OVERALL MORTALITY AND CANCER MORTALITY OF COAL MINERS: ATTEMPTS TO ADJUST FOR HEALTHY WORKER SELECTION EFFECTS

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INTRODUCTION
The presumption of a possibly elevated cancer risk in coalminers is based mainly on two hypotheses. Firstly most coalmine dusts include a relevant quartz dust fraction. With a view to the possibly causal relationship between pure quartz dust exposure/silicosis and lung cancer excess risk it is of interest to investigate whether there exists an elevated lung cancer risk in coalminers. Secondly a fraction of the inhaled coalmine dust particles is cleared from the lung. It is probable that some of the cleared dust is swallowed, which then interacts with the acidic environment in the stomach and finally may cause an elevated gastric cancer risk in coalminers. To explore whether such elevated cancer risks exist, we organised a mortality follow up study on German hard coal miners.

MATERIAL AND DESCRIPTIVE RESULTS
We focused on the cancer risk of coalminers of the Saar area (the second biggest hard coal mining area of Germany) because firstly there is a rather high quartz content in the respirable coalmine dust of that area (on average about 12%) and secondly because the only reliable population based cancer registry in West Germany is working there. Because we had no means to enroll a classical inception cohort we had recourse to a study group of Saar coalminers used for a pneumoconiosis study. The main features of the inclusion criteria at that time were firstly that the miners were known to the personnel departments in 1977 or 1979 and secondly that they had worked at least 5 years underground.

All in all, 4578 coalminers alive at 1st January 1980 were enrolled in the study for a 12 year mortality follow-up to the end of 1991, constructing 52 967 person–years at risk. Vital status could be determined for all coalminers (100%). 317 deaths were documented. For five cases, 1.6%, the cause of death remained unknown.

BASIC ANALYSIS

Methods
Mortality was standardised indirectly by 5 year intervals of age and calendar time on the male population of the Saar area by calculating observed and expected
Overall mortality and cancer mortality of coal miners

Table 1. Estimates of relative standardised mortality ratios RSMR and 0.95-confidence intervals for overall mortality, cancer mortality, lung cancer mortality and stomach cancer mortality (4578 German coal miners, follow up from 01/01/1980 through 12/31/1991)

<table>
<thead>
<tr>
<th>Mortality end point</th>
<th>Observed number</th>
<th>RSMR</th>
<th>0.95-Conf.int.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer</td>
<td>104</td>
<td>1.03</td>
<td>0.84–1.25</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>41</td>
<td>1.11</td>
<td>0.80–1.51</td>
</tr>
<tr>
<td>Stomach cancer</td>
<td>6</td>
<td>0.98</td>
<td>0.36–2.11</td>
</tr>
<tr>
<td>[15 year follow-up]</td>
<td>13</td>
<td>1.46</td>
<td>0.78–2.50</td>
</tr>
</tbody>
</table>

numbers of deaths with the help of the person–years program. We derived SMRs for all causes, all cancers, lung cancer and stomach cancer as well as relative SMRs (RSMR = SMR_{specific}/SMR_{overall}) for the cancer causes of death to adjust for the expected “healthy worker”-selection. Confidence limits for the SMR were estimated via the Poisson distribution and for the RSMR by multiplying the expected number with SMR_{overall}.

Results

Among the 317 deaths 104 cancer deaths, 41 lung cancer deaths and 6 stomach cancer deaths were recorded: SMRs for all causes (0.63), cancer (0.65), lung cancer (0.70) and stomach cancer (0.62) are below one; with the exception of stomach cancer even significantly below one. The low relative overall mortality of 63% points to a pronounced healthy worker selection.

Based on RSMRs (Table 1) slight non-significant increases in cancer and lung cancer risk are described, but they can easily be explained by smoking habits or even as a chance finding. It should be remarked that a 15 year follow-up through 1994 is nearly completed now and the risk estimates for cancer and lung cancer seem to be stabilised near the results of the 12 year follow-up, but for stomach cancer the longer follow up yields an elevated RSMR of about 1.5. Therefore, this basic analysis gives no hint at a cancer or lung cancer excess risk in coal miners but leaves some doubt about stomach cancer risk.

META-ANALYSIS

Material and methods

12 SMR-follow up studies on coal miners (Enterline, 1964; Ortmeyer et al., 1973, 1974; Costello et al., 1974; Rockette, 1977; Armstrong et al., 1979; Atuhaire et al., 1985; Maclaren, 1992; Kuempel et al., 1995; Starzynski et al., 1995; Swaen et al., 1995; Morfeld et al., 1996) and five OR-case control studies on coal miners with external controls (Meijers et al., 1990; Morabia et al., 1992; Muller et al., 1995; Swaen et al., 1987; Gonzales et al., 1991) were pooled according to Greenland, 1987. Because the study of Enterline (1964) gives strikingly high risk estimates and this probably due to an underestimate of the number of exposed, we performed two analyses including and excluding the study of Enterline (1964).

Results

The study designs are clearly different, inclusion criteria vary a lot and it is not surprising that the \( \chi^2 \)-statistics prove a significant heterogeneity between the studies.
on the 5%-level for each endpoint considered. As expected heterogeneity is increased by including Enterline (1964). Therefore the interpretation of the pooled point and interval estimates is strictly limited. However, the results on relative risks of cancer and lung cancer demonstrate no excess risk in coalminers. Moreover we find it remarkable, that the pooling of nine studies on stomach cancer risk in coalminers yields a significantly elevated relative risk estimate of 1.34, together with a just borderline significant statistic of heterogeneity.

Thus to summarise, from Table 2 (Table 1), one might get the impression, that there exists no cancer and no lung cancer excess risk in coalminers, but an elevated gastric cancer risk is indicated, which of course will have to be discussed on the background of confounding in detail.

**EXPLORING HEALTHY-WORKER-SURVIVOR EFFECTS**

Being aware of a growing epidemiological evidence of an association of quartz dust exposure and lung cancer excess risk the negative results on coalminers’ lung cancer risk are somewhat surprising. Therefore we checked whether a healthy worker survivor effect (HWSE) is at work that may bias downward the estimates of relative risk of lung cancer death. A survivor effect working on morbidity endpoints has already been demonstrated for coalminers. A plausible pathway of exposure effects taking a HWSE for mortality into account explicitly can therefore be outlined as follows.

Long term exposure to coal mine dust leads to (lung-)diseases like pneumococ- niosis or chronic bronchitis. After developing a severe degree of disease exposure is stopped (= change in work status). Therefore higher mortality is expected as an indirect outcome of long term exposure mediated by a selection out of the job. Simultaneously this longitudinal selection produces a lower mortality as a direct effect of continued exposure. This selection effect may be amplified by an intervention of occupational physicians stopping exposure for diseased coalminers as it is enforced by law in Germany.
Table 3. Coefficients in SMR-Poisson models by cohort restriction and by inclusion of work status as a covariable. Variables: TSFE = time since first exposure/year, status = 0, during exposure; 1, after cessation of exposure.

<table>
<thead>
<tr>
<th>ICD</th>
<th>TSFE</th>
<th>Model I</th>
<th>Model II</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>$b_{TSFE}$</td>
<td>$b_{STATUS}$</td>
</tr>
<tr>
<td>001–999</td>
<td>≥ 0 year</td>
<td>+ 0.0053</td>
<td>+ 0.634</td>
</tr>
<tr>
<td></td>
<td>≥ 10 years</td>
<td>+ 0.0050</td>
<td>+ 0.640</td>
</tr>
<tr>
<td></td>
<td>≥ 20 years</td>
<td>+ 0.0106</td>
<td>+ 0.578</td>
</tr>
<tr>
<td>140–208</td>
<td>≥ 0 year</td>
<td>+ 0.0098</td>
<td>+ 1.385</td>
</tr>
<tr>
<td></td>
<td>≥ 10 years</td>
<td>+ 0.0149</td>
<td>+ 1.493</td>
</tr>
<tr>
<td></td>
<td>≥ 20 years</td>
<td>+ 0.0174</td>
<td>+ 1.362</td>
</tr>
<tr>
<td>162</td>
<td>≥ 0 year</td>
<td>+ 0.0077</td>
<td>+ 1.529</td>
</tr>
<tr>
<td></td>
<td>≥ 10 years</td>
<td>+ 0.0075</td>
<td>+ 1.529</td>
</tr>
<tr>
<td></td>
<td>≥ 20 years</td>
<td>+ 0.0149</td>
<td>+ 1.386</td>
</tr>
</tbody>
</table>

**Methods**

One simple method to check for the HWSE is to split the total follow up period by work status, into the time during work underground and the time after cessation of work underground and to compare SMR/RSMR-estimates. A death is counted to occur during exposure when cessation of exposure and death happened in the same month.

Time since first exposure (= TSFE) and work status are logically and causally independent. Thus it makes sense to fit SMR/RSMR-Poisson models including the general mean and TSFE (model I) and models extended by work status (model II). Under the HWSE-assumption that nearly all detrimental effects of exposure are indirect, approximately all adverse effects of TSFE are absorbed by the status variable. Therefore the coefficient for TSFE in model II is approximating the direct effect of exposure, the HWSE. Additionally a left censoring of TSFE up to 10 years and 20 years was tried, a time dependent restriction of cohort.

Cox models with time dependent covariables (time underground = duration of exposure, calendar time) are constructed to analyse mortality by age. Specific risk windows are explored (left censoring of the risk period from 0 to 30 years, left censoring in the range from 5 years before to 5 years after cessation of exposure) together with a lagging of exposure (0–20 years). Risk window specification is an extension of the restriction method proposed by Fox and Collier (1976); lagging to control for the HWSE is proposed by Gilbert (1982).

**Results**

(4578 German coalminers, follow up from 01/01/1980 through 12/31/1991).

SMRs during/after cessation of work underground for overall (0.40/0.70), cancer (0.21/0.76) and lung cancer mortality (0.19/0.81) clearly demonstrate a longitudinal healthy worker selection (even when relying on RSMRs).

The restriction of cohort produced the expected outcome: the TSFE-coefficient is rising in general (model I, Table 3). The approximation of the HWSE is empirically reflected by the change in sign of the TSFE-effect (model I vs model II, Table 3).

Adjusted coefficients (probably still biased downward) can simply be derived by calculating the difference between the coefficients in model I and model II. These
adjusted coefficients are quite independent from cohort restriction and remarkably greater than the coefficients from standard analyses (model I, TSFE ≥ 0 year; Table 3). So all the evidence points to the conclusion that a standard analysis suffers from a severe underestimate of the exposure effect on overall mortality, cancer mortality and lung cancer mortality.

Thus, it is not surprising that traditional Cox-models show negative coefficients for the effect of time underground on overall (P = 0.009), cancer (P = 0.12) and lung cancer mortality (P = 0.20).

The first square of the bottom line in Fig. 1 represents the coefficient of the traditional model. Again the results illustrate the possibility of a severe misinterpretation of the effect of time underground on overall mortality in standard models without considering healthy worker survivor effects.

Because death cannot occur before cessation of exposure it is of interest to explore the dependence of risk coefficients on differently specified risk windows starting around the end of work underground. The most interesting result was a change of the significantly negative coefficient of the traditional model into a significantly positive one by choosing a left censoring up to, but excluding the end of work underground (no lag). Basically the same relationship was found for cancer mortality too. This may point at an additional direct adverse effect of exposure on mortality that a standard analysis is unable to detect.

**SUMMARY AND CONCLUSION**

We think that, based on standard analyses, no cancer, no lung cancer, but a
stomach cancer excess risk is demonstrable among coalminers. These findings of
our study are broadly in accordance with the results from other investigations.
Regarding stomach cancer risk the possibility of confounding has to be considered
in detail.

A more sophisticated analysis trying to explore the degree of healthy worker
survivor effects points at probably masked excesses in overall, cancer and lung
cancer mortality among coalminers. Therefore, it has to be discussed whether
models, beyond those traditionally based on cumulative exposure and duration of
exposure, are acceptable or even necessary to describe the exposure–response
relationship for lung cancer in coalminers adequately.

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