Cancer of the respiratory tract in nickel sinter plant workers: effect of removal from sinter plant exposure

David C F Muir, Ni Jadon, Jim A Julian, Robin S Roberts

Abstract

The risk of death due to cancer of the nose or lung was studied in nickel sinter plant workers during the period after they left the sintering operations. It was found that the excess risk of death from both diseases continued for many years after leaving the sinter plant. No effect of age at first exposure could be found. Possible explanations for the continued risk include an irreversible cellular change or the persistence of carcinogenic nickel compounds in the mucosa.

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An increased risk of death from cancer of the lung and nose was reported by Roberts *et al* in nickel sinter plant workers in Ontario.^{1,2} This was similar to previous findings by Doll in nickel workers in Britain.³ In an extensive review of available epidemiological studies, an international committee concluded that more than one form of nickel could give rise to lung and nasal cancer.⁴ Both oxidic and sulphidic compounds of nickel as well as soluble nickel increased the risk of these cancers. There was no evidence that metallic nickel was associated with increased risks of lung and nasal cancer, and no substantial evidence was obtained to suggest that occupational exposure to nickel or any of its compounds was likely to produce cancers elsewhere other than in the lung or nose.

The two sintering operations studied by Roberts *et al* operated between 1948 and 1963 at Copper Cliff (Sudbury) and between 1926 and 1958 at Port Colborne. All male employees of the International Nickel Company (INCO) who had worked for the company in Ontario for six months or more and who had been employed (or been a pensioner) between January 1950 and 31 December 1976 were included in the main study cohort.¹ In the Port Colborne cohort, because the sintering facility was housed in the same building as the leaching and calcining operations about the same time, and as the job descriptions were not unique to the process, it was impossible to isolate the sintering work experience. Therefore, the Port Colborne sinter plant label used in this test actually refers to the combined leaching, calcining, and sintering operations (see L, C, and S department in Roberts *et al*).² The increased risk of lung and nasal cancer was associated with exposure to very high concen-

trations of airborne nickel compounds in the sinter operations. No similar increased risks were identified in other parts of the industry with the exception of certain groups of underground miners (probably unrelated to nickel) and certain defined occupations in the copper refinery.

The purpose of the present investigation was to determine the risk of death from cancer of the lung or nose in sinter plant workers in the years after they had left that operation. The matter is of obvious medical importance in terms of any advice or assistance that can be given to these men, and may also be relevant to an understanding of the nature of nickel carcinogenesis.

Methods

Sinter plant workers identified in the study by Roberts *et al* who had spent more than one month in the sintering operation were followed up to determine their vital status in the years after they left the sinter plant.^{1,2} Information on mortality was obtained by computerised record linkage to the Canadian Mortality Data Base up to the end of 1984.^{1,2} The end of employment in the sinter plant was not synonymous with removal from all nickel exposure, as many were later employed in other parts of the industry. As already mentioned, however, no excess risk of cancer was noted in these areas by Roberts *et al*.^{1,2} Cause specific age and year standardised mortality ratios (SMRs) were calculated with respect to Ontario provincial mortality. Also, the excess risk due to lung and nasal cancer attributable to occupational exposure was calculated by subtracting the expected number of cases from those observed and dividing by the person-years at risk. The scaled value obtained is the excess mortality rate (EMR) per 10 000 person-years. This is also called the standardised risk difference (SRD). The EMR was chosen for presentation of the data because, as reviewed in the discussion section, this may have advantages over the SMR when analysing excess risks in occupational cohorts.

Tables 1 and 2 present the results of this analysis for lung and nasal cancer, in which mortality is stratified by years since last exposure in the sinter operation (TSLE), by duration of exposure, and by age at first exposure. Special attention was given to long term workers with more than five years of exposure in the sinter plant. The overall risk of death from lung or nasal cancer attributable to

McMaster University,
Health Sciences
Center—3H50, 1200
Main Street West,
Hamilton, Ontario,
L8N 3Z5
D C F Muir
N Jadon
J A Julian
R S Roberts

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Table 1 Lung cancer deaths after ≥ 5 years of exposure

Time since last exposure (y)	Age at first exposure <30 y					Age at first exposure ≥ 30 y				
	Observed	Expected	Person-years	SRD*	(95% CI*)	Observed	Expected	Person-years	SRD*	(95% CI*)
<i>Copper Cliff sinter plant</i>										
0-9	6	0.181	1362.8	42.70	(34.05 to 51.35)	4	0.687	928.6	35.68	(10.94 to 60.42)
10-19	9	0.833	1246.9	65.50	(45.21 to 85.79)	12	1.483	718.6	146.35	(99.38 to 193.33)
20-29	2	0.442	345.0	45.16	(-8.26 to 98.57)	1	0.603	185.0	21.46	(-94.89 to 137.81)
30-39	0	0.002	0.8	-25.00	(-1574.52 to 1524.52)	0	0.0	0.0	—	—
≥ 40	0	0.0	0.0	—	—	0	0.0	0.0	—	—
All	17	1.458	2955.4	52.59	(41.26 to 63.91)	17	2.773	1832.2	77.65	(52.46 to 102.84)
<i>Port Colborne leaching, calcining, and sintering</i>										
0-9	4	0.683	1173.5	28.27	(8.75 to 47.79)	12	1.324	1085.2	98.38	(68.99 to 127.77)
10-19	5	1.102	1145.6	34.03	(8.63 to 59.43)	3	1.767	912.6	13.51	(-26.86 to 53.89)
20-29	2	1.044	621.8	15.38	(-30.17 to 60.92)	5	1.501	529.8	66.04	(1.95 to 130.14)
30-39	5	0.905	297.5	137.65	(49.01 to 226.28)	1	0.837	205.8	7.92	(-115.30 to 131.14)
≥ 40	1	0.350	79.8	81.45	(-124.04 to 286.95)	0	0.143	31.0	-46.13	(-384.25 to 292.00)
All	17	4.083	3318.2	38.93	(22.05 to 55.81)	21	5.572	2764.4	55.81	(32.14 to 79.48)

*per 10 000 person-years; SRD = standardised risk difference.

occupational exposure (SRD) in these workers was expressed by combining data from both the Copper Cliff and Port Colborne sinter plants (figs 1 and 2).

In general the results show no evidence of a diminution of the risk for as long as 30 to 40 years after leaving the sinter plant. There seems to be no evidence of an effect of age at first exposure although the numbers may be too small to detect such a result.

Discussion

As previously mentioned, time since leaving the sinter plant was not the same as removal from all exposure to nickel. It is, however, synonymous with working in an area where there has been no documented risk of excess lung or nasal cancer. Therefore, it is reasonable to attribute the sustained risk in these workers to events which took place during their employment in the sintering operation. A complicating factor is that a programme of annual chest radiography and sputum cytology has been provided on a voluntary basis since 1973. At this point, it is not possible to identify individual participants nor to link their names with the epidemiological study. For this reason, the possibility cannot be

excluded that the observed risks of death from lung cancer might have been higher, had this programme not been in place. Controlled trials, however, have not so far shown benefits from such interventions in the case of cigarette smokers,⁵ and the pattern of risk of deaths from nasal cancer in our study is similar to those of the lung (figs 1 and 2). For these reasons, it is suggested that the screening programmes for the early detection and treatment of lung cancer probably did not influence the results. Because of limited numbers, further stratification by calendar year of first exposure was not attempted even though there is good evidence that exposures in Copper Cliff changed with time,⁴ and the same may be true in Port Colborne.

Similarly, prolonged risks of death from cancer of the respiratory tract in nickel workers, even after exposure ceased, were reported in Britain.⁶ An effect of age at first exposure was also noted, which we did not find. The numbers in our study were possibly too small to detect such an effect.

Data of this type may contribute to understanding the nature of nickel carcinogenesis. The multistage model of carcinogenesis⁷ supposes that damage to the genetic material proceeds by a series of independent steps and

Table 2 Nasal cancer deaths after ≥ 5 years of exposure

Time since last exposure (y)	Age at first exposure <30 y					Age at first exposure ≥ 30 y				
	Observed	Expected	Person-years	SRD*	(95% CI*)	Observed	Expected	Person-years	SRD*	(95% CI*)
<i>Copper Cliff sinter plant</i>										
0-9	0	0.007	1362.8	-0.05	(-1.75 to 1.65)	0	0.016	928.6	-0.17	(-3.95 to 3.60)
10-19	1	0.020	1246.9	7.86	(4.72 to 11.00)	4	0.021	718.6	55.37	(49.78 to 60.96)
20-29	0	0.007	345.0	-0.20	(-6.92 to 6.52)	0	0.005	185.0	-0.27	(-10.87 to 10.32)
30-39	0	0.0	0.8	0.0	—	0	0.0	0.0	—	—
≥ 40	0	0.0	0.0	—	—	0	0.0	0.0	—	—
All	1	0.034	2955.4	3.27	(1.54 to 5.00)	4	0.042	1832.2	21.60	(18.50 to 24.70)
<i>Port Colborne leaching, calcining, and sintering</i>										
0-9	4	0.017	1173.5	33.94	(30.86 to 37.02)	5	0.037	1085.2	45.73	(40.82 to 50.65)
10-19	0	0.024	1145.6	-0.21	(-3.96 to 3.54)	4	0.037	912.6	43.43	(37.58 to 49.27)
20-29	0	0.019	621.8	-0.31	(-6.45 to 5.84)	3	0.025	529.8	56.15	(47.88 to 64.43)
30-39	1	0.012	297.5	33.21	(23.00 to 43.42)	1	0.009	205.8	48.15	(35.38 to 60.93)
≥ 40	1	0.003	79.8	124.94	(105.91 to 143.96)	0	0.001	31.0	-0.32	(-28.60 to 27.95)
All	6	0.075	3318.2	17.86	(15.57 to 20.14)	13	0.109	2764.4	46.63	(43.32 to 49.94)

*per 10 000 person-years; SRD = standardised risk difference.

Figure 1 Combined data from Copper Cliff and Port Colborne to illustrate the pattern of risk of death from lung cancer in the years after leaving the sinter plant. SRD = standardised risk difference; OBS = observed deaths; EXP = expected deaths.

that occupational carcinogens may affect only one stage. A single cell gives rise to a malignant tumour only after it has undergone a number of sequential, heritable, changes. This transformation period is followed by a promotion and rapid growth period in which the transformed cell produces a colony of descendants by rapid cell division. Initiators affect the first stages and have a long latency. Co-carcinogens or promoters act at a later stage and have a shorter latency. The two types of hazards have different characteristics. The excess risk from an initiator depends primarily on time since first exposure and continues to rise even after exposure to that carcinogen ceases. The excess risk following a carcinogen affecting the penultimate stage depends on age at first exposure, older exposures being worse, and the excess incidence remains constant after exposure ceases.⁸

In applying these concepts to sets of human data, Bell and Coleman compared the usefulness of different methods of expressing risk.⁷ From computer generated models, they concluded that the excess death rate (EMR or SRD) was preferable because the more familiar SMR contained two components—the excess attributable risks, and the underlying mortality to be expected in the non-exposed population. From fig 1, it is clear that the excess deaths have stayed almost constant in the years after exposure to the sintering operation ceased. The rising expectation of death from lung cancer due to other causes, mainly cigarette smoking, results in a lower SMR after 30 years. As an expression of risk the SMR would thus suggest that the risk has fallen whereas the SRD provides an opposite result.

Application of the multistage model to our data provides conflicting evidence concerning the nature of nickel carcinogenesis. We could

detect no effect of age at first exposure; however, this may be the result of small numbers. We did not find an increasing risk after exposure ended. The possibility that this might, in principle, be the effect of a preventive screening programme in the case of lung cancer has already been discussed. It is possible to conclude only that the risk for both diseases is prolonged for many years after exposure ends without being able to determine the likely stage at which nickel compounds have a carcinogenic effect. Conflicting results were also reported by Kaldor *et al* who consider that the mechanisms for lung and nasal cancer produced by nickel might turn out to be different.⁶ The persistence of an excess risk after the end of exposure is very similar to that reported in cigarette smokers who stop smoking.⁸

The possibility that slow tumour growth had already started before exposure ended must also be considered. This could certainly effect mortality in the early years after exposure. Nasal cancers however, and also many lung cancers contain rapidly dividing cells which make this unlikely to be an issue 30 or 40 years after exposure. Another relevant factor might have practical implications. The assumption has been made that exposure to carcinogenic nickel compounds ended when the workers left the sinter plant. Their employment in other parts of the industry has already been discussed. There is, however, an alternative explanation that might account for an ongoing carcinogenic risk. In studies of retired nickel workers where biopsies of the nasal mucosa have been carried out, substantial amounts of nickel were detected.¹⁹ The data were too limited to provide firm information on the rate of removal of nickel, but certainly for eight or nine years after exposure ended, there was excess nickel in the nasal mucosa. It could not be seen by electron microscopy and the precise anatomical site remains unknown. The nickel is probably submucosal because of the rapid cell turnover in the mucosa itself. Whether it is in a particulate form or bound to protein remains unknown. There are no data on the nickel content of the bronchial mucosa in nickel workers.

Persisting nickel deposits could act as continuing carcinogens. A minor effect could be due to delayed nasal mucosal clearance of other particulate carcinogens as soluble nickel compounds diminish frequency of ciliary beats.¹¹

From the practical point of view, it is important to stress that these workers continue to be at excess risk of death from lung and nasal cancer for many years after leaving exposure. There is no good evidence that the excess risk is diminished with time. Efforts to mitigate the effects are of great importance despite the disappointing results of screening in the case of lung cancer. In this instance, the validity of the multistage model for carcinogens⁷ has practical consequences. If the continuing risk is due to changes in the genetic material, which are irreversible, then

Figure 2 Combined data from Copper Cliff and Port Colborne to illustrate the pattern of risk of death from nasal cancer in the years after leaving the sinter plant. SRD = standardised risk difference; OBS = observed deaths; EXP = expected deaths.

early detection or attempts to improve repair mechanisms and to avoid further carcinogenic insults are the obvious approach. If there is a real possibility that it is due in part to persistence of nickel in the submucosa, then, perhaps, attempts to remove the deposits of nickel might have a part in a preventive programme. The removal of nickel by the local application of a chelating agent is one such possibility. This would not, however, be effective if the nickel is in particulate form. This was investigated by placing small quantities of fine particles of nickel subsulphide and nickel oxide in 10 ml 2% EDTA with the pH adjusted to 4.5, 7.0, 8.0, and 9.0. The suspensions were shaken periodically over four days. Nickel was readily detected in the supernatant fluid, but there was no visible depletion of the solid material.

Although removal from exposure does not lead to a diminution of risk, it is, of course, a most important preventive health measure as the increasing risk with continual exposure is eliminated.

Finally it is stressed that workers who have been employed in an area of the nickel industry where there is an excess risk of cancer must be studied separately from the rest of a cohort of nickel workers. This was the approach used by Roberts *et al.*^{1,2} Failure to do so may generate apparent excess risks of cancer in other parts of the process when such risks do not, in fact, exist.

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