Mortality in women and men in relation to smoking

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Background Mortality from smoking-related diseases in women is increasing worldwide. Studies comparing hazards associated with smoking in women and men based on a sufficient number of heavy smokers of both genders are lacking.

Methods We used pooled data from three prospective population studies conducted in Copenhagen to compare total and cause-specific mortality in relation to smoking habits. A total of 30,917 subjects, 44% women, with initial examinations between 1964 and 1992 were followed until 1994 for date and cause of death.

Results During follow up, 2,900 women and 5,744 men died. Smoking characteristics differed considerably with gender, particularly in the older subjects. Overall mortality rates in smokers were approximately twice those in people who never smoked. Positive associations with smoking in both men and women were confirmed for all-cause mortality as well as mortality from respiratory disease, vascular disease, lung cancer, and other tobacco-related cancers. Despite large gender differences in age at smoking debut, total and cause-specific relative mortality in smokers was similar in men and women. After excluding non-inhalers, relative risks associated with smoking for respiratory and vascular disease were higher for women than men whereas there were no gender differences in smoking related risk of cancers.

Conclusions The relative risks suggest that women may be more sensitive than men to some of the deleterious effects of smoking. However, because of lower baseline mortality rates in women, rate differences may be similar and results should be interpreted with caution.

Keywords Respiratory mortality, cancer, gender difference, tobacco, vascular mortality

Accepted 5 May 1997

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 men, but so far no study has tested this hypothesis. Since the number of women who smoke has increased enormously over recent decades, detailed information on the health hazards of smoking to women's health is obviously desirable from a public health point of view. In addition, some studies have indicated that women are, in some respects, more sensitive to the damaging effects of smoking.1-7 This raises the question whether the effect of smoking on mortality is larger among women than among men.

Surprisingly few large epidemiological studies that include both men and women have compared smoking-related mortality by gender. In the study of British doctors,8,9 female smokers had a lower relative mortality risk than male smokers, and this was also found in CPS-II.10 In the NHANES II and the West of Scotland study,12 relative mortality risks between current and never smokers were similar in males and females.
Smoking among Danish women has been common since the beginning of the 1950s and the proportion of women who smoke remains the highest in Western Europe today.\textsuperscript{13} This is reflected in the fact that mortality rates in Danish women from the diseases closely related to tobacco, i.e. chronic obstructive pulmonary disease (COPD) and lung cancer, are by far the highest in Western Europe.\textsuperscript{14,15} Because of the early start of the female smoking epidemic, a longitudinal study of mortality in Danish women should be particularly informative. The present study includes a sufficient number of heavily smoking women to allow exact estimates of cause-specific mortality. Furthermore, although it is generally acknowledged that men and women's smoking habits differ in terms of quantity smoked, age at smoking debut, and inhalation habits, these differences are seldomly, if ever, considered when comparing smoking related mortality in men and women.

The aim of the present study is thus to compare total and cause-specific mortality in relation to smoking in men and women, taking into consideration differences in smoking behaviour.

Methods

The study is based on data from three longitudinal population studies conducted in the Copenhagen area: the Copenhagen City Heart Study (CCHS), the Glostrup Population Studies (GPS) and the Copenhagen Male Study (CMS). All three studies have been described in detail previously.\textsuperscript{16-19} Briefly, the GPS population comprised 14,205 randomly selected, age-stratified men and women aged $\geq$20 years from a defined area of central Copenhagen who were examined in 1976-1978. In 1981-1983 subjects were re-examined and 1,562 new subjects were included. The GPS have, since 1964, followed different birth cohorts of the population in selected Western suburbs of Copenhagen. All birth cohorts had an equal distribution of men and women. For this study we used data from the following birth cohorts: 484 subjects born in 1897 examined in 1967, 1977 and 1982; 1,254 subjects born in 1914 examined in 1964, 1974, 1984 and 1989; 1,108 subjects born in 1936 examined in 1976, 1981 and 1987; 3,785 subjects randomly sampled from four birth cohorts (1922, 1932, 1942 and 1952) examined in 1982 and 1987; 1,416 subjects (born in 1927, 1937, 1947 and 1957) examined in 1987, and 2,027 subjects (born in 1932, 1942, 1952 and 1962) examined in 1992. The GPS population thus consisted of 10,074 subjects. The CMS, a cardiovascular study set up in 1970, has followed 5,076 males aged 40-59 at study inclusion sampled from 14 large workplaces in the Copenhagen area with examinations in 1970, 1971, 1976 and 1985. The combined study population consisted of 30,917 subjects, 13,465 women and 17,452 men. The overall response rate at first examination was 77% (range 69-88).

In all three population studies, examination included a self-administered questionnaire with detailed questions regarding present and past tobacco consumption and a large number of other health related items. Tobacco consumption was studied using questions to categorize smokers according to present tobacco consumption (i.e. never-smoker; ex-smoker; 1-14 g tobacco per day; 15-24 g tobacco per day and $\geq$25 g tobacco per day), inhalation and type of tobacco (cigarette, cheroot, cigar, pipe or mixed) for present smokers and also years of smoking for both present and former smokers. Age of smoking debut was calculated for smokers by subtracting years of smoking from age. Present tobacco consumption was calculated by equating a cigarette to 1 g, a cheroot to 3 g and a cigar to 5 g tobacco.

Subjects were followed until 9 January 1995 (CMS and CCHS) and 22 November 1995 (GPS) for total mortality, and for cause-specific mortality until the end of 1993. Cause of death was obtained from official death certificates coded at the National Board of Health using the 7th Revision of the International Classification of Diseases for the years 1963-1969 and the 8th Revision for 1970-1993. Because of limited numbers, causes of death were divided into four principal groups: vascular (ICD codes 390-458, 782), respiratory (codes 11-19, 460-469, 471-519), neoplastic (codes 140-239) and other causes (all other codes). In addition, an evaluation of the following selected endpoints was performed: ischaemic heart disease (codes 410-414), cerebrovascular disease (codes 430-438), lung cancer (codes 162-163 and 231), and other tobacco-related cancers, i.e. cancer of the oropharynx, larynx, oesophagus, pancreas, bladder and kidney (codes 140-150, 157, 161, and 188-189).

Statistical analysis

Because subjects were followed for up to 30 years, changes in smoking habits during follow-up were allowed for. This implies that individuals who changed their smoking habits contributed person-years at risk in several tobacco categories. If information on smoking was missing at any examination, the smoking status from the preceding examination was used. Each subject's person-years under observation from study entry until death or censoring were then split into several observations within 5-year age bands and 5-year bands of calendar time. Relative mortality risks (RR) associated with smoking were analysed for each sex separately using Poisson regression. Although mortality rates differed between the three cohorts under study, risk ratio between smokers and non-smokers did not and results regarding risk attributed to smoking are reported for the pooled data.

Mortality rates have been standardized for age using the indirect method by calculating the number of deaths that would have been expected in each 5-year age group in each smoking category if the smoking habit did not affect mortality (i.e. using the age-specific mortality rates of the total study population as reference), summing the corresponding observed and expected numbers and multiplying the ratio of the two by the total mortality rate observed in the population. These adjusted mortality rates were then tested for a linear trend between the three categories never, light, and heavy smokers.

All statistical analyses were performed using the Stata Statistical package.\textsuperscript{20}

Results

After excluding 108 subjects with missing data on smoking status, the study population comprised 30,809 subjects; 13,423 women and 17,386 men, who were followed for up to 30 years, constituting approximately 453,000 person-years. A total of 8,644 subjects died during follow-up, 2,900 women and 5,744 men.

Smoking characteristics at first examinations on the pooled data are given in Table 1. Male smokers smoked more, a higher percentage inhaled and age at smoking debut was younger than...
in the female smokers. Gender differences in smoking characteristics were greater in the older birth cohorts. The Table also shows that prevalence of smoking was high among both men and women and that the study, even at baseline, included many female smokers.

Table 2 shows the age-specific all-cause mortality rates in men and women by smoking category. Mortality was lower in women than in men in almost all age and smoking groups. Up to age 75, overall mortality rates for current smokers were approximately twice those for never smokers in both men and women (with the exception of the youngest women). At age 75-84, mortality ratios were reduced to 1.5 and at age 85 up to 1.2 for both genders.

In Table 3 the age-adjusted cause-specific mortality rates in current, ex- and lifelong non-smokers are shown. For comparison with other studies no adjustment for gender difference in inhalation was made. Furthermore, concerning comparison between men and women stratification by daily consumption was incomplete, because even among the heavy smokers, 30% of the men smoked ≥25 g per day versus only 14% of the women.

Table 3 also gives RR for smoking status adjusted for age, study population and calendar period effects. The RR were similar in men and women for almost all disease groups.

To adjust for differences in inhalation between male and female smokers, analyses were repeated on a subsample of never smokers and inhaling current smokers. Results are shown in Table 4. The RR associated with each smoking category was compared in men and women by Wald tests and corresponding P-values are shown; e.g. women smoking <15 g of tobacco per day had an RR of 4.2. The test for whether these two RR were the same had a P-value of 0.17.

Comparing Tables 3 and 4, the risks associated with smoking increased when non-inhalers were excluded, particularly in women. All-cause mortality ratio for smokers was higher in women then in men, although only significantly so in the heavy smokers (≥25 g/d). This was primarily caused by differences in the mortality ratio in vascular and respiratory disease, whereas the ratio in neoplastic diseases and other causes did not differ between male and female smokers.

Discussion

The present study is prospective and includes a sufficient number of heavily smoking women to allow exact estimates of
### Table 3  Age-adjusted mortality rates and relative risks (RR) by smoking status. Mortality rates were indirectly standardized in 5-year age groups to the total study population

<table>
<thead>
<tr>
<th>Cause of death (no. women/men)</th>
<th>Women</th>
<th>Men</th>
<th>Test for trend&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Test for trend&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Never smokers</td>
<td>Ex-smokers</td>
<td>&lt;15/15 day</td>
<td>&gt;15/15 day</td>
</tr>
<tr>
<td>Respiratory disease (168/308)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RR&lt;sup&gt;b&lt;/sup&gt;</td>
<td>34</td>
<td>76</td>
<td>107</td>
<td>179</td>
</tr>
<tr>
<td>Vascular disease (1023/2214)</td>
<td>400</td>
<td>459</td>
<td>631</td>
<td>664</td>
</tr>
<tr>
<td>RR&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Other causes</td>
<td>209</td>
<td>259</td>
<td>323</td>
<td>324</td>
</tr>
<tr>
<td>RR&lt;sup&gt;b&lt;/sup&gt;</td>
<td>2</td>
<td>1</td>
<td>1.8</td>
<td>2.0</td>
</tr>
<tr>
<td>Cancers (937/1771)</td>
<td>374</td>
<td>388</td>
<td>592</td>
<td>734</td>
</tr>
<tr>
<td>RR&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Other causes (493/994)</td>
<td>192</td>
<td>241</td>
<td>309</td>
<td>337</td>
</tr>
<tr>
<td>RR&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>All causes (2621/5287)</td>
<td>995</td>
<td>1162</td>
<td>1638</td>
<td>1915</td>
</tr>
<tr>
<td>RR&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

<sup>a</sup> Wald test for the null hypothesis of no difference between male and female RR. P < 0.05.

<sup>b</sup> Test for linear trend between never smokers, light and heavy smokers.

<sup>c</sup> Wald test for the null hypothesis of no difference between male and female RR. P < 0.05.

### Table 4  Age-adjusted excess mortality in male and female inhaling smokers by daily tobacco consumption expressed as relative risks (RR) with 95% confidence interval (95% CI) with never smokers' risk set at 1. Number of deaths upon which analyses are based are given in brackets

<table>
<thead>
<tr>
<th>Cause of death</th>
<th>&lt;15 g/day</th>
<th>15-24 g/day</th>
<th>&gt;25 g/day</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>women</td>
<td>men</td>
<td>RR (95% CI)</td>
</tr>
<tr>
<td>Respiratory disease (No. of deaths)</td>
<td>7.5 (4.4-12.8)</td>
<td>1.0 (0.3-2.8)</td>
<td>5.7 (3.8-8.5)</td>
</tr>
<tr>
<td>Vascular disease (No. of deaths)</td>
<td>24 (2.9-34)</td>
<td>2.7 (2.1-3.6)</td>
<td>2.1 (1.6-2.7)</td>
</tr>
<tr>
<td>Other causes (No. of deaths)</td>
<td>1.9 (1.5-2.3)</td>
<td>2.0 (1.6-2.6)</td>
<td>2.1 (1.7-2.6)</td>
</tr>
<tr>
<td>Cancers (No. of deaths)</td>
<td>1.9 (1.5-2.3)</td>
<td>2.0 (1.6-2.6)</td>
<td>2.1 (1.7-2.6)</td>
</tr>
<tr>
<td>Lung cancer (No. of deaths)</td>
<td>9.4 (5.1-17.0)</td>
<td>10.7 (4.7-24.5)</td>
<td>7.9 (3.8-17.0)</td>
</tr>
<tr>
<td>Other tobacco-related cancers (No. of deaths)</td>
<td>1.6 (0.9-3.2)</td>
<td>1.9 (1.1-3.3)</td>
<td>1.7 (1.1-3.3)</td>
</tr>
<tr>
<td>All causes&lt;sup&gt;b&lt;/sup&gt; (No. of deaths)</td>
<td>2.2 (2.0-2.5)</td>
<td>1.9 (1.7-2.2)</td>
<td>2.0 (1.8-2.3)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Wald test for the null hypothesis that the RR estimates for men and women are equal.

<sup>b</sup> Duration of follow-up differs for cause-specific and all-cause mortality (see text).
cause-specific mortality. Based on this we find that the well known strong associations between smoking and both overall and cause-specific mortality apply to women as well as to men. In addition, despite the fact that male smokers started smoking at a considerably younger age, relative mortality from neoplastic disease was equal in female and male smokers and relative mortality from respiratory and vascular disease was actually higher in female smokers.

The prevalence of smoking was high in this study population. Men and women differed not only in prevalence of smoking, but also in average amount smoked daily, inhalation habits, and age of smoking onset. In women there was a marked cohort effect of the age at starting smoking. Although similar trends in gender differences have been reported elsewhere, these differences are usually not adjusted for when comparing smoking-related mortality or morbidity in men and women.

**Mortality rates in males and females**

The relative mortality risk for smokers exceeded non-smokers by a factor two, which is similar to results from other studies, and mortality rates showed the expected pattern for both men and women in causes of death and association with amount of tobacco smoked.

The age-specific mortality rates reported for male smokers, ex-smokers and never smokers were close to those reported in British doctors and a little higher than the study by the American Cancer Society, the CPS-II. Age-specific mortality rates in women were lower than in men but considerably higher than in the women in CPS-II, both in never smokers and smokers. This is consistent with reports that mortality rates in middle-aged Danish women are among the highest in Western Europe.

**Comparison by gender**

Few other studies have compared smoking related mortality by gender, presumably in part because of an insufficient number of heavily smoking women. Some have found that women smokers' risk was smaller than men's, and others that male and female risk was similar. One American study, however, found that loss of life expectancy was greater in female heavy smokers than in male heavy smokers. None of these studies have adjusted in detail for gender differences in smoking behaviour.

Concerning the gender difference in relative risk of respiratory death, other studies have shown that women developed pulmonary impairment with less tobacco exposure than men. In both the Copenhagen City Heart Study and the Glostrup Population Studies we found that the risk of admission to hospital for obstructive pulmonary disease was higher for women than for men after adjusting for differences in smoking habits and, furthermore, that decline in FEV, was relatively faster in heavily smoking women.

For vascular disease, RR associated with smoking were significantly higher in women than in men. To our knowledge, this has not been reported previously. Since vascular disease is multifactorial with tobacco being only one of many contributing factors, analyses that take into account other cardiovascular risk factors should be awaited, in particular since these risk factors (e.g. stress, diet, and exposures at work) may be differently associated with tobacco in men and women.

The present results show that despite large gender differences in age at taking up smoking, when adjusted for inhalation, RR associated with smoking in women are as high, and for respiratory and vascular disease actually higher, than in men. In comparing the effect of smoking on mortality between men and women it could be questioned whether RR is an appropriate measure since RR will vary simply because baseline rates vary, even if the absolute effect is the same. Mortality in never-smoking males is higher than in never-smoking females and if smoking elevated the rates for men and women equally, the RR would be higher in women. It is an ongoing methodological discussion, which is not particular to this study, whether risks should be compared as risk difference using additive models, or as RR using multiplicative models. There are pros and cons for both methods. In the case of smoking and gender, it could be argued that although absolute effects of smoking may be similar in men and women, with higher RR in female smokers, female smokers are at a greater risk than male relative to the risk levels they could achieve by not smoking. In other words, the attributable risk of smoking is greater in women than in men. Finally, multiplicative models dominate statistical models applied in analytical epidemiology and the present study cannot be compared with other studies without applying similar methods.

In conclusion, the present study shows that women who smoke like men also die like men. Despite taking up smoking at an older age than men, the women's RR associated with increasing amounts of tobacco smoked was equal to, and, for vascular and respiratory disease, actually surpassed the men's. If these results can be confirmed in other studies, scientific efforts must be focused on the cause of this gender difference, ranging anywhere from the inherently different airways geometry to more subtle differences in the men and women who choose to smoke.

**Acknowledgements**

We are grateful to Mr David Clayton, MRC Biostatistics Unit, Cambridge, for use of the Lexis programme for Stata. This study was supported by grants from The Danish Ministry of Health, The Health Insurance Fund, The National Union against Lung Diseases, The Danish Heart Foundation and The Danish Medical Research Council (12-1661-1).

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