Risk of pulmonary tuberculosis relative to silicosis and exposure to silica dust in South African gold miners

Eva Hnizdo, Jill Murray

Abstract

Objectives—To investigate the following questions. (1) Is silica dust on its own, without the presence of silicosis, associated with an increased risk of pulmonary tuberculosis (PTB) in workers exposed to silica dust? (2) Is the absence of silicosis the excess risk dose related? (3) What is the predominant chronological sequence between the development of PTB and the development of silicosis after the end of exposure to dust?

Methods—A cohort of 2255 white South African gold miners has been followed up from 1968 to 1971, when they were 45–55 years of age, to 31 December 1995 for the incidence of PTB. During the follow up 1592 (71%) men died. Of these, 1296 (81%) had a necropsy done at the National Centre for Occupational Health (NCOH) to determine the presence of silicosis and PTB. The incidence of PTB in the cohort was studied relative to cumulative exposure to dust and the onset of silicosis. For the miners with necropsy, the incidence for PTB was studied relative to the severity of silicosis found at necropsy.

Results—There were 115 subjects who developed PTB. The total person-years of follow up was 39 319. For the whole cohort, the factors associated with increased risk of PTB were cumulative exposure to dust (mg/m².y) (the adjusted rate ratio (RR) 1.07; 95% confidence interval (95% CI) 1.04 to 1.10), silicosis diagnosed radiologically (3.96 (2.59 to 6.06)), and tobacco pack-years (1.02 (1.01 to 1.03)). The RR (95% CI) for PTB increased with increasing quartiles of cumulative exposure to dust 1.0, 1.51 (0.78 to 2.91), 2.35 (1.28 to 4.32), and 3.22 (1.75 to 5.90). In miners who did not have radiologically diagnosed silicosis (n=1934, PTB=74), the adjusted RR (95% CI) for PTB and cumulative exposure to dust was 1.10 (1.06 to 1.13), and increased with quartiles of cumulative exposure to dust as 1.00, 1.46 (0.70 to 3.03), 2.67 (1.37 to 5.23), and 4.01 (2.04 to 7.88). For the subjects who had a necropsy (n=1296, PTB=70), the adjusted RR (95% CI) for PTB increased with the severity of silicosis found at necropsy; 1.0 for no silicosis, 1.88 (0.97 to 3.64) for negligible, 2.69 (1.35 to 5.37) for slight, and 2.30 (1.16 to 4.58) for moderate or marked silicosis. For subjects who had a necropsy and no silicosis (n=577, PTB=18), the adjusted RR (95% CI) increased slightly with quartiles of cumulative dust 1.0, 1.11 (0.31 to 4.00), 1.42 (0.43 to 4.72), and 1.38 (0.33 to 5.62). Conclusion—Exposure to silica dust was a risk factor for the development of PTB in the absence of silicosis, even after exposure to silica dust ends. The risk of PTB increases with the presence of silicosis, and in miners without radiological silicosis, with quartiles of exposure to dust. The severity of silicosis diagnosed at necropsy was associated with increasing risk of PTB and even <5 nodules—that is, undetectable radiologically—was associated with an increased risk of PTB. The diagnosis of PTB was on average 7.6 years after the end of exposure to dust, at around 60 years of age. The onset of radiological silicosis preceded the diagnosis of PTB in 99.2% of the cases with PTB who had silicosis. The results have implications for medical surveillance of workers exposed to silica dust after the end of exposure.

Keywords: pulmonary tuberculosis; necropsy; silicosis; surveillance.

The association between silicosis and pulmonary tuberculosis (PTB) has been well established. Epidemiological and case studies have shown that workers exposed to silica dust have increased morbidity and mortality from PTB.1–3 Experimental studies have shown an association between changes induced by silica particles and increased susceptibility to mycobacterial infection.4–16

Although the association between silicosis and PTB has been shown in many epidemiological studies, there are still gaps in the epidemiological evidence of the dose-response trend between PTB and cumulative silica dust in the absence of silicosis,7 and no published study has examined the incidence of PTB relative to the onset of silicosis or the end of exposure to dust.

South African gold miners are exposed to dust containing high concentrations of silica, and PTB always had a great impact on the health of gold miners.1–3 A mortality study of 3971 white miners found an increased standardised mortality ratio (SMR) (95% confidence interval (95% CI)) for PTB of 153.8 (41.9 to 394.1) after 9 years of follow up,4 and SMR of 306.4 (192.0 to 463.9) after 20 years of follow up.1 In black South African gold
miners the risk of PTB is even higher than in white miners, because the effect of silica is superimposed on a high rate of PTB within the population, and in more recent years on the high rate of HIV infection. The risk of PTB in black miners was shown to be related to severity of silicosis, and the relative risk (95% CI) due to the effect of silicosis was reported as 2.8 (1.9 to 4.1). During a 7 year follow up, the incidence of PTB increased with age depending on the category of silicosis; from 1% a year for miners with category 0 to 6.3% a year in miners with category 3 silicosis. A more recent study of South African gold miners reported that the adjusted rate ratio for PTB increased with age, with occupational categories known to have higher exposure to dust (drillers, mining team workers, and stope team workers) the incidence rate ratios (RRs) ranged from 2.25 to 2.56, and with the presence of silicosis the incidence RR was 1.54 (95% CI 1.00 to 2.37).

In the present study, we followed up a cohort of 2255 white South African gold miners from 1968–71, when they were 45–53 years of age, to 31 December 1995 for the incidence of PTB. The factors studied relative to the incidence of PTB were cumulative exposure to dust, the onset of radiological silicosis, and necropsy finding for silicosis. HIV was not a confounding factor in this cohort of miners. Objectives of the study were to investigate the following questions. (1) Is silica dust on its own, without the presence of silicosis, associated with an increased risk of PTB in workers exposed to silica dust? (2) In the absence of silicosis is the excess risk dose related? (3) What is the predominant chronological sequence between the development of PTB and the development of silicosis after the end of exposure to dust?

Material and methods

STUDY SUBJECTS

The study subjects comprised a cohort of 2260 white gold miners who were studied in 1968–71 for chronic obstructive lung disease. The study subjects were selected from all white miners who attended the Medical Bureau for Occupational Disease (MBOD) during the four years 1968–71 for a medical examination, and who fulfilled the following criteria: (1) MBOD number within the range B9000-C8999; (2) age 45–54; (3) ≥10 years of underground service; (4) ≥20 years residence in South Africa; (5) <2 years service in mines other than gold mines. An annual medical examination is compulsory for all miners working in dusty occupations in the gold mines. Of the 2260 miners, 2018 were current miners and 240 were inactive miners of whom 107 came to renew their fitness certificate to work underground and 133 came for a benefit examination (a specialised examination to determine disability and eligibility for compensation; this does not mean that they had a disability). Up to 31 December 1995 mortality has been followed up with the Department of Interior records of vital status. Five miners were excluded from the follow up study of PTB as they were diagnosed with PTB before the start of follow up in 1968–71. Of the remaining 2255 miners, 1592 (71%) have died and of these, 1296 (81.4%) had a necropsy at the National Centre for Occupational Health to assess the presence of compensable lung disease. There were 49 miners whose vital status was not established. These miners were assumed to be alive.

INCIDENCE OF PULMONARY TUBERCULOSIS

Pulmonary tuberculosis is a compensable lung disease in South African gold miners. The miners in this cohort who developed PTB while employed, or after retirement, would have come to the MBOD for medical examination and to apply for compensation. Also by law PTB is a notifiable disease and any doctor treating a miner for PTB is obliged to notify the MBOD. The records relating to the diagnosis of PTB done at the MBOD or by non-MBOD doctors (sputum examination, x ray films, etc) are kept in the miners’ medical files at the MBOD. These files were searched for the diagnosis of PTB. There were 180 subjects who were diagnosed with PTB. The x ray films of these miners were reread blindly for signs of PTB by the same reader who previously read these miners were reread blindly for signs of PTB. The x ray films of these miners were reread blindly for signs of PTB by the same reader who previously read these miners were reread blindly for signs of PTB.

Necropsy examinations of the cardiorespiratory organs were performed at the National Centre for Occupational Health according to a standard procedure. The presence of compensable disease was established by macroscopic and microscopic examination of the lungs. Histological examination was done on six tissue blocks taken from the upper, middle, and lower zones of each lung. At necropsy the presence of PTB was diagnosed in the presence of epithelioid granulomas associated with caseous necrosis, other causes having been excluded.

Of the 180 miners diagnosed with PTB, 39 had positive histological evidence at necropsy, 76 had a positive sputum finding in life, five were diagnosed on radiological findings only, and the remaining 60 miners had only a record of being compensated and date of compensation.

For the purpose of this study we have used only the cases where we could find either positive radiological signs, or a positive sputum test, or a positive necropsy finding in the lung parenchyma and who were diagnosed after 1968–71. There were 115 such cases.

ASESSMENT OF SILICOSIS

Radiological silicosis

While employed, the miners had annual radiological examinations. After retirement most of the miners came for radiological examinations, but less often. In the year 1990, the onset of silicosis was determined in the cohort by three experienced readers of x ray films to establish the dose-response trend between silicosis and cumulative silica dust. They examined yearly x ray films, starting from the most recent in the medical file, and identified the year of onset of silicosis. The onset of silicosis was diagnosed when the International Labour Organisation (ILO) category was at least 1/1. No detailed ILO grading was performed. The readings of
Table 1 Characteristics of the cases with pulmonary tuberculosis (PTB) and the rest of the cohort

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>PTB (n=115)</th>
<th>Rest of the cohort (n=2140)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year of birth (mean (SD))</td>
<td>1918.8 (2.4)</td>
<td>1919.1 (2.5)</td>
</tr>
<tr>
<td>Years gold mining (mean (SD))</td>
<td>27.6 (6.0)</td>
<td>26.5 (6.4)</td>
</tr>
<tr>
<td>Year last in dust (mean (SD))</td>
<td>1971.9 (4.1)</td>
<td>1971.7 (5.3)</td>
</tr>
<tr>
<td>Radiological silicosis (n (%))</td>
<td>41 (35.6)</td>
<td>280 (13.1)**</td>
</tr>
<tr>
<td>Age at onset of radiological silicosis (y, mean (SD))</td>
<td>53.5 (6.0)</td>
<td>56.2 (6.9)*</td>
</tr>
<tr>
<td>Deaths by 1995 (n (%))</td>
<td>98 (85.2)</td>
<td>1494 (69.8)**</td>
</tr>
<tr>
<td>Age at death (y, mean (SD))</td>
<td>65.2 (6.4)</td>
<td>64.9 (7.4)</td>
</tr>
<tr>
<td>Necropsy done at death (n (%))</td>
<td>70 (71.4)</td>
<td>1226 (82.1)**</td>
</tr>
<tr>
<td>Age at necropsy (y, mean (SD))</td>
<td>65.0 (6.2)</td>
<td>64.5 (7.3)</td>
</tr>
<tr>
<td>Silicosis found at necropsy (n (%))</td>
<td>52 (74.3)</td>
<td>667 (54.4)**</td>
</tr>
<tr>
<td>Cumulative dust, mg/m³ (y, mean (SD))</td>
<td>17.5 (6.4)</td>
<td>14.3 (6.1)****</td>
</tr>
<tr>
<td>Quartiles of total CDE, mg/m³: y (n (%)):</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤9</td>
<td>16 (13.9)</td>
<td>542 (25.3)</td>
</tr>
<tr>
<td>10–13</td>
<td>20 (17.4)</td>
<td>547 (25.6)</td>
</tr>
<tr>
<td>14–17</td>
<td>31 (27.0)</td>
<td>528 (24.7)</td>
</tr>
<tr>
<td>≥18</td>
<td>48 (41.7)</td>
<td>523 (24.4)</td>
</tr>
<tr>
<td>Cigarettes, pack-years</td>
<td>23.3 (16.0)</td>
<td>20.3 (16.3)*</td>
</tr>
</tbody>
</table>

*p<0.05; **p<0.01; ***p<0.001; ****p<0.0001.

CDE = cumulative dust exposure. Percentage is out of those who died.

the reader with the highest correlation with necropsy findings for silicosis21 were used in this study.

Necropsy silicosis
At necropsy, the presence and degree of silicosis was determined from macroscopic and histological examination of the lung. At the macroscopic examination the degree of silicosis was classified according to the number of palpable silicotic nodules, as follows: no silicosis, negligible (<3 nodules), slight (<14 nodules), moderate (15–30 nodules), and marked (>30 nodules). The presence of silicosis was confirmed by histological examination.

ESTIMATION OF CUMULATIVE EXPOSURE TO DUST
The occupational histories were coded for each miner from the Chamber of Mines personal files, which show the number of shifts worked in the particular mine and the occupation during a given period. With estimates of average exposure to dust for occupational categories in the South African gold mines derived by a study done by Beadle in 1970 (published by Page-Shipp and Harris),7 occupations were grouped into occupational categories and assigned an average dust concentration and an average time spent underground.22
Cumulative exposure to dust in terms of mg/m³·y was calculated as cumulative exposure to dust=Σ(number of dusty shifts × the mean mass respirable dust concentration for an occupational category × the average hours spent underground for an occupational category)/(270x8). The summation (Σ) was over all jobs in which a miner worked, 270 is the average number of shifts a year standardised to an 8 hour shift. Cumulative exposure was calculated as a time dependent variable (see statistical analysis).

SMOKING HABITS
Details of smoking habits were obtained by a questionnaire during the 1968–71 examination and answers were checked against smoking histories recorded in the medical file. Tobacco consumption was calculated in terms of cigarettes pack-years up to 1968–71.21

STATISTICAL ANALYSIS
The proportional hazards model was used to estimate the association between the risk of PTB and the potential risk factors. The SAS program PROG PHREG was used.23 The measure of association estimated was the incidence RR. The follow up time started from the year a subject was enrolled into the cohort study in 1968–71. At each time, t(I), when a case of PTB was diagnosed, all subjects who were still at risk of developing PTB and the PTB case formed a risk set, R(I). For each risk set R(I), the explanatory variables (cumulative exposure to dust, the presence of radiologically diagnosed silicosis, and age) were calculated up to the time t(I).

Because the degree of silicosis was only assessed at necropsy, and these findings are more reliable than the radiological findings, we analysed the subjects who had a necropsy in a separate analysis. As the necropsy silicosis was diagnosed at the end of a follow up (at death), the inclusion of necropsy silicosis in the analysis as a time dependent explanatory variable would have biased the estimated RR. Only subjects with PTB would be found to have silicosis at necropsy, most of those without PTB who were found to have silicosis at death (the end of follow up) would be censored before death and their silicosis would not contribute to the calculation of the maximum likelihood statistics. Therefore the necropsy silicosis was treated as if it was present or absent during the whole follow up and the estimated RRs were adjusted for the years of follow up and for cumulative exposure to dust. The use of this model can be justified by the fact that silicosis is a progressive disease and it is difficult to determine its onset radiologically.

Results
The miners were born on average in 1919 (SD 2.5; range 1913–24), started mining in the 1940s and retired from dusty occupations in 1971.7 (SD 5.3), at around 52.4 (SD 5.4) years of age. During the follow up (1968–71 to 1995), 115 miners developed PTB according to the criteria used for the study. Only the first incidence in one person was considered. The total person-years of follow up was 39,319. Table 1 shows characteristics of the cases with PTB and the rest of the cohort. The cases had more silicosis diagnosed radiologically (41 (35.6%) v 280 (13.1%)) and were on average younger at the onset of silicosis (53.5 (SD 6.0) v 56.2 (6.9)).

A higher percentage of the cases with PTB than the rest of the cohort died by the year 1995 (85.2% v 69.8%) but a lower percentage of PTB cases had a necropsy at death (71.4% v 82.1%). Silicosis diagnosed at necropsy was found in 52 (74.3%) cases and in 667 (54.4%) miners without PTB. The cases had significantly higher cumulative exposure to dust and cigarette pack-years than the rest of the cohort.
ASSOCIATION BETWEEN PTB, DUST, AND SILICOSIS

Radiologically diagnosed silicosis
Table 2 shows the smoking adjusted RR for PTB estimated from the proportional hazards model for the whole cohort and for those without silicosis. The presence of silicosis (diagnosed radiologically) increased the risk of PTB by about four times (RR 3.96) after adjustment for cumulative dust (model 3). The RR for PTB increased with increasing cumulative exposures to dust in the whole cohort (models 3 and 4) and also in miners who did not have silicosis (models 5–8). The effect of cigarette pack-years was significant, and for all models the estimated RR was constant (RR 1.02 (95% CI 1.01 to 1.03)). The RR for increasing age at death categories (<60, 61–70, 71–80, >80) did not show a significant trend and age at death was not included in the model.

Silicosis diagnosed at necropsy
Table 3 shows the results for miners who had a necropsy. The RR for PTB increased with the increasing severity of silicosis diagnosed at necropsy (model 1). However, when cumulative dust was adjusted for, the RR in the highest exposure category decreased from 2.71 to 2.06 (model 2) and to 2.30 (model 3). The RR for PTB was increased even for a negligible degree of silicosis (RR 1.86, 95% CI 0.96 to 3.58). There were only 577 subjects who did not have any nodules found at necropsy. Although the RR showed some trend with increasing dust (models 4 and 5), this was not significant. However, the number of miners in this group was small.

The distribution of necropsy findings for silicosis according to the PTB diagnosis is as follows. Of the 70 cases of PTB who had a necropsy, 18 (25.7%) did not have silicotic nodules, 18 (25.7%) had negligible, 16 (22.9%) had slight, 14 (20.0%) had moderate, and 4 (5.7%) had marked degree of silicosis found at necropsy. Of the 1226 subjects who did not have PTB, 559 (45.6%) did not have silicotic nodules, 292 (23.8%) had negligible, 180 (14.7%) had slight, 140 (11.4%) had moderate, and 55 (4.5%) had marked degree of silicosis at necropsy. This difference in the distribution of necropsy silicosis in the cases with PTB and in the rest of the subjects was significant (Mantel-Haenszel $\chi^2=10.7$, df=1, $p=0.001$).

Diagnosis of tuberculosis in relation to the end of exposure to dust and onset of silicosis
In the cases with PTB, the average age at the last exposure to dust was 52.7 (SD 5.2) and the age at diagnosis of PTB was 60.3 (SD 5.7). There were 15 subjects who were diagnosed with PTB before the end of exposure to dust, six subjects were diagnosed in the same year as exposure to dust stopped, and 99 subjects were diagnosed after the end of exposure to dust. The figure shows the distribution of age at last exposure to dust for the cohort, of age at the onset of radiological silicosis for miners with silicosis, and of age at the diagnosis of PTB.

Of the 115 cases with PTB, 41 (35.7%) had radiologically diagnosed silicosis. In four cases, the onset of radiological silicosis was during the same year as the diagnosis of PTB, and in 37 cases the diagnosis of PTB was after the onset of silicosis. On average the age at the onset of silicosis in the cases with PTB was 53.5 (SD 6.0) years, and the average age at diagnosis of...
that exposure to silica dust is associated with increased mortality from PTB after adjustment for pneumoconiosis. The limitation of this study is that silicosis was established from the death certificates and that occupational exposure was obtained indirectly by interviewing the next of kin. Thus misclassification of disease and exposure was likely to have been present in this study.

The first two objectives of our study were to investigate with radiological and necropsy data for the diagnosis of silicosis whether silica dust on its own, without the presence of silicosis, is associated with an increased risk of PTB and whether the excess risk is dose related.

The results show that the risk of PTB increases with the presence of radiologically diagnosed silicosis, with increasing cumulative exposure to silica dust, and with tobacco pack-years. The presence of silicosis diagnosed radiologically increased the risk of PTB by about four times after adjustment for cumulative dust and smoking (table 2, models 3 and 4). The RR for PTB showed a significant trend with quartiles of cumulative exposure to dust (table 2, model 4). The results indicate that the miners in the highest category of exposure to dust who were diagnosed with radiological silicosis had a 13.4 times (3.22 x 4.18) increased risk of developing PTB during the follow up period than the miners who did not have radiological silicosis and had the lowest exposure to dust.

Although the results in table 2 show that dust remains a significant risk factor after silicosis is considered in the model (model 4), it can, however, be argued that in this model cumulative silica dust can be acting as a surrogate variable for increasing severity of silicosis. In the next step in the analysis we therefore estimated the association between PTB and cumulative dust in miners who did not have radiological silicosis (models 5 and 6) and in miners who had not had silicosis diagnosed radiologically or at necropsy (models 7 and 8). For both sets of models the association between PTB and cumulative exposure to dust was significant and close to that found for the whole cohort. Of the 1388 subjects used in models 7 and 8, 572 (41.2%) had a necropsy, thus potentially there might have been some subjects who developed silicosis after their radiological follow up ended.

We therefore analysed separately only subjects who had had a necropsy, to investigate whether silica dust remains a significant risk factor after the degree of silicosis found at necropsy was taken into account. The results show that after the degree of silicosis found at necropsy was taken into account, dust still remained a significant risk factor and that the trend in RR with increasing dust persisted (table 3, models 2 and 3). A miner with moderate or marked silicosis found at necropsy who had high exposure to dust has 2.30 x 2.54 = 5.8 times increased risk of developing PTB after the end of exposure to dust. Although the miners without silicosis at necropsy do not show a significant trend with increasing levels of dust
Pulmonary tuberculosis, silicosis, and silica dust in South African gold miners

The results indicate that the silica dust which miners accumulate in their lungs during exposure is a lifelong risk for the development of PTB, even if silicosis is not present in the lungs. Furthermore, even after exposure to dust ends, ex-miners continue to be at risk of developing silicosis and the development of silicosis places them at even greater risk of developing PTB. Moreover, the data show that miners with very few silicotic nodules (negligible and slight degree of silicosis) have significantly increased risk of getting PTB and that this degree of silicosis is seldom diagnosed radiologically. The results of this study show that even after exposure to silica dust has ended, lifelong surveillance for silicosis and especially for PTB is important in workers exposed to silica dust. In Southern Africa, where the population of ex-miners is extensive, it is important that healthcare providers are informed about the increased risk of PTB in ex-miners, so that patients with respiratory symptoms who have a previous mining history are rigorously investi-
We express our gratitude to Dr Wiles who established the initial miners cohort; the late Dr Sluis-Cremer who read the x ray films for the study and whose research into occupational lung diseases inspired this study, and the pathologists from the National Centre for Occupational Health who performed the necropesies over the years. The study received funding from the Safety in Mining Research Advisory Committee.


Occupational and Environmental Medicine and the electronic age

OEM has an Email address which is 100632.3615@compuserve.com. We welcome contact by Email, including letters to the editor. Many of our reviewers send us their reports by Email, helping to speed up the peer review process.