Are women particularly susceptible to the effects of smoking on lung cancer?

Author : P N Lee
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Introduction

There have been a number of suggestions in the literature that women may be more susceptible than men to the effects of tobacco smoking on health, particularly in respect of the effect on lung cancer. This note is intended to give some brief comments on the validity or otherwise of the claims.

There are a number of theoretical problems in evaluating these claims. The first arises from the definition of susceptibility. One could argue that women are more susceptible to men if, all other things being equal (i.e. same smoking habits and same exposure to other relevant non-smoking variables), women can be shown to have a higher lung cancer risk than men. Such analysis would require detailed data on all relevant aspects of smoking, including inhalation characteristics, and perhaps also data on weight (as women are lighter than men, so dose per unit body weight may vary between the sexes). One could also argue that women are more susceptible because they inhale differently, or because a given number of cigarettes a day implies a greater effective dose to a women than a man, so perhaps one should not adjust for inhalation or body weight. Clearly the way susceptibility is defined might affect the answer to the question. In practice, limitations of (available or reported) data in many studies means that one will normally limit attention to a comparison of men and women with adjustment only for age, number of cigarettes per day and duration of smoking (or perhaps age + pack-years only).

The second theoretical problem is what comparison to make. In case-control studies it is usually only possible to estimate relative risks and a method to investigate the problem might be to compare risks for smokers of a defined amount and duration (or pack-years) relative to never smokers separately for men and women. If smoking the given amount/duration multiplies risk more for women than for men, susceptibility might be regarded as demonstrated. If, however, the effect of smoking on risk is additive rather than multiplicative, differences in background (nonsmoker) risk between men and women might be relevant. For example, if (in

suitable units), absolute risks for a nonsmoker and a smoker are 2 and 22 for men and 1 and 21 for women, the relative risks are 11 and 21 respectively, though in one sense at least the effects are the same. One can usually investigate absolute risks only in prospective studies (though one might convert relative risks in case-control studies to absolute risks given data on frequency of smoking and overall lung cancer rate in the population studied). However, it is relevant to note that, in never smokers, absolute risks of lung cancer tend only to be slightly higher in men than in women (see below).

The third problem is that of sampling variation. Unless a study is very large, numbers of lung cancers in never smokers tend to be quite small, so that relative risk estimates have substantial variation. Male/female ratios of relative risk will have even higher variation. Not all studies take this into account.

Trends in national lung cancer rates over time

Because smoking was taken up later by women than men in many countries (e.g. US and UK), national lung cancer rates and current smoker/never smoker relative risks were much higher in men than in women. However, as women smoke more and have smoked for longer national rates for women have risen relative to men in recent years and current smoker/never smoker relative risks in women have also risen substantially. While these observations of themselves do not of course imply a greater susceptibility of women, rocketing lung cancer rates in women have led to the concern that ultimately rates in women might overtake rates in men, especially if women were more susceptible. I note that rates in women at present have not overtaken rates in men. For England and Wales, for 1999, lung cancer rates (per million) by age are as shown in the table below. On a superficial examination, these data do not suggest any marked excess susceptibility in women. The higher rates in older men will be due to their having a larger proportion of long-term smokers. The approximate equality in the age groups 25-34 and 35-44 seems consistent with smoking habits in younger men and women having been quite similar in England and Wales over the last 20 years or so, though rates and estimated consumption per adult remain slightly higher in men.

	Men	Women
25-34	2	2
35-44	37	33
45-54	275	193
55-64	1146	618
65-74	3237	1612
75-84	5403	2148
85+	5511	1512

The Risch study

An early study which looked at the issue of possible greater susceptibility in men than in women was that by Risch et al in 1993.[1] In that paper, the authors started by presenting (unreferenced) ever smoker/never smoker relative risks from over 50 epidemiological studies separately for men and for women. For men a smoothed average of the individual data points showed estimates rising from about 4 in 1940 to about 8 in 1960 then falling slightly. For women the rise was from about 2 in 1950 to 4 in 1975 and 8 in 1985, by which time the average slightly exceeded men. The authors noted that "possible explanations for a higher relative risk among female ever smokers could include 1) proportionately more current smokers and fewer ex-smokers compared with males, 2) higher cigarette consumption among female ever smokers, and 3) greater susceptibility of females to lung cancer at a given level of cigarette consumption." This analysis, which is clearly quite superficial, involving only ever/never smoker relative risks and with no estimation of sampling variation, led to their carrying out an epidemiological study to address the possibility that women might be more susceptible. [NB. We will shortly be in a position to carry out a more relevant and better analysis of trends in smoker/nonsmoker relative risks over time for the two sexes using the data collected from the IESLC project.]

This study involved 442 female histologically verified lung cancer cases aged 30-79 diagnosed in Canada in 1981-85 and similar sets of male cases, female population controls and male population controls matched to the female cases on age and area of residence. Using a model in which risk of lung cancer was related to pack-years and years since quitting by the relationship

$$\log \text{odds} = \beta_1 \log(1 + \text{pack-years}/5) + \beta_2 \text{ years since quitting}$$

they reported a statistically significant interaction between sex and the log(1 + pack-years/5) term with a p-value of 0.010. From their fitted model they estimated that current smokers of 40 pack-years had an odds ratio of 27.9 (95% CI 14.9-52.0) for women and 9.6(95% CI 5.64-16.3) for men, with odds ratios higher for women than for men for all four major lung cancer types.

The authors noted some limitations of the study, including low response rates and reliance on proxy data in a number of cases. There also seem to be problems with the mathematical modelling used, which involves various assumptions about how amount and duration of smoking should come into the model and the inclusion of a years since quitting variable for which never smokers would not seem to have an appropriate value. I would have much preferred a simpler, less model based approach. In any case the p-value of 0.010 is not particularly low and the study can at best be regarded as putting forward a suggestion to be confirmed by future work.

In subsequent correspondence in the journal various points were raised. One, by McDuffie,[1] who cited data reporting that women develop lung cancer at an earlier age than men, even though they begin to smoke cigarettes at an older age and smoke fewer cigarettes per day for fewer years, was irrelevant as analyses based on comparisons of age of onset of lung cancer with no reference to control data are known to be essentially meaningless. (Women get lung cancer at a younger age than men because female smokers are younger than male smokers in the population.)

More relevant were letters by Hoover and Wilcox[2] [3]who raised the problem already noted of reliance on relative rather than absolute risk data. In reply Risch et al[4] cited an estimate based on a meta-analysis of data from seven prospective studies of 0.78 (95% CI 0.71-0.86) for the relative risk of women to men in never smokers. They argued that this relative risk was too close to unity to affect their conclusions seriously.

Six years later, in a review paper, Pope et al[5] claimed that data from six other recent studies supported the claim by Risch et al.[6] I have available all but one of these references, and comment on them below.

The Harris study

Harris et al[7] described results from the American Health Foundation's case-control studies conducted over the previous 20 years. Based on over 4000 lung cancer cases and a similar number of controls matched on age, sex, race, and year of interview they reported the following relative risks (compared to never smokers):

Level of cumulative	Female/male relative risks (95% CI)	
tar exposure (kg)	Ever smokers	Current smokers
1-4	1.0 (0.6-1.4)	0.9 (0.5-1.3)
5-8	2.0 (1.2-2.8)	1.8 (1.1-2.5)
>8	1.9 (1.1-2.7)	1.7 (1.1-2.3)
Combined estimate	1.7 (1.2-2.2)	1.5 (1.1-2.9)

Cumulative tar exposure was estimated by the product of cigarettes per day, average tar and duration of exposure. The problem with this analysis is that it assumes that duration and dose have the same relationship to risk when ample evidence suggests this is not the case, with the relationship to duration having a much stronger relationship to lung cancer risk than does amount smoked (or tar). As women smoke less cigarettes/day and lower tar yield cigarettes than men, equality of cumulative tar exposure implies longer duration by women than men, hence higher risk of women in the analysis. While effects of duration may be weaker in an analysis involving age-matched cases and controls, I find it impossible to tell whether the reported finding of a higher risk in women is real or an artefact of a misguided analysis.

The Osann study

Osann et al[8] reported results from a case control study involving about 2000 lung cancer cases in Orange County. The major findings are reproduced in the table following. As one can see, most of the comparisons show no evidence of a higher odds ratio for women than men. Only for small-cell carcinoma were estimates higher for women than for men. However, the authors

note that "differences between men and women were not statistically significant." In fact, the authors' argument that "women may be more susceptible to the effects of cigarette smoking" arises from the fact that odds ratios are quite similar for men and women, despite women adopting low tar cigarettes earlier, but no analysis is carried out taking tar into account.

Age and race adjusted odds ratios for smoking by cell type

Histology and gender	Ever smoked cigarettes		Smoked <2 pk/d		Smoked ≥2 pk/d	
	OR[1]	95% CI	OR[1]	95% CI	OR[1]	95% CI
All lung cancer						
Males	19.7	14.4-26.8	17.7	12.6-24.8	42.8	30.5-60.1
Females	15.0	11.8-19.1	14.4	11.0-18.9	40.9	29.3-57.1
Squamous-cell carcinoma						
Males	36.1	17.8-73.3	35.3	17.0-73.3	76.0	36.8-157
Females	26.4	14.5-48.1	24.0	12.7-45.5	72.3	36.8-142
Small-cell carcinoma						
Males	37.5	13.9-102	27.6	9.8-77.4	95.3	34.7-262
Females	86.0	31.6-234	76.7	27.5-215	316.1	111-900
Adenocarcinoma						
Males	17.9	10.4-31.0	16.5	9.3-29.3	37.5	21.3-66.0
Females	9.5	6.8-13.8	8.8	6.1-12.8	24.2	15.8-37.2

[1] Odds ratios relative to never smokers.

The Engeland study

Engeland et al[9] (see also Review 883) describe results from a prospective study of 26,000 Norwegian men and women. They reported that, after adjustment for age at start of smoking, type of cigarette and amount smoked, risk to women was 33% higher in cigarette smoking women than in cigarette smoking men. However, this estimate, being based on 65 cases in women and 258 cases in men, was only marginally significant (I estimate 95% CI of 1.01-1.75) and may well be biased. Smoking habits were recorded only once, in 1964-1965, and are likely to have changed over the 28 year follow-up period, quite likely differentially between men and women.

The Zang study

Zang and Wynder,[10] in a paper "Differences in lung cancer risk between men and women: examination of the evidence" also reported findings from the American Health Foundation case-control studies. I have discussed this paper at length in Review 863. Among points I noted, in this rather unconvincing paper, are:

1) At one point in the paper the authors argue illogically that because females with lung cancer had less exposure to cigarette smoke than males with lung cancer in their study, this indicates greater susceptibility of women to lung cancer. This is a *non sequitur*, as the observation would arise simply because women as a whole have less exposure than males.

2) Although they presented results, separately for squamous/epidermoid carcinoma and for adenocarcinoma, which claimed to show a stronger relationship of risk to cumulative tar, to pack-years and to most recent number of cigarettes per day in women than in men, their claim of statistical significance for nearly all comparisons seemed difficult to justify from the data presented. If one examines the data presented in their Table 4 for tar, for example, one sees that for 1-2 kg the odds ratio for females (24.5) is lower than for males (33.1), for 3-5 and 6-9 kg it is about the same (3-5 kg F 38.5, M 36.8; 6-9 kg F 56.2, M 54.3), and only for $\geq$9 kg is it higher (F 129.3, M 81.5). However, even here there is massive overlap of the confidence limits (F 47.3-353.2, M 38.3-173.2) and the difference is clearly not significant How then do they arrive at summary dose-response statistics of 3.2 (95% CI 2.7-3.8) for females and of 2.1 (95% CI 1.9-2.3) for males, which are very clearly not the same, implying a highly significant difference? Something seems wrong here.

3) I also noted (and this is a point which applies elsewhere too) that there may be a problem due to misclassification of smoking status. More men than women are ex-smokers and, since we know a moderately high proportion of ex-smokers report being never smokers on interview, the proportion of ex-smokers in the group reporting being never smokers will be higher in men than in women. As the misclassified ex-smokers will have higher lung cancer risk than true never smokers, this will lead to an underestimate of the smoker/never smoker risk ratio which will be more evident in men than in women, so

helping to explain the observation Zang and Wynder make.

The Tulinius study

Tulinius et al[11] describe results of a 27 year follow-up study of 22946 Icelanders. Relative to never smokers, they presented the following estimated relative risks for men and for women:

	Males	Females	Female/ male*
Former smoker	2.91 (1.47-5.74)	3.73 (1.73-8.07)	1.28 (0.46-3.58)
1-14 cigarettes/day	6.49 (3.25-13.0)	9.39 (4.99-17.7	1.45 (0.57-3.70)
15-24 cigarettes/day	13.5 (7.08-25.6)	30.7 (16.8-56.0)	2.27 (0.94-5.49)
25+ cigarettes/day	28.7 (14.9-55.1)	44.1 (21.1-91.8)	1.54 (0.57-4.11)

(*Estimated by me)

According to my calculations none of the four female/male ratios is statistically significant, although that for 15-24 cigs/day is reasonably close to being so. The fact that the female/male ratios are all above 1 may simply reflect that by chance there were relatively many lung cancer cases in male never smokers or relatively few in female never smokers. As for the Norwegian study data on smoking were only reported at one time point, and this could cause bias.

The meta-analysis by English

Pope et al[5] also cite results from a meta-analysis of 16 studies by English et al.[12] Based on nine cohort and seven case-control studies Pope et al present the following relative risk estimates for current versus never smokers:

	Males	Females	Female/ male*
Any	13.0 (12.2-13.7)	11.4 (10.5-12.3)	0.88 (0.79-0.97)
1-14 cigarettes/day	6.49 (5.48-7.70)	7.41 (6.52-8.41)	1.14 (0.92-1.41)
15-24 cigarettes/day	8.56 (7.07-10.4)	13.3 (11.7-15.2)	1.44 (1.14-1.81)
25+ cigarettes/day	15.1 (13.5-16.9)	20.5 (18.2-23.0)	1.36 (1.15-1.60)

(*Estimated by me, but see comments below)

As one can see, at each level of smoking the risk of lung cancer is greater in women than in men, with the difference significant for smokers of 15-24 and 25+ cigarettes/day. At present I do not have the source reference, nor know which 16 studies were used in the meta-analysis nor what their weaknesses are. It should be noted that my estimation of the female/male ratio incorrectly treats the male and female estimates as independent. More relevant is to meta-analyse the 16 individual study estimates of female/male ratio, but without these data I cannot do this.

Overview of evidence cited as supporting the hypothesis of increased susceptibility in women

It can be seen that the basis for the claim of greater susceptibility in women than in men is by no means fully established from the material cited in support of the hypothesis. Indeed Pope et al[6] note that "not all studies support the conclusion that women are more likely than men to develop lung cancer from the same exposure to tobacco smoke. More research is needed, particularly analytic studies of population-based cohorts." They do not draw attention to the various sources of bias I have alluded to above. Nor do they seriously attempt to study all the relevant evidence, and it is highly possible the studies they cite are selective in their results.

Analysis of the IESLC data will clarify the issue in due course. However, it is worth drawing attention to three other major studies at this stage.

Some other papers not considered by Pope

One is the paper by Kreuzer et al[13] based on pooled data from six IARC Western European case-control studies involving a total of almost 5000 lung cancer cases. Based on a detailed analysis using methodology I regard as reasonable (see Review 1100 for details) they

concluded that "for comparable exposure to tobacco smoke, the risk of lung cancer is comparable in women and men."

The other two studies are CPS I and CPS II. Based on detailed data presented by Thun et al,[14] I have estimated the relative risk of lung cancer by sex. As shown in the table below, the results for both surveys do not indicate that women are more susceptible than men, rather the reverse. Among current smokers, after adjustment for age, duration and amount smoked, the relative risk for females/males were 0.39 and CPS I and 0.65 in CPS II, both highly significant differences. Among never smokers risk was also lower in women, but no so markedly, with the age-adjusted relative risk 0.61 in CPS I and 0.83 in CPS II. (These analyses were conducted for data for all races, including prevalent cancers. Excluding non-whites and prevalent cancers made little difference.)

			Males		Females		
Study	Subset	Adjustment variables	O	E	O	E	R
CPS I	Never smokers	Age	80	55.26	198	222.74	0.61
	Current smokers						
	20/day	Age, duration	358	318.99	24	63.01	0.34
	40/day	Age, duration	121	116.63	8	12.37	0.62
	All	Age, duration, amount	479	435.62	32	75.38	0.39
CPS II	Never smokers	Age	119	103.57	305	320.43	0.83
	Current smokers						
	20/day	Age, duration	539	437.92	344	445.08	0.63
	40/day	Age, duration	330	295.48	121	155.52	0.70
	All	Age, duration, amount	869	733.40	465	600.60	0.65

(O = observed cases of lung cancer, E = expected assuming rates the same in men and women, R = ratio of O/E for females to O/E for males.)

Overall conclusion

More work is needed and will be done later by us using IESLC data. At this time I would regard the claim that women are more susceptible than men to the carcinogenic effects of tobacco smoke to the lung as being unproven.

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