Letter to the Editor

A Retrospective Cohort Mortality Study in Jinchang, the Largest Nickel Production Enterprise in China

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Nickel is an essential trace metal used in the occupational setting, resulting in both occupational and nonoccupational exposures to individuals at varying levels. Exposure to nickel has been associated with several toxicities and the International Agency for Research on Cancer has concluded that there is sufficient evidence in humans associating exposure to nickel compounds with risk of lung cancer and sinonasal cancer. This study confirmed a significant excess of mortality from diseases of the lung including silicosis, lung cancer, and cor pulmonale among workers involved in nickel mining or smelting in China.

Nickel is ubiquitously found in the general environment and used in various occupational settings, including in mining, smelting and refining, and the alloy production and welding industries. Given the common occurrence of this exposure, several epidemiological studies have examined the health hazards associated with nickel exposure, particularly among individuals working in industries where nickel is used and exposure levels are higher relative to levels in the general population. Moreover, increased risks of both lung and nasal cancers have been reported in epidemiological studies of workers exposed to nickel[1].

Globally, the rate of nickel production has increased by about 3% from 2000 to 2010, and has increased by 21% in China over this period[2]. Thus, the high production and consumption of nickel in China has significant public health implications both for occupationally exposed workers and to the general public resulting from environmental pollution, and further studies are needed particularly in this highly exposed population to evaluate the potential adverse health effects associated with this exposure.

In order to further investigate the health hazards associated by exposure at work, including both cancer and non-cancer outcomes, we conducted a historical cohort study among workers in a nickel plant in China. This is the first occupational study of nickel exposure in China. The nickel production enterprise in this study in China was established in 1958, and today is the third largest nickel and second leading cobalt mine in the world, as more than 90% of the production of nickel and platinum compounds in China come from there.

Workers in this enterprise plant are routinely exposed to nickel as well as several other contaminants, including industrial dust, particulate matter and gaseous pollutants, cobalt, covellite, and chromium. Many of these substances are considered as definite or possible carcinogens[3-5].

A total of 432 526 employees including active workers and retired workers had worked in the enterprise during the observation period, about 63% of whom were men. About 55% of workers were less than 45 years old, 36% were between 45 and 65 years, and 9% were more than 65 years old. By December 31, 2010, 2 576 workers died including 2 179 men and 397 women. Nearly 70% of the deaths occurred among subjects over the age of 60 years. The mean age of death was about 65 years and was higher in men (about 66 years) compared to women (about 59 years). Half of the deaths occurred in 2007-2010, and about 81% of the workers who died were employed in either the production or service sectors.

Malignant neoplasms were the primary cause of death, accounting for 36.6% (*n*=925) of total deaths, with the predominant sites of the tumors being lungs (*n*=309, 33.4%), stomach (*n*=172, 18.6%), liver

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(*n*=158, 17.1%), and esophagus (*n*=83, 9.0%). The overall mortality rates from 2001 to 2010 was 595.57/100 000 in the cohort, and the mortality rate of lung cancer, cor pulmonale, silicosis and diabetes was 71.44/100 000, 17.80/100 000, 29.36/100 000, and 25.43/100 000, respectively (Table 1).

As shown in Table 1, all-cause mortality was half lower than expected from the third death causes retrospective sampling survey in Gansu Province. Between 2001 to 2010, 2 576 workers had died, compared with an expected number of about 4 817, resulting in a significant SMR of 0.53 (95% CI: 0.51-0.55).

In addition, fewer deaths than expected were observed for the majority of causes of death (Table 1), except for lung cancer (SMR 2.05, 95% CI: 1.84-2.29), cor pulmonale (SMR 4.08, 95% CI: 3.32-5.01), silicosis (SMR 13.59, 95% CI: 11.90-15.52), and diabetes (SMR 1.48, 95% CI: 1.23-1.78). The range of the SMRs for individual diseases varied from 0.26 (Essential Hypertension) to 13.59 (Silicosis) (Table 2). In addition, most SMRs for specific cancer types were also below the expected number, except for lung cancer. No increased mortality risk was found for diseases of the circulatory system (692 observed; SMR 0.47; 95% CI: 0.44-0.50; $P<0.001$), digestive diseases, or deaths resulting from accidents.

Table 2 shows the results stratified by sex, year of death, and for the specific sector categories. Both male (SMR 0.50, 95% CI: 0.48-0.52) and female (SMR 0.47, 95% CI: 0.43-0.52) workers had significantly reduced mortality compared to the expected. Workers with deaths occurring in all of the three year intervals had a lower SMR than expected. The workers of the second mine had a SMR of 0.65 (95% CI: 0.59-0.71) for all causes of death, whereas the SMR for workers employed in the service industry was 0.44 (95% CI: 0.39-0.50; Table 2).

In an analysis of deaths from silicosis according to sex and the sector category, there was a significantly elevated SMR in both males (SMR = 8.47, 95% CI: 7.31-9.82, $P<0.001$) and females (SMR=16.98, 95% CI: 9.00-32.03, $P<0.001$). A significantly elevated SMR for silicosis mortality was also observed regardless of the time interval considered. Among the three sector categories, all of the SMRs for silicosis were above unity, including for the second mine, power plant, and service workers in which significant elevations were observed (Table 2). Workers in the second mine had the highest SMR for silicosis of 25.77 (95% CI: 21.21-31.32, $P<0.001$). Moreover, analyses of deaths from lung cancer, cor pulmonale, and diabetes according to sex and sector category showed a significantly elevated SMR (Table 3). Significantly elevated SMRs for mortality from these three diseases were also observed regardless of the time interval considered. Among the three sector categories, all of the SMRs for lung cancer were

Table 1. Mortality Rates (1/100 000), Number of Observed Deaths, SMRs, and 95% CIs for the Main Causes of Death in the Cohort

Causes of Death	Mortality Rates	Observed/Expected	SMR	SMR 95% CI
Main categories				
I Neoplasms	213.86	925/1 362.79	0.68	0.64, 0.72
Lung cancer	71.44	309/151.04	2.05	1.84, 2.29
Gastric cancer	39.77	172/553.49	0.31	0.27, 0.36
Liver cancer	36.53	158/224.29	0.70	0.68, 0.73
Esophageal Cancer	19.19	83/165.50	0.50	0.4, 0.62
II Circulatory system	164.85	692/1 486.41	0.47	0.44, 0.50
Cerebrovascular disease	60.80	263/654.23	0.40	0.36, 0.45
Cor pulmonale	17.80	77/18.87	4.08	3.32, 5.01
Acute myocardial Infarction(AMI)	17.57	76/267.31	0.28	0.23, 0.35
Essential Hypertension	13.18	57/221.49	0.26	0.20, 0.33
III Respiratory system	55.49	240/961.63	0.25	0.22, 0.28
Silicosis	29.36	127/9.35	13.59	11.90, 15.52
IV Injure	50.40	218/435.3	0.50	0.44, 0.57
V Digestive system	27.98	121/126.95	0.95	0.79, 1.15
VI Diabetes	25.43	110/74.15	1.48	1.23, 1.78
Total	595.57	2 576/4 816.35	0.53	0.51, 0.55

above unity. Workers in the second mine had the highest SMR for lung cancer of 2.93 (95% CI: 1.25-2.34, *P*<0.001), and workers in the service industry had the lowest SMR of 1.78 (95% CI: 1.24-2.54, *P*<0.001). A significantly elevated SMR was observed for cor pulmonale in the second mine (SMR=2.60, 95% CI: 1.33-5.08) and service industry workers (SMR=5.61, 95% CI: 3.34-9.41), but no significant elevations were observed for diabetes for any of the three sector categories.

This study examined the all-cause and cause-specific mortality of Chinese workers involved in nickel production or utilization and is one of the largest studies of these associations to date. Our results supported previous evidence suggesting an hint of the association between exposure to nickel and

Table 2. SMRs and 95% CI in the Cohort According to Gender and Occupational Factors

Items	Overall			Silicosis		
	Observed/ expected	SMR	SMR 95% CI	Observed/ expected	SMR	SMR 95% CI
All workers	2576/4 816.35	0.53	0.51, 0.55	127/9.35	13.59	11.90, 15.52
Gender						
Men	2179/4 358.62	0.5	0.48, 0.52	122/14.40	8.47	7.31, 9.82
Women	397/847.96	0.47	0.43, 0.52	5/0.29	16.98	9.00, 32.03
Year of death						
2001-2003	625/1 147.63	0.55	0.51, 0.59	28/2.14	13.09	9.84, 17.41
2004-2006	709/1 379.81	0.51	0.47, 0.55	27/2.70	10.02	7.38, 13.60
2007-2010	1242/2 288.42	0.54	0.51, 0.57	72/4.51	15.95	13.45, 18.92
Sector category						
The second mine	493/752.70	0.65	0.59, 0.71	42/1.63	25.77	21.21, 31.32
Power plant	119/227.17	0.52	0.44, 0.62	6/0.41	14.63	8.11, 26.40
Service	225/511.75	0.44	0.39, 0.50	7/0.99	7.07	3.78, 13.22

Table 3. SMRs and 95% CIs in the Cohort According to Gender and Occupational Factors

Items	Lung Cancer			Cor Pulmonale			Diabetes		
	Observed/ expected	SMR	SMR 95% CI	Observed/ expected	SMR	SMR 95% CI	Observed/ expected	SMR	SMR 95% CI
All workers	309/151.04	2.05	1.84, 2.29	77/18.87	4.08	3.32-5.01	110/74.15	1.48	1.23, 1.78
Gender									
Men	268/150.26	1.78	1.59, 2.00	66/18.03	3.66	2.94, 4.56	83/57.63	1.44	1.16, 1.79
Women	41/24.17	1.69	1.55, 1.84	11/2.57	4.28	2.50, 7.33	27/16.38	1.65	1.13, 2.40
Year of death									
2001-2003	83/36.98	2.24	1.82, 2.76	23/3.94	5.84	4.10, 9.31	28/17.84	1.57	1.09, 2.26
2004-2006	62/43.35	1.43	1.12, 1.83	20/5.19	3.85	2.57, 5.77	31/21.36	1.45	1.02, 2.06
2007-2010	164/70.71	2.32	2.03, 2.70	34/9.74	3.49	2.55, 4.77	51/34.95	1.46	1.11, 1.92
Sector category									
The second mine	70/23.89	2.93	1.25, 2.34	8/3.08	2.6	1.33, 5.08	17/11..90	1.43	0.75, 2.72*
Power plant	17/6.89	2.47	1.56, 3.92	2/0.90	2.2	0.58, 8.34*	6/3.40	1.76	0.80, 3.81*
Service	29/16.28	1.78	1.24, 2.54	11/1.96	5.61	3.34, 9.41	11/7.93	1.39	0.90, 2.15*

Note. *$P>0.05$.

lung cancer, and further indicated an elevated risk of mortality from cor pulmonale, silicosis, and diabetes in our cohort of occupationally exposed workers compared to the general population of Gansu province. Stratified analyses of the silicosis finding by gender and job category suggested that the highest SMRs were in females and production workers. Thus, our study provides evidence that in addition to an increased risk of mortality from lung cancer, nickel exposure is also associated with mortality from other non-carcinogenic health effects and public health efforts are needed to protect workers employed in this industry from this occupational hazard.

Nickel and nickel compounds have many industrial and commercial uses, but they represent a hazard to human health. Several epidemiological investigations and experimental studies have shown that nickel dusts and compounds resulting from occupational exposures are potent carcinogens of lung and nasal[6].

For other endpoints, such as all-cause mortality and other carcinogenic outcomes aside from lung cancer, our results showed a decreased SMR compared to expected based on the mortality statistics of Gansu province in China. This is likely the result of a ‘healthy worker effect’, whereby workers are generally healthier compared to the general population[7]. The lower SMR for all cause mortality, which we observed in both males and females, is similar to that reported in other industries[8].

With respect to carcinogenic outcomes, different SMRs were observed according to the cancer site, including for lung cancer, gastric cancer, liver cancer, and esophageal cancer. None of the SMRs associated with any of these tumors were higher than expected except for lung cancer, which confirms the significant excess in mortality from lung cancer in workers exposed to nickel that has been reported in other studies[6]. An excess in mortality from silicosis was also observed in our study, based on 122 deaths in men and 5 deaths in women. Although the risk from silicosis and nickel haven’t been about reported, the evidence that nickel exposure related to the mortality of respiratory diseases has become increasingly clear[9]. This conclusion was supported by the increase in silicosis mortality according to sector category. Internal comparisons of mortality from silicosis within the cohort showed that the second mine workers had a higher mortality from silicosis compared to workers in the power plant and service categories or the general population of Gansu. The nickel concentrations to which the study subjects were actually exposed to are unknown because there has not been available data on nickel concentrations in the enterprise to date. However, the workers involved in the mine had many opportunities for direct exposure to nickel because they spent much of their working time touching raw materials. Conversely, workers in service industries were exposed to nickel indirectly but continuously resulting from air pollution. We also recognize that there are other metal exposures among these workers which could have also contributed to the observed effects. For example, cobalt output in Jingchuan company ranked second in the world, copper output ranked third in China, and the platinum group metals ranked first in China.

This study is the first to describe the mortality of the workers exposed to nickel and other metal exposures in China and spans ten years. Exposure to nickel may have played a part in the observed excess risk of diabetes and diseases involving the lung among the workers in the enterprise. Studies have shown that nickel levels detected in serum were reduced during the initial stage of diabetes, but no epidemiological study has been conducted to investigate the relationship between nickel exposure levels and risk of diabetes[10].

Because this study is a retrospective study, we had limited data on duration of employment for individuals. In addition, because of the lack of detailed information on exposure levels of nickel exposure, the study cannot establish a clear exposure-response relationship between nickel exposure and mortality from the diseases reported in this study. Further, because of the exposure to other metals in the population, future laboratory and epidemiological studies of joint exposure to nickel, cobalt, copper, and human health in this population are needed.

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