion of tumors more than 20 mm in diameter was actually lower in the women than in the men (0.23 [36/156] vs 0.30 [34/113], respectively). Thus, insofar as some of the diagnosed cases actually were symptomatic and differentially so between the sexes, this again more likely diluted rather than accentuated the apparent role of patient sex.

Third, could the higher prevalence of detected cancer in women have resulted from a generally lesser aggressiveness—lower rate of growth—of the women's cancers compared with those of the men? Referring to Table 5, we note that for the slowest-growing malignancies, typical carcinoids and adenocarcinomas of the bronchioloalveolar subtype, the proportions in women's and men's cases were 6% (9/156) and 4% (5/113), respectively. Also, for the fastest-growing type, small cell carcinoma, the corresponding proportions were 3% (4/156) and 11% (12/113), respectively. The degree of aggressiveness of the women's cancers thus tended to be slightly lower than that of the men's. But if in 10% of the women's cases the growth rate was, for example, one half of that in the men's cases, this would have made the prevalence OR (incidence density) no higher than 1.1. Table 5 clearly indicates that insofar as a given level of smoking causes lung cancer more commonly in women than in men, the excess cases are principally adenocarcinomas, as has been shown in other studies.[9,13-15]

The hypothesis that women may be more susceptible to tobacco carcinogens is biologically plausible.[32,33] While evidence from some epidemiological cohort studies does not substantiate this idea,[10-12] a subsequent study based on the national SEER registry[9] again suggested the increased susceptibility of women. If additional studies add supporting evidence, the notion of women's susceptibility to tobacco carcinogens warrants serious consideration.

If lung cancer risk for women who smoke is indeed higher than the risk for men of the same age who smoke, as indicated by the evidence presented here, this suggests that antismoking efforts directed toward girls and women need to be even more serious than those directed toward boys and men. In the same vein, insofar as screening for lung cancer is practiced among smokers, female sex calls for screening at lower levels of smoking history than the corresponding indication threshold in men. Specifically, if men of a given age are to be screened if the number of pack-years of past smoking is at least X, the regression analysis of the 2 screening series combined suggests that the corresponding threshold for women would be X−0.662/0.0138=X−48 pack-years, where 0.662 and 0.0138 are the fitted coefficients of the indicator of female sex and pack-years of smoking; that is, that the screening threshold for women of a given age should be 50 pack-years lower than that for men of the same age.

Table 5. Cell Type Distribution of the Diagnosed Cases of Lung Cancer

	No. (%)		
Cell Type	Women (n = 156)	Men (n = 113)	Total (N=269)
Carcinoid, typical	6 (4)	1 (1)	7 (3)
Adenocarcinoma (bronchioloalveolar)	3 (2)	4 (4)	7 (3)
Adenocarcinoma (other)	111 (71)	63 (56)	174 (64)
Squamous cell carcinoma	22 (14)	19 (17)	41 (15)
Non–small cell carcinoma, NOS	3 (2)	6 (5)	9 (3)
Carcinoid, atypical	2 (1)	0	2 (1)
Large cell carcinoma	5 (3)	4 (3)	9 (3)
Small cell carcinoma	4 (3)	12 (11)	16 (6)
Other	0	4 (3)	4 (2)

Abbreviation: NOS, not otherwise specified.

Table 6. Multivariate Cox Regression Analysis of 269 Baseline Diagnosed Cases of Lung Cancer for the Hazard Ratio of Fatal Outcome, Women vs Men by Controlled Covariates*

Covariates	Coefficient (SE)*	Hazard Ratio (95%CI) Estimate	*P* Value†
None	−1.12 (0.31)	0.33 (0.18-0.61)	<.001
Smoking, stage, cell type, and resection	−0.75 (0.32)	0.48 (0.25-0.89)	.02

Abbreviation: CI, confidence interal.
*Coefficient of sex indicator: 1 if female, 0 otherwise.
†Two-sided.

It is well-established by the evidence accumulated over the past 20 years that women with lung cancer survive the disease better than men,[9,12-20] and that this difference is more pronounced when the cancer is diagnosed at an early stage.[18-20] Cancer stage at diagnosis, cell type, or treatment do not appear to be entirely explanatory of this difference.[21] As 85% (229/269) of the cases considered here were clinical stage I at diagnosis, the fatality hazard ratio in favor of women, conditional for pack-years of smoking, disease stage, tumor cell type, and resection was more pronounced than those reported by others.[21] Despite the conditionality, it is not clear whether this survival difference is because lung cancer in women tends to be more commonly curable or less malignant. If lung cancer is more commonly curable in women, then the need to screen women at a lower threshold than men is warranted. If lung cancer is less malignant in women, there may be less need to screen women at a lower threshold.

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cate that for patients with dementia to qualify for hospice they must be at or beyond FAST stage 7 *and* be unable to ambulate independently. This effectively makes the cut-off stage 7c on the FAST scale.[2]

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CORRECTION

Unreported Financial Disclosures: In the Original Contribution entitled "Women's Susceptibility to Tobacco Carcinogens and Survival After Diagnosis of Lung Cancer" published in the July 12, 2006, issue of *JAMA* (2006;296[2]:180-184) and in the Letter entitled "Computed tomography screening for lung cancer" published in the August 1, 2007, issue of *JAMA* (2007;298[5]:514-515), financial disclosures were not reported. See also related letter in this issue. The paragraph should have read as follows:

Financial Disclosures: Drs Henschke and Yankelevitz reported being listed as coinventors for the following patent and patent applications: US Patent No. 7,274,810, "System and Method for Three-Dimensional Image Rendering and Analysis" (patent issued to CRF September 25, 2007); US Patent Application No. 10/245,782, "System, Method and Apparatus for Small Pulmonary Nodule Computer Aided Diagnosis from Computed Tomography Scans" (CRF pending patent application); US Patent Application No. 11/827,985, "System and Method for Three-Dimensional Image Rendering and Analysis" (CRF pending divisional application); US Patent Application No. 11/827,994, "System and Method for Three-Dimensional Image Rendering and Analysis" (CRF pending divisional application); US Patent Application No.10/688,267, "System, Method and Apparatus for Small Pulmonary Nodule Computer Aided Diagnosis from Computed Tomography Scans" (CRF pending patent application); US Patent Application No. 10/901,316, "System and Method for Providing Remote Analysis of Medical Data" (CRF pending patent application); US Patent Application No.10/932,443, "System and Method for Analyzing Medical Data to Determine Diagnosis and Treatment" (CRF pending patent application); US Patent Application No. 10/901,362, "System and Method for Conducting a Clinical Trial Study" (CRF pending patent application); US Patent Application No. 11/688,980, "Medical Imaging Visibility Index System and Method for Cancer Lesions" (CRF patent cooperation treaty application also pending); US Patent Application No. 11/377,031, "Method for Expanding the Domain of Imaging Software in a Diagnostic Workup" (CRF pending patent application) (foreign patent applications also pending); US Patent Application No. 11/858,855, "System and Method for Position Matching of a Patient for Medical Imaging" (CRF pending patent application); and "Medical Imaging System for Accurate Measurement Evaluation of Changes in a Target Lesion" (foreign patent applications pending) (Henschke/Yankelevitz pending patent application). Dr Henschke reported receiving compensation for serving as a member of a National Cancer Institute study section. Dr Yankelevitz reported being an inventor on a pending patent related to biopsy needles assigned to PneumRX, being a paid medical advisor to PneumRX, and holding stock in PneumRX.

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