ORIGINAL ARTICLE

Lung cancer and dust exposure: results of a prospective cohort study following 3260 workers for 50 years

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Aims: To study the lasting health impact of occupational dust exposure on life expectancy and specific causes of death.
Methods: Male Viennese workers, selected at age ⩾40 (mean 54) years during preventive check-ups between 1950 and 1960, were followed prospectively until death. Half of them (1630) were exposed at work to (non-fibrous) particulates, while the non-exposed workers were matched for year, age, and smoking status at the start of observation.
Results: Average life expectancy of those exposed was 1.6 years less than that of those non-exposed. Only a small part of this decrease in life expectancy (hazards ratios in brackets) was related to acknowledged occupational diseases such as silicosis and silicotuberculosis (67.12). Chronic obstructive lung disease (1.82) and cancer of the lung (1.42) and stomach (1.77) were found more frequently among those exposed.
Conclusions: Results support the hypothesis that high exposure to insoluble particulates such as silica in the metal, glass, ceramics, and stone industries promotes bronchial cancer and chronic obstructive pulmonary disease. The finding of an increased incidence of stomach cancer might be related to particles swallowed after clearance from the airways.

In the 1950s the increasing death rate from bronchial cancer, apparent since the beginning of the century, troubled many health professionals. Although papers published in the 1930s and 1940s had already indicated a causal link to cigarette consumption,[1] it was not until publication of the studies by Levin and colleagues[2] and Wynder and Graham[3] that smoking was widely recognised as the leading cause for bronchial cancer. However, many questions regarding causes remained to be solved.

In the 1950s a group of medical doctors working in the fields of preventive occupational medicine and pneumology formulated the hypothesis that ''unspecific'' irritation of the bronchial epithelium by mineral dust might lead to a proliferative stimulus on the epithelial layer provoking lung cancer; they tested this on a cohort of Viennese workers.[4]

Although one of the aims of the preventive check-ups from which this cohort was sampled was to find early stages of silicosis, the cancer hypothesis was not restricted to quartz as a possible causal factor, but also included other (non-fibrous) mineral dusts.

Little was known in the 1950s about other possible causes that might act as confounding factors. But controls were matched for smoking habits (yes/no at introduction into the study) and age. Ongoing observations of both the dust exposed and the control group ascertained that workers were not exposed to other important respiratory carcinogens at the workplace, such as radon or asbestos.[5]

Meanwhile particulates have been discussed as key ambient air pollutants responsible for premature deaths in the general population[6 7] and as important occupational contributors[8 9] for lung cancer and chronic obstructive pulmonary disease (COPD). IARC[10] found ''sufficient'' evidence for crystalline silica (inhaled in the form of quartz or cristobalite from occupational sources) to be a human carcinogen, and the US Occupational Safety & Health Administration[11] reclassified crystalline silica from ''reasonably anticipated'' to ''known to be a human carcinogen''. As a contribution to this current discussion we decided to reanalyse the cohort study, which to our knowledge is the only prospective study on this subject with long term follow up. Because nearly all of the subjects under study have died, we are now able to give survival estimates combined with analysis of causes of death based on postmortem examination diagnoses, both for the dust exposed and the non-dust exposed workers.

METHODS

Subjects

A mobile team of the Viennese occupational health care unit visited 1089 enterprises throughout the 1950s for preventive medical check-ups on 247 064 workers.[12] All workers obviously exposed to respirable dust at the workplace were registered and underwent additional medical examinations such as *x* ray and lung function tests. At the same time the doctors in charge also collected data from workers without occupational dust exposure—that is, Viennese workers from the same sample population, matched by age, year of first examination, and smoking status (smoking: yes/no; 69% were smokers on introduction into the study). They gathered 1630 male workers exposed to dust and the same number of control subjects, all living and working in Vienna and being born before or in the year 1910. The mean age (SD) of the subjects on introduction into the study was 53.6 (6.9) years. On first examination all were considered healthy—that is, fit for work.

Dust exposure

Filter and conimeter measurements of dust exposure were rarely performed in dusty enterprises under observation

Abbreviations: COPD, chronic obstructive pulmonary disease; IARC, International Agency for Research on Cancer; ICD 9, International Classification of Diseases, 9th revision; WHO, World Health Organisation

before 1960 by the Austrian Dust Prevention Board, founded in 1948. Exposure status in the 1950s was mainly assessed by visual inspection. Until the early 1960s most enterprises from which subjects of the Viennese cohort were recruited had been included in the first measuring campaigns. Although these measurements did not fulfil modern standards and even differed within themselves as to methodology and duration of measurement (eight hour means versus short time measurements), it can be concluded from these data that dust exposure was generally high in the exposed workers and frequently exceeding the former workplace standards for respirable dust (eight hour means) of 6 mg/m^3 or 600 particles/ml,[13] with silica contents mainly above 2%, in foundries between 5% and 40%. The highest instance of exceeding former workplace standards was in a foundry of 1964: 1.8–40-fold in the moulding area (16% silica) and 4.3–30-fold in the fettlers shop.[14]

Health data and follow up on job status

Three exposed and six non-exposed workers had to be excluded from the study because of incomplete or implausible birth dates and spelling mistakes that made further comparisons with the registrar's data impossible.

By systematic inquiries at the registrar's office, public health offices, and the Workers' Compensation Board, date and causes of death were registered for both exposed and control workers. By the end of 2000, date of death from 1610 dust exposed and 1607 not exposed controls could be obtained. Underlying causes of death (as listed as ''primary cause'' on death certificates) were obtained from 1598 and 1582 respectively and grouped according to ICD 9 (table 1). From 17 of the dust exposed and 17 controls, no death certificate was obtained by the end of 2000. Some were still thought to be alive, but others were lost to follow up for several reasons. For statistical reasons their observation period was terminated by default as of 31 December 2000.

Cases of silicosis were registered according to death certificate or regular payments for silicosis or silicotuberculosis by the Austrian Workers' Compensation Board. Changes of job after recruitment were noted by the Austrian Workers' Pension Insurance and analysed as to possible confounding exposures. On the Austrian death certificates both ''primary'' (underlying) and ''secondary'' causes of death as well as ''other important diseases at time of death'' (especially chronic diseases and cancer, even if they did not lead directly to death) are registered. For comparing cancer rates of the lung and of the stomach with the rate of silicosis in the exposed workers' ''other important diseases at time of death'' served as additional source of information (table 1).

Statistical analysis

Statistical calculations were performed with SPSS for Windows (release 10.0.7). Hazard ratios were calculated applying Cox regression. Graphical presentations of cumulative survival rates were obtained with the help of the Kaplan-Meier method. These calculations were performed on each single group of causes of death, with the time variable being the age at death and all other causes of death as censoring events.

RESULTS

Follow up of job history

From 1607 of the exposed workers, sufficient data on job history were obtained so that check-ups were possible with the Workers' Compensation Board with regard to compensation for silicosis and other acknowledged occupational diseases. Little job fluctuation was observed. Only 63 of the dust exposed workers changed job classification after introduction into the study and therefore could not be

Table 1 Grouping of causes of death according to ICD 9 with absolute numbers (primary causes of death according to death certificate, primary and secondary causes of death for cancer of lung and stomach, hazard ratio with 95% CI, and p value estimated by Cox regression analysis)

Primary cause of death	ICD code	Dust exposed	Not exposed	Hazard ratio	95% CI	p
All malignancies	140–208	451	409	1.26	1.10 to 1.44	0.001
Bronchial cancer	162	189	149	1.42	1.14 to 1.76	0.002
Other malignancies of the respiratory tract	160, 161, 163–165	4*	4*	1.14	0.28 to 4.55	0.86
Stomach cancer	151	81	52	1.77	1.25 to 2.51	0.001
Other malignancies of the gastrointestinal tract	140–150, 152–159	93	104	1.04	0.78 to 1.37	0.81
Other malignancies	170–208	84	100	1.00	0.75 to 1.34	1.00
Chronic obstructive lung diseases	490–496	86	55	1.82	1.30 to 2.56	0.001
Pneumoconiosis, other parenchymal lung diseases, including:	500–508, 515–517,	60	1	67.12	9.30 to 484.39	<0.001
Silicosis		33	0			
Silicotuberculosis		19	0			
Other parenchymal diseases		8	1			
Tuberculosis†	010–012	17	15	1.28	0.64 to 2.57	0.49
Acute respiratory diseases	460–466, 480–487, 510–513	66	62	1.28	0.91 to 1.82	0.16
Cardiovascular diseases	390–459	718	838	1.03	0.93 to 1.14	0.56
Other diseases, accidents, suicide	001–009, 013–139, 210–389, 470–478, 514, 518–999	200	202	1.13	0.93 to 1.38	0.21
All causes of death		**1610**	**1607**	**1.18**	**1.10 to 1.26**	**<0.001**
No diagnosis		12	25	0.62	0.31 to 1.23	0.17
No date of death (terminated at 31 Dec 2000)		17	17	1.82	0.91 to 3.64	0.09
Sum		**1627**	**1624**			
No data (excluded from study)		3	6			
Sum		**1630**	**1630**			
Both primary cause of death and additional diseases:						
Bronchial carcinoma		195	153	1.43	1.16 to 1.77	0.001
Stomach cancer		82	53	1.76	1.25 to 2.49	0.001

*Includes no mesothelioma.
†Not including 19 dust workers with silicotuberculosis listed under ''pneumoconiosis''.

Table 2 Percentage of silicosis and bronchial cancer stratified for job categories

Job category	Number	Silicosis (%)	Bronchial carcinoma (%)	Mean life expectancy
Foundries	748	15.4%	12%	72.12
Other metal industries	459	2.0%	9.4%	72.06
Brick and stone industry	85	7.1%	18.8%	70.62
Glass and pottery works	186	8.6%	15.1%	71.25
Others	66	15.2%	9.1%	70.74
Multiple	63	17.5%	9.5%	71.87
All dust exposed workers*	1607	10.4%	11.8%	71.84

*All dust exposed workers with sufficient job data that enabled check-ups at the Austrian Workers' Compensation Board.

classified to a single category. The others were classified according to table 2. Controls came from varying industries, and even the same enterprises as the exposed workers, but without apparent dust exposure. Social status and education were not noted, but important differences between those exposed and controls are not likely because both groups were drawn from the same source population of blue collar workers.

Follow up of smoking history

At recruitment 69% of the dust exposed and 69% of the non-dust exposed workers were smokers. To check whether the matching remained stable over time and to compare the smoking rate of the cohort to the general population (for which data were only available in 1979 and later), a random sample of 163 cohort members (5% of cohort) was contacted by mail and additionally by telephone about their current smoking habits in 1979. This was performed by an interviewer blinded to the former dust exposure status. From these 163 persons, 101 were reached, either as themselves or as their widows or other close relatives. Seventeen of those dust exposed and 19 of the controls were found still alive in 1979 and could be interviewed personally. Twenty nine per cent of those dust exposed, and 21% of the control workers declared to be smokers (five and four persons respectively). From all interviews (including proxy interviews), a trend was seen for those dust exposed to quit smoking less frequently. (This trend, however, could be explained in part by the shorter survival of those dust exposed, during which their chance to quit smoking was lower than during the longer survival of the non-dust exposed.)

In the age group 60 years and older, 31.2% of male Austrians did smoke in 1979 (microcensus data[15]). No separate data on older age groups are given by the central statistical office. All our workers were older than 70, at which age the frequency of smoking is generally decreasing. Thus the smoking frequency of the cohort most probably was comparable to the Austrian population of the same age and gender in 1979.

Life expectancy, postmortem examination rates, and causes of death

Most of the workers were followed until the end of their life. By the end of 2000 a death certificate could be obtained from 1610 of the dust exposed workers (98.96%) and 1604 of the controls (98.77%).

Overall postmortem examination rates were high, and were carried out in 56.7% of those dust exposed and 52.8% of the controls. Postmortem examinations were performed in 57.0% (dust exposed) and 54.6% (controls) of those diagnosed with a neoplasm as primary cause of death. The difference in postmortem examination rates between those exposed and controls is mainly due to the year of death (see below). Postmortem examination rates were highest in the first decades of the study and declined to less than 40% towards the end. This is partly due to the fact that postmortem examination in Austria is performed less frequently in older persons, but also to improvements of intra vitam diagnoses over time, which reduced the necessity for postmortem examination verification. When controlled for year of death in logistic regression, group status (exposed or controls) no longer contributed significantly to postmortem examination status.

Overall a shorter life expectancy of dust exposed workers (71.84 years) compared to control workers (73.41 years) was found, the difference of 1.57 years being significant ($p<0.001$). Furthermore, for special causes of death significant differences were found (lung and gastric cancer, chronic pulmonary disease). No difference in life expectancy between those exposed and controls was seen with cardiovascular deaths (table 1, figs 1–5).

No significant differences could be found in life expectancy and cancer risk within the different jobs of dust exposed workers (foundries, other metal industries, brick and stone industry, glass and pottery works, others; table 2).

Of the 1607 exposed workers with sufficient job data, 167 (10.39%) developed silicosis or silicotuberculosis (primary or secondary cause of death according to death certificate or regular payments by the Austrian Workers' Compensation Board). None of the controls did. Eight dust exposed workers and one control died from chronic parenchymal pulmonary diseases other than silicosis. None of the exposed workers or controls developed asbestosis or mesothelioma.

While tuberculosis was the primary cause of death in about 1% both in controls (0.94%) and in dust exposed workers who did not develop silicosis (1.18 %), ''silicotuberculosis''

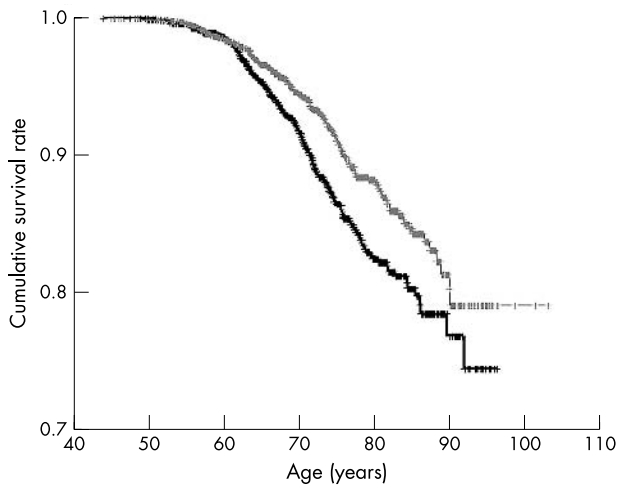

Figure 1 Kaplan-Meier estimate of cumulative survival rates for bronchial carcinoma (dark line: dust exposed; light line: not exposed).

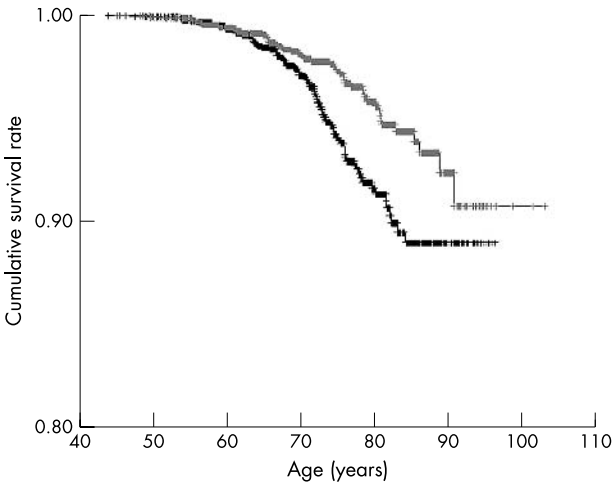

Figure 2 Kaplan-Meier estimate of cumulative survival rates for stomach cancer (dark line: dust exposed; light line: not exposed).

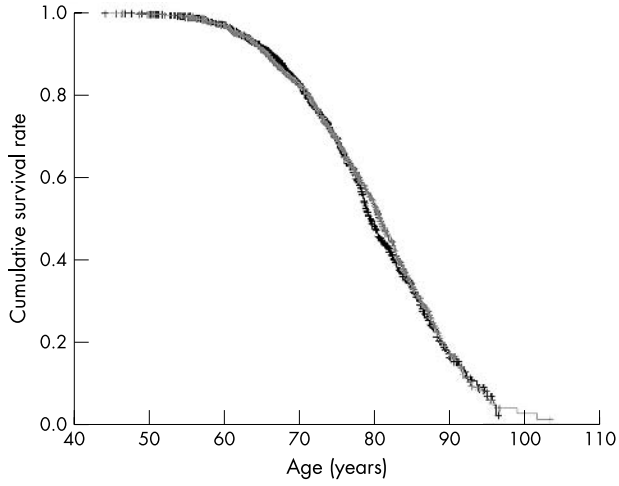

Figure 3 Kaplan-Meier estimates of cumulative survival rates for cardiovascular diseases (dark line: dust exposed; light line: not exposed).

was diagnosed as the primary cause of death (according to the death certificate) in 10% of the silicotics.

The frequency of silicosis did not differ significantly among job categories, except for the group "other metal industries" which showed a lower incidence of 2% (table 2). The hazard ratio for silicosis was also reduced in this group, while it was significantly increased in foundry workers. On the other hand, bronchial cancer showed a quite different relation to job categories in the Cox regression, being increased in brick and stone, and glass and pottery industries (table 3).

Within the group of dust exposed workers, those with a diagnosis of silicosis had a comparable risk to die from lung and stomach cancer as the others (table 4).

DISCUSSION

The group of dust exposed workers showed a significant decrease in life expectancy with an increase of only few specific causes of death. Pneumoconiosis as a specific disease for this type of exposure only accounted for a small part of the loss of life expectancy. Dust exposed workers had significantly higher risks of dying from obstructive lung disease, and bronchial and gastric cancer, which contributed to their loss of life expectancy.

Little thought was given to possible confounding factors in the 1950s, except for the matching of controls according to current smoking status. Nevertheless different smoking intensity might be a possible confounder, although in the sample interviewed in 1979 there was still no significant difference in smoking prevalence; thus an important difference in smoking intensity between dust workers and controls does not seem likely. There was, however, a hint in 1979 that controls tended to stop smoking more frequently, which might indicate that smoking workers of the control cohort were less dependent and therefore possibly less heavy smokers. On the other hand, it is possible that control workers simply had a longer chance to quit because they reached a higher age and survived into the period when quitting came into fashion. Also no difference was seen in survival of dust exposed workers and control workers from cardiovascular deaths, which again makes influential differences in smoking behaviour unlikely.

Differences in age and gender can be ruled out as possible confounders because of the study design. Differences in other occupational exposures have been discussed in detail elsewhere.[5] In short, occupational exposures to asbestos had been excluded and occupational exposures to radon or other sources of radiation were found negligible in this workforce. Also the follow up of other occupations after registration for this study did not reveal any jobs with confounding exposures to lung carcinogens. Finally lung cancer was found increased in all subgroups of dust exposed workers (foundries, other metal, ceramics, glass, stone) for which different confounders would have to be assumed. Differences in social status between the two groups are not likely because both the exposed and controls are drawn from a socially quite uniform group of blue collar workers having the same health insurance and living in the same city at the same time, which also makes differences in lifestyle unlikely.

If we assume comparable nutritional habits (which have not been investigated), then the association of gastric cancer with occupational dust exposure could also be causal. Similar observations made in other studies[16–19] were attributed to a variety of dust components such as silica and other minerals, metals, and polycyclic aromatic hydrocarbons, but also free radicals in freshly generated dust, nitrosamines in cutting oils, and combined effects (for example, infection with *Helicobacter pylori*).

While ultrafine particles from combustion sources are now of considerable interest, the Viennese cohort was also

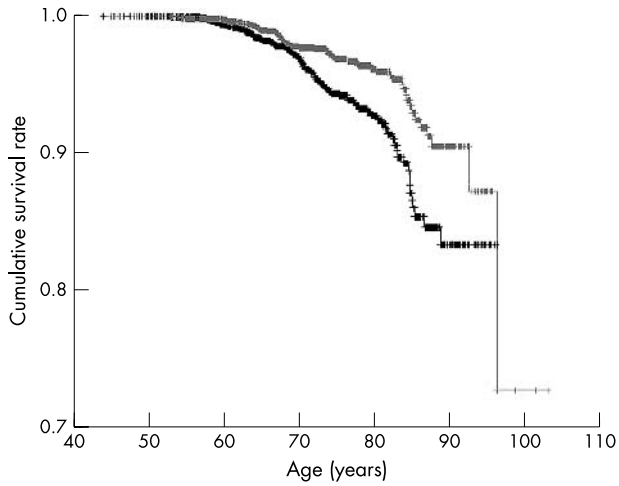

Figure 4 Kaplan-Meier estimate of cumulative survival rates for chronic obstructive lung disease (dark line: dust exposed; light line: not exposed).

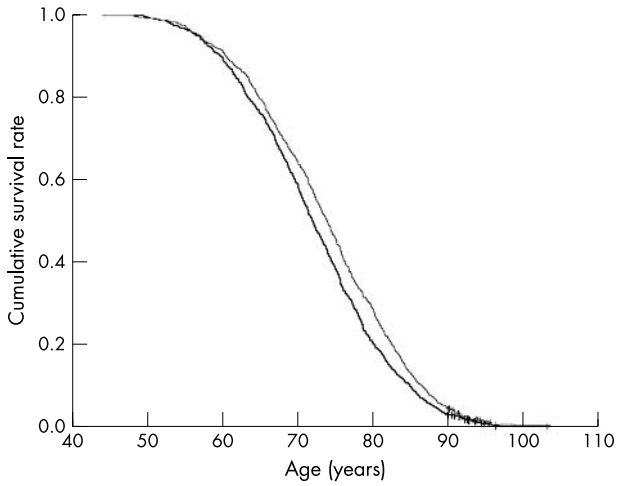

Figure 5 Kaplan-Meier estimate of cumulative survival rate for all causes of death (dark line: dust exposed; light line: not exposed).

exposed to rather coarse mineral particles. Certainly the subjects were exposed to a varying degree of fine particles and also gaseous substances. Conimeter measurements indicate that 30–50% of the particle mass consisted of particles with a diameter less than 5 µm. Inhaled coarse particles are subject to mucociliary clearance, and thus most are swallowed and reach the stomach. Both lung and stomach are the organs that are effected in the exposed group. This specificity in target organs supports causality of the observed associations.

From the results of this cohort study we conclude that the difference in both life expectancy and number of deaths due to bronchial (and gastric) carcinoma is causally linked to occupational exposure to mineral particulates. From the dust samples obtained in the early 1960s we know that the silica content varied between the different workplaces. Correspondingly we found a significantly higher rate of silicosis in foundry workers, but a lower rate in workers from ''other metal industries''. However, these workers did not differ from other dust exposed workers in life expectancy or bronchial cancer rate. Furthermore, silicotics had the same risk of developing lung cancer (primary cause of death or additional disease) as had the other dust exposed workers. These findings do not indicate that silica dust was the cause of cancer.

At closure of the occupational health care unit, only the bare personal data of the workers (name, birthday, address, working place, dust exposure: yes/no), but unfortunately not the original histories with the individual smoking status were retained. This is unfortunate because a matched pair analysis would have increased the statistical power of the study and enabled an analysis of combined effects of dust and smoking. From theoretical considerations[20] we would expect dust to enhance proliferation of epithelial cells and to act as a promoter rather than an inducer of carcinogenesis.

Table 4 Cancer* (bronchial and gastric) and silicosis*; hazard ratio for silicosis compared to dust exposed workers without diagnosis of silicosis

	Hazard ratio	95% CI	p
Bronchial carcinoma	1.25	0.79 to 1.97	0.34
Stomach cancer	0.83	0.36 to 1.90	0.65

*Bronchial and stomach cancer: both primary cause of death and additional disease; Silicosis: according to death certificate (cause of death and additional disease) or based on compensation payments.

Findings are in line with the original hypothesis[4] of the unspecific irritating and inflammatory potential of mineral dusts which—if insoluble in the lung—may lead to bronchial cancer via chronic inflammatory and regenerative changes, including increased rates of epithelial metaplasias and dysplasias.[5 21 22] Not only crystalline silica, but also many different particulates are capable of activating alveolar macrophages to release mediators which affect epithelial cells via oxidants, proteases, growth factors, cytokines, etc,[23 24] and have been found to increase mortality from malignant and non-malignant respiratory disease.[25]

The combined effects of dust and smoking also have to be considered with respect to overall life expectancy. The number of subjects interviewed in 1979 is too small to draw any conclusions on single causes of death (of all 101 subjects, seven died from lung cancer (four dust workers and three controls); all seven were smokers when introduced into the study). Overall life expectancy in the 101 subjects was 2.77 years shorter for smokers, although this difference did not reach significance at the 5% level.

At the start of observation all subjects were far beyond the middle of their working life and expecting retirement already. All were healthy enough to go to work at recruitment for this study and at first (preventive) medical check-up, only the expected (and then preclinical cases) of silicoses were detected. So we have to assume a pronounced ''healthy worker effect'' from selection in and out of dusty jobs, because only those who physically managed many years of work in a dusty environment came under study. With the cut-off of the first half of life possible, early deaths due to dust exposure—which (if they happened) would put a heavier weight on life expectancy—were out of scale.

Conclusions

Occupational exposure to mineral dust, even in a group of workers who are clinically healthy and near the end of their working life, still leads to a reduction in life expectancy,

Table 3 Hazard ratio (job category against all other dust exposed) for silicosis* and bronchial carcinoma* for each job category

	Silicosis*			Bronchial carcinoma*		
	Hazard ratio	95% CI	p	Hazard ratio	95% CI	p
Foundries	2.49	1.80 to 1.46	<0.00	0.98	0.74 to 1.30	0.90
Other metal industries	0.13	0.07 to 0.26	<0.00	0.72	0.52 to 1.01	0.06
Brick and stone industry	0.76	0.33 to 1.71	0.50	1.76	1.06 to 2.94	0.03
Glass and pottery works	0.85	0.51 to 1.42	0.53	1.51	1.03 to 2.22	0.04
Others	1.68	0.89 to 3.18	0.11	0.81	0.36 to 1.83	0.61
Multiple	1.83	0.99 to 3.38	0.05	0.81	0.36 to 1.82	0.60

*Bronchial cancer: both primary cause of death and additional disease. Silicosis: according to death certificate (cause of death and additional disease) or based on compensation payments.

caused by an increase in specific groups of causes of death—pneumoconiosis, COPD, and bronchial and gastric cancer.

Crystalline silica exposure is an important indicator of dangerous mineral dust exposure; however, our data do not suggest that silica is the sole causal factor for COPD, and bronchial and gastric cancer.

Most of the workers experienced their work related disease only after retirement. This underlines the importance to integrate occupational health aspects in medical check-ups of elderly and retired persons.

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