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Women's susceptibility to tobacco carcinogens☆

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Summary *Study objectives:* To assess lung cancer risk of smoking women relative to that of equally smoking men. *Methods:* The study base was constituted by baseline CT screenings for lung cancer on 1202 women and 1288 men, at least 40 years of age and with at least 10 pack-years of cigarette smoking. The prevalence-odds (incidence-density) ratio contrasting women with men was calculated. Confoundings by age and the particulars of smoking history were controlled in logistic regression analysis. *Results:* For the prevalence-odds ratio contrasting women with men, upon control of age and smoking history, the point estimate was 2.7 and the 95% interval estimate 1.6–4.7. The diagnosed cancers were of equally 'aggressive' types between the two genders. *Conclusions:* At variance with evidence from cohort studies, this evidence from a screening experience calls for further consideration of the hypothesis that women are more susceptible to tobacco carcinogens than are men.

1. Introduction

In the United States in 2000, lung cancer is estimated to have accounted for 67,600 deaths in women, a number which was only slightly lower than the corresponding one for men, 89,300 [1]. The incidence of lung cancer in women has continued to increase, so that as of 1987 in the United States the number of deaths from lung cancer among women has been higher than that from breast cancer. In March 2001, the Surgeon General noted that smoking-related diseases have become ''epidemic'' among women, with almost four of each 10 smoking-related deaths now occurring in women, a proportion that is more than double that in 1965 and largely due to disproportionate rise in lung cancer mortality among women [2].

It has been hypothesized that women are more susceptible to tobacco carcinogens than are men. The epidemiologic literature on this topic was recently succintly reviewed by Thun et al. [3]. They stated the following:

> At least ten case-control studies have reported that women who smoke have a higher relative risk of developing lung cancer from smoking than do male smokers ... . Women have similar or lower death rates from lung cancer than do men in large cohort studies... within equivalent strata

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> of age and smoking... [and] all of the studies that postulate greater risk in women than men are case-control studies that estimate relative, but not absolute, risk.

In summary they stated that:

> There is currently no good evidence that women are more susceptible to develop lung cancer ... from smoking than men, ... and there is much evidence that this is not the case.

The purpose of the present study was to address further the *absolute* risk for lung cancer of smoking women relative to that of equally smoking men, using an approach not used in any of the previous studies.

2. Methods

Our study was based on two sources of data, both of them derived from baseline CT screening for lung cancer. The screenings were confined to asymptomatic volunteers with no history of cancer (other than non-melanotic skin cancer), fit to undergo thoracic surgery and consenting to the screening. The first source was the series of 1000 volunteers, 459 women and 541 men, at least 60 years of age and with a history of least a 10 pack-years of smoking, at baseline CT screening for lung cancer within the Early Lung Cancer Action Project (ELCAP) from 1993 to 1998 [4]. The women in this series had a median age of 67 years and their median of pack-years of smoking was 41; for the men the corresponding values were 66 years and 47. The second source was a series of 1490 volunteers, 743 women and 747 men, at least 40 years of age and with a history of at least 10 pack-years of smoking, undergoing in 1999 to 2001 the same baseline CT screening for lung cancer that was used for the first series. For the women in this series the median age was 59 years and the median number of pack-years of smoking was 33; for the men the corresponding values were 60 years and 37. In both series the median age of starting smoking was quite the same between the two genders. All of these data are given in Table 1.

For both series, detailed information about smoking history was recorded at the time of the baseline screening. It was elicited in a detailed interview by a well-trained interviewer. Starting with the age at which habitual smoking began, and using various 'life events' as points of reference, the interviewer identified successive spans of age each characterized by its particular, typical number of cigarettes smoked per day. A computer algorithm translated these data to the lifetime cumulative number of pack-years of cigarette-smoking and also to the average daily number of cigarettes smoked in each of the four most recent decades of life prior to the screening.

The protocol for the diagnostic work-up following the initial test's positive result—the identification of 1—6 non-calcified nodules—was the same in the two series. If the largest one of those nodules was less than 10 mm in diameter, follow-up CT in 3 months was recommended to assess growth; and for instances of documented growth, biopsy was recommended. For those among the 1—6 non-calcified nodules that were more than 10 mm in diameter, biopsy was recommended in accordance with the prevailing standards of care. Biopsies performed outside of these recommendations did not produce any diagnosis of lung cancer.

The diagnoses reported here are the consensus diagnoses by a panel of five international experts on lung pathology (Elizabeth Brambilla, Darryl Carter (chair), Adi Gazdar, Masayuki Noguchi, William Travis). The panel followed the ELCAP pathology protocol [5]. All but five of the diagnosed cancers were resected. The diagnoses reported here were based on the histology of the 60 surgical specimens and the cytology of the biopsy in the five unoperated cases.

Women versus men incidence-density ratio for lung cancer was addressed as the ratio of the corresponding prevalence-odds (cancer present versus

Table 1 Comparison of the genders according to age and history of smoking, separately for the two series of baseline screening for lung cancer

	First series		Second series	
	Women	Men	Women	Men
Number of screenings	459	541	743	747
Median age (years)	67	66	59	60
Median pack-years of smoking	41	47	33	37
Median age (years) of starting smoking	18	17	17	17

cancer absent odds), conditional on age and history of smoking. In logistic regression analysis (unconditional), with the dependent variate an indicator of cancer present ($Y = 1$ if cancer, 0 otherwise), we controlled possible confounding by age (single quantitative term, there being no apparent actual confounding; Table 1), and the definite confounding by the particulars of smoking history (pack-years of cigarette smoking and, separately, rate of cigarette smoking in each of the four most recent decades of life prior to the screening, the confounding being 'negative,' diluting the association; Table 1). There was no confounding by chest radiography nor chest CT in the antecedent 2 years: the first series derived from screening for which absence of such imaging was an admissibility criterion; and in the second series the question was asked, but none of the screenees had undergone such imaging.

3. Results

In the ELCAP baseline screening, 22 lung cancers were diagnosed in the 459 women and 8 in the 541 men. Thus, for the crude women versus men prevalence-odds ratio the point estimate was $[22/(459-22)]/[8/(541-8)] = 3.4$, statistically in highly significant excess of 1.0 ($P = 0.001$, one-sided). Table 2 gives this same result from logistic-regression discrimination between the case ($n = 30$) and non-case ($n = 970$) series.

Table 2 also gives the corresponding results when jointly controlling age and history of cigarette smoking. When the smoking history was represented by a single linear term for the cumulative number of pack-years of smoking, the point estimate was 3.8 and the 95% interval estimate 1.6—8.6. When this representation was replaced by separate terms for the average numbers of cigarettes smoked per day in each of the four most recent decades of life, the result was essentially the same (Table 2).

From the second series of 1490 volunteers, upon control of age and smoking, the point and 95% interval estimates for the prevalence-odds ratio were 2.1 and 1.0—4.3, respectively. This result (OR = 2.1) was not, statistically, significantly different ($P = 0.09$, one-sided) from that from the first series (OR = 3.8). For this analysis there were 23 diagnosed cases among the 743 women and 12 among the 747 men.

From the combined study base, upon control of age and smoking, the incidence rate ratio point and 95% interval estimates were 2.7 and 1.6—4.7, respectively (Table 2).

Table 3 provides the cell-type particulars of the final diagnoses (60/65 of them post-surgical, histologic), separately for the two genders. The proportions of adenocarcinoma among the women's and men's cases were $32/45 = 71\%$ and $10/20 = 50\%$, respectively ($P = 0.05$, one-sided).

4. Discussion

The ELCAP baseline screening experience with 1000 high-risk persons together with the added experience with 1490 similar though younger persons provides substantial numerical evidence indicating that smoking women have a higher incidence/risk of lung cancer than equally smoking men of the same ages; but what about the validity of this evidence?

Table 2 Logistic regression analysis of lung cancer prevalence-odds ratio (OR), women versus men, specific for the two series of baseline screening and for the two series combined, separately according to the 10 determinants that were controlled

Series	10 determinants	Coefficient[a]	Standard error	OR estimate	
				Point	Interval (95%)
1	None	1.21	0.42	3.4	1.5—7.6
	Age and smoking[b]	1.32	0.42	3.8	1.6—8.6
	Age and smoking[c]	1.35	0.43	3.8	1.6—9.0
2	None	0.67	0.36	2.0	1.0—4.0
	Age and smoking[b]	0.74	0.36	2.1	1.0—4.3
1 + 2	None	0.90	0.27	2.5	1.4—4.2
	Age and smoking[b]	1.00	0.28	2.7	1.6—4.7

[a] Gender indicator equal to one if female, zero otherwise.
[b] Pack-years of cigarette smoking.
[c] Average number of cigarettes smoked per day, separately for each of the four most recent decades.

Table 3 Consensus diagnoses (histologic in 60/65) of the Expert Pathology Panel, by gender

Diagnosis	Gender				Total	
	Female		Male			
	n	%	*n*	%	*n*	%
Carcinoid	3	7	2	10	5	8
Adenocarcinoma, BAC[a]	4	9	2	10	6	9
Adenocarcinoma, other	32	71	10	50	42	65
Squamous-cell carcinoma	2	4	2	10	4	6
Non-small-cell carcinoma	3	7	2	10	5	8
Small-cell carcinoma	1	2	2	10	3	4
Total	45	100	20	100	65	100

[a] Adenocarcinoma with bronchioloalveolar features.

Are the diagnoses credible? The pathologic diagnoses were initially derived in the institutions in which the screenees were cared for, but 60 of the 65 diagnoses were independently reviewed by an expert panel of pulmonary pathologists. The resulting expert consensus did not exclude any of the initially diagnosed cases, changing only the cell-type particulars in some of the malignancy diagnoses. The subtypings reported here represent the expert panel's consensus. The apparent underrepresentation of squamous and small-cell carcinomas was to be expected: the malignancies diagnosed on baseline CT screening tend not to include the more commonly squamous endobronchial ones, nor the relatively fast-growing small-cell types; and they reflect the marked shift to adenocarcinoma that also is manifest in cancer registries in the United States and elsewhere.

Might the pursuit of malignancy diagnosis have been more vigorous with female screenees? We see no reason to presume this, as the diagnostic protocol was the same for the two genders and it was followed by both to the same extent the recommendation for biopsy was routinely followed, except that it was refused for some time by three, all women. But if such a bias nevertheless was present, proportionally more malignancies would have been diagnosed in the smallest nodules radiographically noted in the women (being that relatively small nodules are, in themselves, less suspicious). The facts contradict this. The modal category of tumor diameter for the diagnosed cancers was 10—20 mm, and the ratio of the number of tumors under 10 mm in diameter to that of tumors 10—20 mm in diameter was actually lower in the women than in the men ($13/26 = 0.5$ versus $7/8 = 0.9$; $P = 0.03$, one-sided). Thus, insofar as there was differential diligence in the diagnostic pursuit, it more likely accentuated case detection in the men, thereby diluting the association of interest.

Might women more commonly have presented themselves for screening on the prompting not merely of risk but the furtive presence of cancer-suggestive symptoms? Again, we see no reason to presume this. But if this nevertheless was the case, proportionally more malignancies would have been diagnosed in association with the largest nodules in the women (as larger cancers are more likely to be symptomatic). But this, too, is contradicted by the facts: the ratio of the number of tumors over 20 mm in diameter to that of tumors 10—20 mm in diameter was actually lower in the women than in the men ($6/26 = 0.2$ versus $5/8 = 0.6$; $P = 0.02$, one-sided). Thus, insofar as some of the diagnosed cases actually were symptomatic and differentially between the genders, this again more likely diluted rather than accentuated the apparent role of gender.

The median category of tumor size (diameter 10—20 mm) included 71% (32/45) of women's cancers in contrast to 50% (10/20) of men's. The difference is of some note statistically ($P = 0.05$, one-sided). We suspect that this is a matter of mere chance.

Could the higher prevalence of detected cancer in women have resulted from lesser degree of 'aggressiveness'—lower rate of growth—of the women's cancers relative to those of the men? Insofar as this was the case, it presumably was principally a consequence of gender differences in the distribution of the screen-diagnosed cancers by cell type. Referring to Table 3, we note that the slowest-growing malignancy types presumably are the carcinoids together with bronchioloalveolar carcinomas, and that their respective proportions in women's and men's cases were $7/45 = 16\%$ and $4/20 = 20\%$ respectively, so that the proportion of

the women's cases actually was lower than that of the men's. The fastest-growing type obviously is small-cell carcinoma; and for this, the proportions in women's and men's cases were insignificant (1/45 and 2/20, respectively). All in all, then, differential rate of growth does not appear to be explanatory of the observed association between lung cancer prevalence and gender (conditional on age and smoking history).

Apart from these fringe patterns of cell-type distributions, bearing on validity of the evidence in respect to gender-differential risk, Table 3 clearly indicates that insofar as a given level of smoking indeed causes more lung cancer in women than in men, these 'excess' cases are principally adenocarcinomas.

The remaining possible source of bias explanatory of the observed association between gender and lung cancer is residual confounding by smoking, based on relative underreporting of the extent of past cigarette smoking by women. If one suspects that such differential reporting may be the case in general, one then must wonder about the extent to which this also might be true of women who seek screening for lung cancer. A major, to us incredible, difference ought to be postulated to explain the results here.

The results here do involve residual confounding by smoking, because the control of it was based on imprecise data. But the confounding is 'negative,' resulting in a diluted association (Table 2), and therefore the residual confounding also has this diluting effect on the apparent association. And as for potential confounding by other airborne carcinogens, the exposures presumably are more common and more pronounced among the men, with the consequent bias again diluting rather than accentuating the apparent role of gender.

The idea that women may be more susceptible to tobacco carcinogens does have biologic credibility [6,7]. On the other hand, epidemiologic evidence from cohort studies substantially contradicts this idea. Should other screening-based studies turn out to support the hypothesis, we would be at a loss to explain the difference in the results of these two types of study. For now, no question, the bulk of the evidence is against the hypothesis.

If smoking women's lung cancer risk indeed were to be higher than equally smoking men's to the extent that is indicated by the evidence presented here, this would mean that anti-smoking efforts directed to girls and women need to be even more serious than those directed to boys and men. In the same vein, insofar as screening for lung cancer is practiced among smokers, female gender would call for screening at lower levels of past smoking relative to the corresponding indication threshold in men.

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