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Are women more sensitive to smoking than men? Findings from the Renfrew and Paisley study

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Background Prescott *et al.* found that the relative risks associated with smoking for respiratory and vascular deaths were higher for women who inhale than for inhaling men, and found no gender differences in relative risks of smoking-related cancers. The purpose of the present study was to assess whether these findings are reproducible, using data from the Renfrew and Paisley study.

Methods Age-standardized mortality rate differences and age-adjusted mortality rate ratios (using Cox's proportional hazard model) were calculated for male and female smokers by amount smoked compared with never smokers. These analyses were repeated after excluding non-inhalers.

Results The all-cause mortality rate ratio was higher for men than for women in all categories of amount smoked, although this difference was only statistically significant in the light smokers (1.83 [95% CI : 1.61–2.07] for men and 1.41 [95% CI : 1.28–1.56] for women, $P = 0.001$). The cause-specific mortality rate ratios tended to be higher for men than for women, and this difference was most substantial for neoplasms (2.57 [95% CI : 2.01–3.29] for male light smokers and 1.35 [95% CI : 1.14–1.61] for female light smokers, $P < 0.001$) and, in particular, for lung cancer (11.10 [95% CI : 5.89–20.92] for male light smokers and 4.73 [95% CI : 2.99–7.50] for female light smokers, $P = 0.03$). Furthermore, looking at the rate differences the effects of smoking were uniformly greater in men than in women. These results were virtually unchanged after excluding non-inhalers.

Conclusion We found similar results to Prescott *et al.* when all smokers were considered, but could not reproduce their findings when non-inhalers were excluded. Given the fact that we showed greater rate differences in men than in women, we think that it is too early to conclude that women may be more sensitive than men to some of the deleterious effects of smoking.

Keywords Smoking, mortality, gender-difference, Renfrew & Paisley study

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In many countries the number of women who smoke has increased substantially over recent decades, and as a result mortality from smoking-related diseases in women is increasing.[1] It is often suggested that if women smoked like men, the number of women who died from tobacco-related disease would eventually be similar to that of men, since heavy smokers and inhaling smokers are known to have higher mortality risks.[1] Furthermore, there seems to be some evidence that women are, in some respects, more sensitive to the damaging effects of smoking.[2–4] For these reasons the study of Prescott *et al.* set out to compare the effect of smoking on mortality among women and men.[5]

There are other studies that have compared smoking-related mortality by gender. The female smokers in the British Physician's study for instance had lower relative mortality risks than male smokers,[6–8] and this was also found in Cancer Prevention Study (CPS) I and CPS-II,[1,9] in the Framingham study when considering coronary heart disease,[10] and in the Established Populations for Epidemiologic Studies of the Elderly.[11] In the NHANES-I,[12] a sub-sample of the Renfrew and Paisley study,[13] and in the Framingham study when stroke was considered,[14] relative mortality risks associated with smoking seemed similar in men and women. However, none of these

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studies have looked specifically at gender differences in smoking-related mortality and have formally tested for a difference in the relative mortality risk between men and women. This is important in particular since not only smoking behaviour in men and women differs in terms of amount smoked, but also the age at which they started to smoke and inhalation habits may be different.

In the study of Prescott *et al.*[5] a sufficient number of both men and women who are heavy smokers is included. In this way, differences in smoking habits between men and women in terms of the amount smoked, the age at which they started to smoke, and inhalation habits, could be taken into account. They found that despite large gender differences in age at which they started to smoke, all-cause and cause-specific mortality associated with smoking was similar in men and women. After excluding non-inhalers, the relative risks associated with smoking for respiratory and vascular disease were higher for women than for men, but there were no gender differences in relative risks of smoking-related cancers. They conclude that women may be more sensitive than men to some of the deleterious effects of smoking, but that rate differences may be similar, so that results should be interpreted with caution.

We used data from the Renfrew and Paisley study to assess whether these results are reproducible. This is a large prospective study carried out in the West of Scotland, which includes a considerable number of heavily smoking men and women. In addition to studying the relative mortality risks we also looked at the risk differences between men and women, to take into account the lower baseline mortality rates in women.

Subjects and Methods

The Renfrew and Paisley study is a longitudinal study of 15 406 adults aged 45–64 when first examined between 1972 and 1976. The study population is representative of the general population in that area of the West of Scotland (80% response). Full details of the study methodology and the measurements taken have been described previously.[15–17] An extensive questionnaire completed by the subject was checked by experienced interviewers at the screening examination. Smoking was classified into the categories: current smokers (1–14 cigarettes per day, 15–24 cigarettes per day and ⩾25 cigarettes per day), former smokers and never smokers. Those who smoked a pipe or cigars were categorized into a separate category. The age at which people started to smoke and inhalation habits were also assessed.

Men and women who had died over the 20 years of follow-up were identified by flagging at the National Health Service Central Register in Edinburgh. We excluded individuals who emigrated, since the vital status of these individuals is unknown, leaving 7045 men and 8348 women. Causes of death were divided into the same groups as those used by Prescott *et al*: vascular disease (ICD-9 codes 390–459), respiratory disease (codes 11–18, 460–466, and 472–519), neoplasms (codes 149–239) and all other causes. Furthermore, neoplasms were divided into tobacco-related cancers, i.e. cancer of lung (codes 162–163), oropharynx, larynx, oesophagus, pancreas, bladder and kidney (codes 140–150, 157, 161, and 188–189) and other cancers.

We calculated the mortality rate difference and the mortality rate ratio for male and female smokers by amount smoked compared with never smokers. These analyses were repeated after excluding non-inhaling smokers. Mortality rates were calculated using a person years at risk life-table approach. These were standardized for age by the direct method, using the total study population as the standard. We tested for differences in the mortality rate differences between men and women using a z-test. Cox proportional hazard analysis[18] was used to compute age-adjusted mortality rate ratios for male and female inhaling smokers by amount smoked. We tested for differences in the mortality rate ratios between men and women by including an interaction term between sex and smoking in the proportional hazard model.

Results

Table 1 shows some smoking characteristics of the Renfrew and Paisley study population at baseline examination. Comparing men and women, these figures show that men start to smoke at younger ages, that more men smoke and more of the men smoke heavily, and that a somewhat higher percentage of the men inhale. If we compare our study population to that of Prescott *et al.*, the Renfrew and Paisley study population has relatively more never smokers and fewer smokers than the Danish population. However, of those who smoke in the Renfrew and Paisley study population, smoking was started at younger ages and inhalation was more common than is the case for smokers in the Danish study population. On the other hand, the percentage of heavy smokers seems to be much higher in the Danish study population, although the definition of heavy smoking differed between the two studies so that the comparison is not exact.

Table 2 shows mortality rate ratios for male and female smokers compared with never smokers. The all-cause mortality rate ratio is higher for men than for women in all categories of amount smoked, although this difference is only statistically significant in the light smokers. The cause-specific mortality rate ratios tend to be higher for men than for women, and this difference is most substantial for neoplasms and, in particular, for lung cancer among light smokers. There are no statistically significant gender differences in all other primarily tobacco-related causes, such as respiratory diseases, vascular diseases and other tobacco-related neoplasms. The results are similar after excluding non-inhalers, with higher all-cause mortality rate ratios in men than women in all groups but a significant difference only in light smokers (Table 3).

Table 1 Smoking characteristics of entire study population at baseline examination by age and sex

	Men		Women	
	45–59	60+	45–59	60+
Sample	5472	1573	6374	1974
% never smokers	17.1	15.6	42.2	57.4
% former smokers	23.6	28.2	7.4	7.8
% smokers	59.3	56.2	50.4	34.8
of which % ⩾15 cigarettes per day	78.3	68.9	61.7	50.2
of which % inhaling	84.4	78.3	80.8	67.7
mean age at starting smoking (SD)	17.1 (4.3)	17.7 (5.0)	20.5 (7.3)	25.1 (9.9)

Table 2 Age-adjusted mortality rate ratios (RR) with 95% CI in male and female smokers compared with never smokers and significance tests comparing mortality rate ratios in men and women

	Daily amount smoked								
	1–14 cigarettes			15–24 cigarettes			25+ cigarettes		
	Men RR (95% CI)	Women RR (95% CI)	*P*-value	Men RR (95% CI)	Women RR (95% CI)	*P*-value	Men RR (95% CI)	Women RR (95% CI)	*P*-value
Vascular disease	1.60 (1.35–1.89)	1.43 (1.25–1.63)	0.17	1.74 (1.51–2.01)	1.91 (1.69–2.16)	0.90	1.80 (1.54–2.12)	1.63 (1.22–2.18)	0.19
Respiratory disease	2.12 (1.39–3.23)	2.28 (1.62–3.21)	0.77	2.45 (1.70–3.52)	3.08 (2.25–4.22)	0.33	3.62 (2.46–5.32)	2.87 (1.48–5.58)	0.58
All neoplasms	2.57 (2.01–3.29)	1.35 (1.14–1.61)	0.0001	3.07 (2.48–3.79)	1.85 (1.59–2.16)	0.0007	3.55 (2.83–4.46)	2.49 (1.88–3.29)	0.13
Lung cancer	11.10 (5.89–20.92)	4.73 (2.99–7.50)	0.03	16.42 (8.96–30.06)	9.04 (5.97–13.68)	0.13	17.99 (9.71–33.32)	19.22 (11.55–31.99)	0.77
Other tobacco-related	1.90 (1.07–3.38)	1.49 (0.91–2.43)	0.52	2.00 (1.22–3.27)	1.82 (1.17–2.84)	0.88	3.02 (1.80–5.04)	2.83 (1.33–6.05)	1.00
Non-tobacco related	1.50 (1.07–2.11)	1.01 (0.82–1.26)	0.09	1.39 (1.04–1.85)	1.19 (0.97–1.44)	0.61	1.55 (1.12–2.14)	0.91 (0.56–1.49)	0.15
Other causes	1.34 (0.90–1.99)	1.13 (0.84–1.52)	0.50	1.48 (1.06–2.05)	1.54 (1.18–2.00)	0.79	1.32 (0.89–1.96)	1.60 (0.90–2.82)	0.54
All causes	1.83 (1.61–2.07)	1.41 (1.28–1.56)	0.001	2.06 (1.86–2.29)	1.91 (1.75–2.08)	0.17	2.27 (2.02–2.56)	2.00 (1.67–2.40)	0.16

Table 3 Age-adjusted mortality rate ratios (RR) with 95% CI in male and female inhaling smokers compared with never smokers and significance tests comparing mortality rate ratios in men and women

	Daily amount smoked								
	1–14 cigarettes			15–24 cigarettes			25+ cigarettes		
	Men RR (95% CI)	Women RR (95% CI)	*P*-value	Men RR (95% CI)	Women RR (95% CI)	*P*-value	Men RR (95% CI)	Women RR (95% CI)	*P*-value
Vascular disease	1.66 (1.39–1.98)	1.54 (1.32–1.79)	0.27	1.76 (1.53–2.04)	2.12 (1.87–2.41)	0.42	1.79 (1.52–2.13)	1.67 (1.22–2.30)	0.22
Respiratory disease	2.17 (1.39–3.39)	2.39 (1.62–3.52)	0.77	2.47 (1.70–3.57)	3.34 (2.40–4.65)	0.25	3.46 (2.31–5.19)	2.85 (1.37–5.93)	0.61
All neoplasms	2.58 (2.00–3.34)	1.36 (1.11–1.67)	0.0002	3.23 (2.61–4.00)	1.97 (1.68–2.32)	0.001	3.86 (3.06–4.87)	2.55 (1.88–3.46)	0.08
Lung cancer	11.38 (5.98–21.68)	6.46 (4.03–10.39)	0.16	17.28 (9.42–31.68)	10.51 (6.90–16.00)	0.19	19.66 (10.58–36.55)	21.30 (12.56–36.14)	0.82
Other tobacco-related	1.80 (0.97–3.32)	1.49 (0.85–2.60)	0.67	2.17 (1.32–3.56)	1.85 (1.16–2.96)	0.78	3.38 (2.00–5.71)	2.55 (1.08–6.03)	0.71
Non-tobacco related	1.52 (1.06–2.17)	0.87 (0.67–1.14)	0.03	1.45 (1.08–1.94)	1.21 (0.98–1.49)	0.53	1.64 (1.17–2.30)	0.90 (0.53–1.55)	0.12
Other causes	1.38 (0.90–2.10)	1.32 (0.95–1.83)	0.85	1.58 (1.14–2.20)	1.54 (1.16–2.04)	0.91	1.28 (0.84–1.95)	1.50 (0.79–2.86)	0.67
All causes	1.88 (1.65–2.14)	1.50 (1.34–1.67)	0.01	2.13 (1.91–2.37)	2.07 (1.89–2.26)	0.38	2.32 (2.06–2.62)	2.04 (1.67–2.48)	0.12

Table 4 Difference in age-standardized mortality rates (per 10 000 person-years) of male and female smokers compared with never smokers and significance tests comparing mortality rate differences in men and women

	1–14 cigarettes			15–24 cigarettes			25+ cigarettes		
	Men	Women	*P*-value	Men	Women	*P*-value	Men	Women	*P*-value
Vascular disease	46.5	19.6	<0.001	55.6	40.1	<0.001	60.0	21.0	<0.001
Respiratory disease	11.9	7.0	<0.001	15.2	11.1	<0.001	29.1	10.0	<0.001
All neoplasms	46.9	10.9	<0.001	62.5	27.3	<0.001	72.9	49.5	<0.001
Tobacco-related neoplasms	37.8	10.3	<0.001	54.9	21.7	<0.001	63.0	50.2	<0.001
Other neoplasms	9.1	0.7	<0.001	7.4	5.6	<0.001	9.7	–0.6	<0.001
Other causes	5.5	1.6	<0.001	7.4	6.5	0.13	4.7	6.3	0.007
All causes	110.6	39.4	<0.001	140.2	85.1	<0.001	165.9	87.6	<0.001

Table 5 Difference in age-standardized mortality rates (per 10 000 person-years) of male and female inhaling smokers compared with never smokers and significance tests comparing mortality rate differences in men and women

	1–14 cigarettes			15–24 cigarettes			25+ cigarettes		
	Men	Women	*P*-value	Men	Women	*P*-value	Men	Women	*P*-value
Vascular disease	51.1	22.8	<0.001	57.8	47.6	<0.001	61.1	21.1	<0.001
Respiratory disease	12.2	7.4	<0.001	15.4	12.1	<0.001	26.7	9.3	<0.001
All neoplasms	47.0	11.5	<0.001	66.7	30.6	<0.001	81.9	49.3	<0.001
Tobacco-related neoplasms	37.9	13.8	<0.001	58.0	24.2	<0.001	69.6	51.3	<0.001
Other neoplasms	9.1	–2.3	<0.001	8.6	6.5	<0.01	12.0	–1.9	<0.001
Other causes	6.1	3.7	<0.001	9.1	6.6	<0.01	4.1	4.9	0.26
All causes	116.3	45.7	<0.001	149.1	97.4	<0.001	174.1	85.0	<0.001

Again the difference in cause-specific mortality rate ratio is most pronounced for neoplasms, but now in particular for non-tobacco related neoplasms. Again there are no statistically significant gender differences in all other primarily tobacco-related causes.

Table 4 shows that the mortality rate difference between smokers and never smokers is significantly greater for men than for women in all but one group (other causes among heavy smokers). Very similar results were found after excluding non-inhalers (Table 5).

Discussion

In the present study we found that the mortality rate ratios tended to be higher for male than for female smokers compared with never smokers. When these differences between men and women were tested statistically, the difference in all neoplasms for light and moderate smokers, lung cancer mortality for light smokers and all-cause mortality for light smokers were significant. There were no significant gender differences in all other primarily tobacco-related causes, such as respiratory diseases, vascular diseases and other tobacco-related neoplasms. Furthermore, we found that the mortality rate differences were greater for men than for women for all causes of death and categories of amount smoked. These results were virtually unchanged when non-inhalers were excluded. The most likely explanation for the greater rate differences in men with respect to smoking-related causes of death is the difference in smoking duration between men and women, since the Renfrew and Paisley men started to smoke at younger ages. The average smoking duration was 36.60 and 32.15 years for male and female smokers, respectively (t-test of difference t = 25 195, d.f. = 7357, $P < 0.0001$). For neoplasm mortality the greater rate ratios in men than women reflect the fact that for women a major contributor to neoplasm mortality—breast cancer—is not strongly (if at all) related to smoking.

These findings are contrary to those found by Prescott *et al.*, who found higher relative risks for women for respiratory and vascular disease. Only the difference with respect to cerebrovascular disease was statistically significant in their study. Furthermore, as in the present study, higher relative risks were found for men for neoplasms and in particular lung cancer. Only the difference with respect to all neoplasms was statistically significant. When non-inhalers were excluded, the study by Prescott *et al.* found higher relative risks for women for respiratory and vascular disease and no gender differences in smoking-related risk of cancer, although only the difference with respect to vascular disease, and in particular cerebrovascular disease, was statistically significant. Their conclusions are based on the latter results.

Comparing the magnitude of the rate ratios in the two studies, which is complicated by the fact that the definition of smoking amount is different, it becomes apparent that the all-cause mortality rate ratios are slightly higher in the Danish males, but that this difference is much greater for women, in particular for the heavy smokers. A similar picture appears when looking at cause-specific mortality, except for cancers. The rate ratios for cancers are lower in the Danish males than in the men from the Renfrew and Paisley study, while the opposite is true for women, with higher mortality rate ratios for the Danish females. So it seems that the difference in findings between the two studies is mainly caused by the difference in findings in females, where the mortality rate ratios in the Danish females are much higher. This cannot be explained by

the age at which the women started to smoke, since the Danish women started to smoke at older ages. It cannot be explained by inhaling habits, since similar results were found when excluding non-inhalers in the two studies. The remaining explanations may be that the Danish women smoked more, since the two studies were not completely comparable with regard to amount smoked, or that the distribution of age or other risk factors differed between the two studies and between men and women.

The conclusions in the study by Prescott *et al.* are based on their analyses when excluding non-inhalers. This might have been done since pipe and cheroot smokers were included, and in this way they attempted to score smoking habits in terms of grams of tobacco per day. Although self-reports of inhaling may not be very useful for cigarette smokers since they all inhale to at least a moderate extent, they may be of greater value for discriminating higher and lower risk pipe and cigar smoking. However, Prescott *et al.* may have introduced a gender bias into their study by attempting to include different tobacco products within the same analysis, since the use of these differs between men and women. The present study does not have this bias since pipe and cigar smokers were categorized separately and we focussed on cigarette smokers in our analyses. As a result of this bias we think that the conclusions from the study by Prescott *et al.* cannot solely be based on the analyses including only inhalers, but should also consider the results when all smokers are included. These latter results were similar to the findings in the present study.

We tabulated rate differences as well as rate ratios and it is striking that in this case the effects of smoking are uniformly greater in men than in women. This was also found in the CPS-II study[9] and in the Established Population for Epidemiologic Studies of the Elderly.[11] When deciding whether a factor is a more important risk marker in one group or another, basing this on rate ratios or rate differences can lead to different conclusions. These may have different implications for understanding the aetiology and for evaluating the public health importance of a particular exposure. Given this, and the possibility of the previously discussed gender bias with respect to inhalation habits of different tobacco products, we feel that it is too early to conclude that women may be more sensitive than men to some of the deleterious effects of smoking.

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