Original Contribution

High Cumulative Risk of Lung Cancer Death among Smokers and Nonsmokers in Central and Eastern Europe

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The authors have calculated cumulative risks of lung cancer from a case-control study conducted between 1998 and 2002 involving 2,633 lung cancer cases and 2,884 controls in Hungary, Poland, the Czech Republic, Slovakia, and Russia. The odds ratios for smoking history were combined with national lung cancer mortality rates to obtain the cumulative risk of lung cancer. The cumulative risk of death from lung cancer by the age of 75 years among current male smokers was 14.6% in Romania and Russia and 15.8% in Poland, similar to levels reported in Western Europe, although higher risks were found in the Czech Republic (19.8%), Hungary (21.9%), and Slovakia (28.2%). Cumulative risks of lung cancer death among never smokers of over 1% were observed in Hungary among both men and women and among men in Poland. The effect of quitting smoking on the lifetime cumulative risk was substantial, with between 67% and 83% of lung cancer risk among men being avoided by quitting before the age of 50 years. This substantial reduction in risk among former smokers confirms that lung cancer mortality in Central Europe over the next three decades will be determined by the extent to which current smokers can successfully quit smoking.

case-control studies; Europe, Eastern; lung neoplasms; mortality; risk; smoking

Very high lung cancer mortality rates have been observed in Central Europe over the last decade, with cumulative risks among men by the age of 75 years in the region of 10 percent in several countries including Hungary, Poland, Russia, and the Czech Republic (figure 1) (1). These risks are similar to the peak cumulative risks observed in the United Kingdom during the 1960s and 1970s, and they far exceed the peak rates observed in the United States. Indeed,
the current national lung cancer mortality rate in Hungary represents the highest ever observed in a national setting.

Measures of the effect of tobacco on lung cancer among smokers relative to nonsmokers are not informative regarding their role in the high mortality rates and, in order to understand the role of tobacco in causing the lung cancer epidemic in Central Europe, absolute risks of lung cancer by smoking habit are essential. Obtaining an accurate measure of the absolute risk of lung cancer for different smoking habits typically requires information on large cohorts with extensive baseline information on smoking and long-term follow-up. An alternative and more efficient approach is to combine estimates of risk ratios from case-control studies with national incidence or mortality data. In a recent example of this approach in southwest England, the cumulative risk of death from lung cancer by age 75 years among lifetime smokers in the United Kingdom was estimated at 15.9 percent for men and 9 percent for women, rising to 24.4 percent among men and 18.5 percent among women for lifetime smokers who reported smoking at least 25 cigarettes per day (2). Moreover, the benefit of quitting smoking at various ages was demonstrated with cumulative risks of lung cancer death of 10 percent, 6 percent, 3 percent, and 2 percent for men who stopped smoking at ages 60, 50, 40, and 30 years, respectively. The cumulative risk of lung cancer death among never smokers was estimated at 0.2 percent, slightly less than estimates obtained from several large cohort studies including the American Cancer Society cohort of over one million Americans, which suggests a cumulative risk of 0.44 percent for men and 0.42 percent for women (3). In the absence of other cofactors, one would expect similar levels of cumulative risk among men in other countries where the male lung cancer epidemic has matured, such as in Central Europe.

Using a large multicenter case-control study of lung cancer in Central Europe, we have investigated whether the higher overall lung cancer mortality rates in this region are due to higher cumulative risks of lung cancer death in lifetime smokers, implicating the presence of other lung carcinogens. We also aimed to provide measures of the reduction in cumulative risk for smokers who quit smoking in these countries.

**MATERIALS AND METHODS**

The analysis is based on a case-control study that was conducted according to an identical protocol in 15 centers in Romania, Hungary, Poland, Russia, Slovakia, and the Czech Republic. In each center, cases included subjects with histologically confirmed lung cancer who were living in the study areas for at least 1 year and who were interviewed within 3 months of diagnosis between 1998 and 2002. Controls were frequency matched by age (±3 years), sex, and...
study area. Hospital controls were included in 14 of the study areas from an extensive list of neoplastic, non-tobacco-related diseases, with no more than 10 percent of controls coming from any particular diagnostic group. Population controls were recruited in one center (Warsaw) by randomly selecting age- and sex-matched subjects from the electronic register of Polish residents.

A total of 2,893 cases and 3,161 controls satisfied initial eligibility criteria and were requested to participate in the study. Of the eligible cases, 260 (9.0 percent) were not included in the study (27 had been discharged from hospitals before the interview, 26 were too ill to be interviewed, six had died before the interview, and 201 refused to participate). In addition, 277 (8.8 percent) eligible controls were not included in the study (16 had been discharged from the hospital before the interview, 20 were too ill to be interviewed, 239 refused to participate, and two were excluded before analyses because of missing data). The final study population included in analyses comprised 2,633 cases and 2,884 controls. Further details of the study areas have been reported elsewhere (4–7).

A lifestyle questionnaire to elicit information on basic demographic characteristics, outdoor air pollution, medical history of occupational diseases, family history of cancer, history of tobacco consumption, passive smoke exposure, and other potential lung cancer carcinogens was administered by trained interviewers. All subjects who had regularly smoked at least one cigarette per day for at least 1 year were considered ever smokers. Current smokers were those who still smoked at the time of interview or who had quit less than 2 years previously, while former smokers were those who had quit smoking 2 or more years previously. When information on different time periods was available for current smokers, the most recent number of cigarettes smoked was used. Information on other tobacco-smoking products was also included after weighing for the amount of tobacco (1 g of pipe tobacco = one cigarette, one cigarillo = two cigarettes, one cigar = four cigarettes, and one papyros (unfiltered cigarette) = 0.7 cigarette).

Country-specific relative risks of lung cancer were estimated separately for men and women by means of odds ratios and 95 percent confidence intervals by use of unconditional logistic regression (8) and adjustment for age and center. Smoking categories were introduced as dummy variables, and odds ratios were estimated for each smoking category compared with never smokers.

The cumulative risks were estimated by multiplying the relative risks for different smoking categories by a unique common factor, calculated so that the combination of these risks with the prevalence of smoking habits among study controls resulted in the age-specific cancer incidence rate in each country for that age group (refer to the Appendix for further details on these calculations). Our assumption was that within each age group the smoking distribution of each national population was represented by our control distribution. Finally, we calculated the cumulative rate (C) for the different categories of smoking by adding age-specific absolute rates (in 5-year age groups) and then the lifetime cumulative risk by age 75 years using the standard formula 100(1 – exp(–5 × C/10^5)) (9). The cumulative risk may be interpreted as the probability that an individual will die from lung cancer before the age of 75 years in the absence of competing causes of death; 95 percent confidence intervals for odds ratios and cumulative risks were calculated by use of floating absolute risks to obtain the variance of the logarithm of the odds ratio (var(log r)) (10) and subsequently incorporating a Taylor series expansion. The method of floating absolute risks leads to confidence intervals that are approximately independent and are therefore readily interpreted (11). As accurate, age-specific lung cancer incidence data are not available from the majority of the participating countries, we used national lung cancer mortality figures instead. Our cumulative estimates should therefore be interpreted as the lifetime risk of death from lung cancer. Given that 5-year relative survival from lung cancer is generally less than 10 percent (12), the cumulative risk of developing lung cancer may be up to 10 percent higher than our calculated figures. Sampling variations in smoking prevalence estimates are also not included in the calculation of the confidence intervals, resulting in intervals that may be somewhat too narrow. The extent of this underestimation is likely to be inversely related to the size of the control group and is therefore more of a concern for the calculations of cumulative risk among women.

RESULTS

The country-specific odds ratios and floating 95 percent confidence intervals for never, former, and current smokers among men and women are shown in table 1. Cumulative risks of lung cancer among never smokers were generally higher than the risks estimated for men and women in the United Kingdom of 0.2 percent and 0.4 percent, respectively. Among men, high cumulative risks of 0.7 percent (95 percent confidence interval: 0.1, 1.4), 0.9 percent (95 percent confidence interval: 0.3, 1.5), 1.1 percent (95 percent confidence interval: 0.4, 1.7), and 1.1 percent (95 percent confidence interval: 0.3, 1.9) were observed in the Czech Republic, Russia, Poland, and Hungary, respectively. Among women, a particularly high cumulative risk of 1.2 percent (95 percent confidence interval: 0.9, 1.5) was observed in Hungary. For current male smokers, the cumulative risk of death from lung cancer was 14.6 percent (95 percent confidence interval: 8.9, 19.9) in Romania, 14.6 percent (95 percent confidence interval: 12.4, 16.6) in Russia, and 15.8 percent (95 percent confidence interval: 13.2, 18.2) in Poland, similar to levels reported in the United Kingdom, although these risks of 19.8 percent (95 percent confidence interval: 14.9, 24.5), 21.9 percent (95 percent confidence interval: 16.8, 26.6), and 28.2 percent (95 percent confidence interval: 21.7, 34.0) were higher in the Czech Republic, Hungary, and Slovakia, respectively. The cumulative risk among heavy smokers was particularly high, reaching over 40 percent (95 percent confidence interval: 32.8, 48.6) among men in the Czech Republic. Among women, cumulative risks among current smokers were less than 10 percent in all countries with the exception of Hungary, where they were 13.2 percent (95 percent confidence interval: 6.2, 19.7). As expected, cumulative risks...
among former smokers were intermediate for both men and women.

The effect of quitting on the cumulative risk of lung cancer death was analyzed further among men after stratification on the age at quitting and calculation of age-specific cumulative risk for each category of smoking (given the small number of female former smokers, cumulative risk estimates among women for different ages at quitting tended to be unstable and are not presented). A strong decreasing trend in the cumulative risk was observed with an earlier age at quitting smoking in all six countries (figure 2). The cumulative risk of lung cancer death ranged between 5.1 percent and 12.0 percent for those who quit smoking at the ages of 50–59 years, between 3.5 percent and 7.4 percent for those who quit at the ages of 40–49 years, and between 1.0 percent and 3.0 percent for those who quit before the age of 40 years. Furthermore, based on estimates of cumulative risk from figure 2, the proportion of excess cumulative risk of lung cancer death, compared with never smokers, that was avoided by quitting smoking at age 40 years was over 90 percent in all six countries, ranging between 67 percent in Russia and 84 percent in Poland for those who quit between 40 and 49 years and between 38.4 percent in Poland and 67.9 percent in Romania for those who quit between the ages of 50 and 59 years.

The cumulative risks for male current smokers according to the number of cigarettes smoked per day are presented in table 2. With the exception of Romania, extremely high cumulative risks were observed for those who smoked more than 30 cigarettes/day, ranging from 27 percent in Hungary to 41.2 percent in the Czech Republic. The reduced cumulative risk in Romania is likely explained by the small numbers of cases and controls who smoked more than 30 cigarettes/day.

**DISCUSSION**

Based on an analysis similar to that reported here, the lifetime risk of death from lung cancer among male never,

**TABLE 1. Odds ratios and cumulative risks of lung cancer death by age 75 years among men and women who were never, former, and current cigarette smokers, by Central European country, 1998–2002**

<table>
<thead>
<tr>
<th>Country</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases/controls (no.)</td>
<td>Odds ratio*</td>
</tr>
<tr>
<td>Romania</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonsmoker</td>
<td>4/50</td>
<td>1.0</td>
</tr>
<tr>
<td>Former smoker</td>
<td>25/47</td>
<td>6.1</td>
</tr>
<tr>
<td>Current smoker</td>
<td>110/70</td>
<td>24.5</td>
</tr>
<tr>
<td>Russia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonsmoker</td>
<td>9/92</td>
<td>1.0</td>
</tr>
<tr>
<td>Former smoker</td>
<td>72/151</td>
<td>4.5</td>
</tr>
<tr>
<td>Current smoker</td>
<td>430/267</td>
<td>17.3</td>
</tr>
<tr>
<td>Czech Republic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonsmoker</td>
<td>5/92</td>
<td>1.0</td>
</tr>
<tr>
<td>Former smoker</td>
<td>53/108</td>
<td>8.2</td>
</tr>
<tr>
<td>Current smoker</td>
<td>160/97</td>
<td>31.6</td>
</tr>
<tr>
<td>Hungary</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonsmoker</td>
<td>9/71</td>
<td>1.0</td>
</tr>
<tr>
<td>Former smoker</td>
<td>70/89</td>
<td>6.4</td>
</tr>
<tr>
<td>Current smoker</td>
<td>213/85</td>
<td>22.5</td>
</tr>
<tr>
<td>Poland</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonsmoker</td>
<td>11/102</td>
<td>1.0</td>
</tr>
<tr>
<td>Former smoker</td>
<td>116/202</td>
<td>5.2</td>
</tr>
<tr>
<td>Current smoker</td>
<td>404/246</td>
<td>16.2</td>
</tr>
<tr>
<td>Slovakia</td>
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<td></td>
</tr>
<tr>
<td>Nonsmoker</td>
<td>4/93</td>
<td>1.0</td>
</tr>
<tr>
<td>Former smoker</td>
<td>72/103</td>
<td>17.2</td>
</tr>
<tr>
<td>Current smoker</td>
<td>194/76</td>
<td>82.7</td>
</tr>
</tbody>
</table>

* Odds ratios and 95% confidence intervals calculated by logistic regression analyses, adjusted for age and center.
† Confidence intervals based on floating variance.

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former, and current smokers in the United Kingdom was calculated as 0.2 percent, 5.5 percent, and 15.9 percent, respectively, reaching 24.4 percent among heavy smokers (>5 cigarettes/day) (1). Corresponding estimates for women were 0.4 percent, 2.6 percent, and 9.5 percent, respectively, reaching 18.5 percent among current heavy smokers. These risks were substantially higher than corresponding risks calculated from a case-control study conducted in the United Kingdom in 1950, reflecting the fact that current smokers in 1990 were likely to have started smoking in their teens or early 20s, which was not the case for the majority of current smokers in earlier periods. Similarly, the higher lung cancer cumulative risks among men as opposed to women were thought likely to be due to a greater proportion of women who started smoking at a later age.

The primary aim of the current analysis was to determine whether the cumulative risks of developing lung cancer for various groups of smokers in Central European countries are similar to those previously reported for other countries where cigarette smoking habits have been established for several decades. Overall, the cumulative risks among never smokers appeared to be higher than those previously reported, particularly in Hungary, with only men in Slovakia and women in Poland providing estimates.
consistent with those in the United Kingdom and the United States. Regarding current smokers, cumulative risks among men in Romania, Russia, and Poland were similar to those observed in the United Kingdom and the United States, although they were substantially higher in the Czech Republic, Hungary, and Slovakia. Cumulative risks among women current smokers were generally low in all countries except Hungary.

Similar lifetime cumulative risks have also been estimated from large case-control studies of lung cancer for male smokers in Italy (14.3 percent) and Germany (13.8 percent), although they were somewhat lower in Sweden.
(6.6 percent) (13). Among never smokers, the cumulative risks were 0.6 percent for German and Italian men and 0.4 percent for Swedish men, and among heavy smokers they varied between 12.6 percent for Swedish men and 25.7 percent for German men.

Prior to these reports, estimates of cumulative risk of lung cancer by smoking status came primarily from cohort studies. Probably the most informative study is the Cancer Prevention Study II, a cohort mortality study of nearly 1.2 million adults enrolled in 1982 (2). Based on a 6-year follow-up to 1998, the cumulative risk of lung cancer by age 75 years, after taking into account competing causes, was 10.6 percent in men and 4.9 percent in women among current smokers. Cumulative risks by age 74 years among never smokers were 0.45 percent among men and 0.38 percent among women. These results for men are between those obtained in Sweden and other Western European countries.

The higher cumulative risks among male never and current smokers in Central Europe could be explained by a number of factors, the first being biased estimation. The measures necessary in calculation of the cumulative risks are the age-specific mortality rate, the relative risk for different smoking categories, and the estimated prevalence of smoking by age group in the population. Bias in any of these three measures could result in biased estimation of cumulative risk. There is no reason to believe that national age-specific mortality rates of lung cancer are likely to be seriously biased and, given the large numbers on which they are based, they are likely to be measured with little sampling variation. Lung cancer diagnoses that are detected prior to autopsy are usually confirmed by histology or cytology in Central and Eastern European countries. Although it is unlikely that lung cancer estimates are inflated by incorrect diagnoses, it is possible that some lung cancers are not detected or confirmed, although these are likely to predominate in age groups older than 75 years.

Relative risks of the effect of smoking may also be biased, because either the cases or the controls are not representative of the underlying populations, or the information collected on smoking is not valid. Previous large case-control and cohort studies would indicate a relative risk from around 10- to 20-fold for men and women, although there is substantial variation (14). The one estimate that seems to depart from this in the current analysis among men is that of Slovakia, with a reported relative risk of 82.7 among current smokers. This anomalously high relative risk is unlikely, however, to explain the high cumulative risk among current smokers. This is because the cumulative risks in each exposure group must add up to the overall cumulative risk, and any overestimation in current smokers will have to be balanced by an underestimation among nonsmokers and former smokers, where the estimated cumulative risks do not appear conspicuously low.

Finally, estimates of the prevalence of smoking in the population may be biased. Although we have little reason to believe that the control smoking prevalence is likely to be biased among men, given the coherent relative risk estimates, bias may have resulted from the use of hospital controls recruited in 14 of the 15 centers. The effects of such a bias would be difficult to predict, although they would act in an opposite direction for never and current smokers; that is, if one was biased upward, the other would be biased downward. It is also of interest that the odds ratios for lung cancer by tobacco history were very similar between Warsaw, which recruited population controls, and the second Polish center in Lodz, which recruited hospital controls (detailed results not shown). Indeed, the only form of bias that could result in systematic inflation of cumulative risk for all exposure groups is overestimation of the national mortality rates and, as explained above, there is no reason to expect this to have occurred.

If the cumulative risks among men have not been systematically biased upward, then this would argue for a real higher cumulative risk in these countries, especially in Hungary, the Czech Republic, and Slovakia. One possible explanation for this would be that smokers in these countries start smoking at an earlier age. The average age of initiating smoking among male controls was 17.1 years in Hungary, 18.5 years in Romania, 18.7 years in Poland, 18.6 years in the Czech Republic, 19.5 years in Slovakia, and 19.1 years in Russia. This compares with 17.1 years among male controls who were current smokers in the study from the United Kingdom (Sarah Darby, University of Oxford, personal communication, 2005). The age at initiating smoking would therefore not appear to explain the higher cumulative risks observed in some Central European countries.

An alternative explanation for the high cumulative risks among smokers could be a greater carcinogenic potency associated with cigarettes in some Central European countries. Although the risk of developing lung cancer does appear to be greater among smokers of higher than medium or lower tar cigarettes (15), firm data are lacking on historical levels of cigarette tar in these countries. Furthermore, nitrosamine levels are known to vary widely between countries, even for the same brand of cigarette, and may also contribute to different lung cancer risks. In a survey of three popular cigarette brands in 27 countries, over ninefold differences were found between the highest and lowest nitrosamine levels for the same brand of cigarettes (16). No clear trends were observed, however, with different regions of Europe.

Although some estimates are based on small numbers, the trend for higher cumulative risks among never smokers did appear to be consistent over the six countries and also for both men and women. This would argue for the presence of other lung carcinogens in these countries, acting either on their own or synergistically with tobacco. Occupational exposures including exposure to asbestos, metals, and polycyclic aromatic hydrocarbons could be suspected, although they are likely to affect men primarily. Potential carcinogen exposures that may also be relevant for women include indoor and outdoor air pollution, high levels of alcohol consumption, and also poor nutritional status. An overall cumulative lifetime risk of between 0.5 percent and 1 percent, as experienced by never smokers in our study, for a specific cancer site is not negligible and, taking recent rates in the United Kingdom as an example, is similar to the lifetime cumulative risk of skin melanoma, pancreatic cancer, or kidney cancer (17). While tobacco explains the vast majority of the lung cancer burden in these countries,
the role of non-tobacco-related carcinogens also deserves further attention. Within the current study population, we have recently reported an increased risk of lung cancer for multiple occupational x-rays, which was particularly prominent among never smokers, as well as an increased risk from the use of solid fuels for heating and cooking (5, 7). Further analysis of known and suspected lung carcinogens is underway, and the extent to which they explain the high cumulative lifetime risk among never smokers will be of much interest.

In summary, these results provide evidence of higher cumulative risks of lung cancer death among never smokers for both men and women from Central Europe than those observed in Western Europe and the United States and also among current smokers for men. Regarding women current smokers, the lung cancer epidemic is still maturing in Central Europe, and the cumulative risks presented here will increase in the future as later cohorts age. The effect of quitting smoking on the lifetime cumulative risk was also substantial and reinforces the conclusion that, for people who have been smoking for many years, giving up smoking in middle age means avoiding most of the subsequent risk of developing lung cancer. For the countries of Central and Eastern Europe, this has major public health implications, and tobacco-related mortality in these countries over the next three decades will be determined by the extent to which current smokers can be persuaded to quit smoking.

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APPENDIX

The cumulative risk was calculated using methods similar to those described by Peto et al. (2). The following steps summarize the main measures used to obtain the cumulative risk.

\[ r_i = \text{the relative risk in the } i\text{th smoking category. (step 1)} \]

where the smoking categories are 1 = never smokers; 2 = former smokers subdivided in some analyses by age quit smoking (<40, 40–49, 50–59, ≥60 years); and 3 = current smokers subdivided in some analyses by number of cigarettes per day (<10, 10–19, 20–29, ≥30 cigarettes).

\[ p_{ij} = \text{the percentage of the controls in the } j\text{th age group and the } i\text{th smoking category, (step 2)} \]

where the age categories are as follows: 35–39, 40–44, 45–49, 50–54, 55–59, 60–64, 65–69, and 70–74 years.

\[ S_j = r_1 p_{1j} + \ldots + r_i p_{ij}; \quad \text{step 3) } \]

\[ h_j = \text{the age-specific incidence rate. (step 4) } \]

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\[ f_j = h_j(S_1 + \ldots + S_j). \] (step 5)

\[ a_{ij} \text{ is the absolute rate in the } (i,j)\text{th cell, and } a_{ij} = (f_j \times r_i). \] (step 6)

\[ C_i \text{ is the cumulative rate, and } C_i = \sum_j R_j a_{ij}. \] (step 7)

where \( R_j \) is the width of the \( j \)th age category in years.

Cumulative risk (percent) = 100 \times (1 - \exp(-C_i)). \) (step 8)

Briefly, to estimate the cumulative risk, we need first to calculate the relative risks in the various smoking categories (step 1). In our study, the relative risks of lung cancer were estimated by means of the odds ratios using unconditional logistic regression, and lifelong nonsmokers formed the reference category.

The next step was to calculate the percentage of controls in each smoking category and for each age group (step 2) using the assumption that, within each country, the smoking distribution of the population was represented by the smoking distribution observed among the study controls.

The third step was the estimation of common factors combining the relative risk (step 1) for the different smoking categories with the age-specific prevalence of such smoking habits among study controls (step 2), thus obtaining the quantities denoted (step 3).

Combining the age-specific cancer incidence rates of each country (step 4) with the common factors (step 3), we obtained the proportions given (step 5). Multiplying these proportions with the relative risks for the different smoking categories produced the age-specific absolute risks in the different smoking categories (step 6).

Next, we calculated the cumulative rates (step 7) for the different categories of smoker by adding age-specific absolute rates, and then finally the cumulative risks by age 75 years were estimated using the standard formula (step 8). The cumulative risk may be interpreted as the probability that an individual will develop lung cancer before age 75 years in the absence of competing causes of death.