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Cancer risk among Japanese chromium platers, 1976–2003

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Objective The aim of our prospective cohort study was to assess cancer mortality risks among chromium platers.

Methods The cohort comprised 1193 male platers (626 with exposure to chromium, the remainder with no exposure) with a follow-up period of 27 years (1 October 1976 to 31 December 2003). Mortality risk was assessed by the standardized mortality rate (SMR) with reference to the national population.

Results Lung cancer mortality was elevated only in the chromium plater subgroup, with borderline statistical significance [SMR=1.46, observations (Obs)=28, 95% confidence interval (95% CI) 0.98–2.04]. The chromium plater subgroup also showed elevated mortality risks for brain tumor (SMR=9.14, Obs=3, 95% CI 1.81–22.09) and malignant lymphoma (SMR=2.84, Obs=6, 95% CI 1.05–5.51). Risks were particularly elevated for lung cancer (SMR=1.59, Obs=23, 95% CI 1.01–2.38) and malignant lymphoma (SMR=3.80, Obs=6, 95% CI 1.39–8.29) among those with initial chromium exposure prior to 1970.

Conclusions In Japan, occupational exposure to chromium through work as a chromium plater is a risk factor for lung cancer, especially for platers working prior to 1970. Occupational chromium exposure may also increase the risk of brain tumor and malignant lymphoma.

Key terms brain tumor; chromium plating; cohort study; lung cancer; malignant lymphoma.

Chromium plating involves the use of an electrolytic solution of chromic acid (chromium in the hexavalent form [chromium(VI)]), and a chromic acid mist forms during the plating process. Chromium platers may also be highly exposed to chromium(VI) during the mixing of acid powders and when carrying articles to and from plating baths.

In the past, high-level exposure to chromium(VI) was common, although modern control technologies have reduced airborne exposure in the workplace. In 1990, a working group of the International Agency for Research on Cancer (IARC) concluded that there was sufficient evidence for carcinogenicity of chromium(VI) compounds in humans “as encountered in the chromium-plating industries” (1). In Japan, a few large-scale plants produce chromates, whereas many small-scale factories form the chromium plating industry.

Only a few studies have examined cancer risks among workers engaged in chromium plating. To examine the health hazards of this industry, a prospective cohort was formed among workers in small-scale chromium plating plants in Tokyo, Japan, in 1976. Several follow-up studies of these workers have already been conducted (2–4). We now extend the study through 2003 to enable the evaluation of an additional 11 years of follow-up data.

Methods

Subjects comprised active members of the Tokyo Health Insurance Society of the Plating Industry (THISPI), established in April 1970, which essentially covered all

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workers in plating factories with ≥ 5 employees in the Tokyo metropolitan area. A preliminary list of candidate cohort members was prepared by reviewing all members of THISPI. To be included in the cohort, a member was required to be: male, employed for ≥ 6 months between April 1970 and September 1976, alive and aged ≥ 35 years on 30 September 1976.

Collection of information

Since 1976, a Japanese national ordinance has required employers of chromium-plating factories to file an annual medical examination card for each worker, including chronic acid exposure history (5). Using a mailed questionnaire, in 1976, we requested factory employers to send us plating histories (including detailed histories of chromium plating) for all employees in the factory. Complete information was received from 415 of the 589 (70.5%) factories. From among the candidate list of workers whose working histories were identified, we excluded those with no plating experience and workers whose domicile could not be confirmed. Our final cohort for follow-up consisted of 1193 male platers. Members of the cohort were classified into two subgroups according to work history: 626 workers (52%) had ≥ 6 months of experience in chromium plating (chromium subgroup) and 567 (48%) had no lifetime chromium exposure but ≥ 6 months plating experience using metals other than chromium (ie, nickel, zinc, precious metal, aluminum), hereafter the non-chromium subgroup. Other details of the cohort have been described elsewhere (3).

In the current study, all cohort members in both subgroups were followed up from 1 October 1976 through 31 December 2003. Vital status of all platers was traced through the *Koseki* system, which is the permanent family registration system in Japan. For deceased persons, causes of death were confirmed from death certificates.

Statistical analysis

The underlying cause of death was coded according to the tenth revision of the International Classification of Diseases (ICD-10). Three workers could not be located and were excluded, yielding a total of 1190 male platers for analysis. For the principal causes of death, we tabulated the observed (Obs) and expected (E) numbers of deaths and calculated standardized mortality rates (SMR) and their 95% confidence intervals (95% CI). The expected numbers of deaths were determined by multiplying the person-years of observation by cause-, gender-, and age-specific (5-year age groups) national death rates for each year from 1976–2003. Mortality from all causes, all cancers, lung cancer, brain tumor, and malignant lymphoma were separately evaluated in detail (ie, by observation period, duration of exposure,

and year of initial exposure to chromium plating). We performed all analyses for the entire cohort and separately for the two subgroups using the statistical package SAS version 9.1.3. (SAS Institute, Cary, NC, USA).

The Ethical Committee of the University of Occupational and Environmental Health, Japan, approved this study (approval No 02–18: Mortality risks of chromium plating workers in Japan: a 26-year follow-up study).

Results

Table 1 shows the age distribution of the cohort when follow-up commenced (1 October 1976) and vital status when it ended (31 December 2003). The average age at the beginning of follow-up was about 50 years, with the non-chromium subgroup being about 1 year older on average than the chromium subgroup. The study comprised over 26 000 person-years of observation with about 1700 more person-years in the chromium platers than in “other platers” subgroup. Three non-chromium platers could not be traced and were excluded from further analysis. Of the 1190 subjects analyzed, 250 (39.9%) in the chromium and 261 (46.0%) in the non-chromium subgroup had died, giving a total of 511 (42.8%) deaths in the entire cohort.

Mortality risks by cause of death are shown in table 2. Sites of cancer were listed when the number of observed deaths was ≥ 5 or when the SMR was

Table 1. Age distribution and vital status of the chromium and the non-chromium platers (males only, 1976–2003). Workers were followed for 27.3 years from 1 October 1976 to 31 December 2003. Only 3 untraceable workers were excluded from further analysis.

	Chromium platers ^a		Non-chromium platers ^b		All platers ^c	
	N	%	N	%	N	%
Age at baseline (years)						
35–44	250	39.9	216	38.1	466	39.1
45–54	219	35.0	172	30.3	391	32.8
55–64	106	16.9	113	19.9	219	18.4
≥ 65	51	8.1	66	11.6	117	9.8
Total	626	100.0	567	100.0	1193	100.0
Vital status at end of follow-up						
Dead	250	39.9	261	46.0	511	42.8
Traced alive	376	60.1	303	53.4	679	56.9
Not traced	–	–	3	0.5	3	0.3
Total	626	100.0	567	100.0	1193	100.0
Sum of observed person-years	13 992.5		12 300.6		26 293.1	

^a Mean age at baseline = 49.5 years.

^b Mean age at baseline = 50.8 years.

^c Mean age at baseline = 50.2 years.

statistically significant. Observed numbers for all-cause and all-cancer mortality were close to expected values in both subgroups (none of the SMR were statistically significant). Lung cancer was the most common type of cancer in both subgroups, and the chromium subgroup showed an elevated risk of borderline significance (SMR=1.46, Obs=28, 95% CI 0.98–2.04). Brain tumor (SMR=9.14, Obs=3, 95% CI 1.81–22.09) and malignant lymphoma (SMR=2.84, Obs=6, 95% CI 1.05–5.51) were significantly higher than expected in the chromium subgroup, although these figures are based on a small numbers of deaths. For the combined group of all platers, only the incidence of brain tumor was significantly higher than expected (SMR=6.43, Obs=4, 95% CI 1.74–14.09).

Table 3 analyzes mortality for the aforementioned three specific cancers according to the follow-up period, exposure duration, and year of first exposure. Lung cancer mortality in the chromium subgroup was significantly elevated in the earlier period of follow-up (SMR=1.98, Obs=11, 95% CI 1.00–3.29). There were no significant trends for SMR to increase or decrease with duration of exposure or with year of first chromium exposure, for any of the three causes of death. However, mortality from both lung cancer (SMR=1.59, Obs=23, 95% CI 1.01–2.38) and malignant lymphoma (SMR=3.80, Obs=6, 95% CI 1.39–8.29) were significantly elevated among platers first exposed to chromium before 1970 (ie, time since first exposure was ≥ 33 years).

Discussion

After 27 years of follow-up, the risk of lung cancer mortality in the chromium subgroup was 46% higher than the expected value based on national mortality, albeit with borderline significance. Exposure to chromium plating during earlier years (defined as year of first exposure before 1970) was associated with a 59% higher risk, with statistical significance.

In previous reports, we found elevated or near-elevated risks for lung cancer among the chromium subgroup at several stages of follow-up (2–4). With an additional 11 years of observation since the last follow-up, the lung cancer mortality risk associated with chromium plating, our endpoint of primary interest, remained elevated.

The “healthy worker effect” is an important source of potential confounding in SMR analyses. The overall lower-than-expected SMR value of all causes in both subgroups, though statistically non-significant, may be explained in part by this effect. This is supported by the fact that, all-cause mortality risk, when differentiated by former and latter periods of observation, showed a diminishing pattern in the healthy worker effect with the course of time: 95% CI 0.91–0.93 in the chromium subgroup and 95% CI 0.87–1.01 in the non-chromium subgroup (data not shown). However, one should interpret the results with caution as none of the respective confidence intervals precluded the null value of 1.

Table 2. Mortality from selected causes among the chromium and the non-chromium platers (males only, 1976–2003). (Obs = observed; E = expected; SMR = standardized mortality rate; 95% CI = 95% confidence interval)

Causes of death ^a	Chromium platers				Non-chromium platers				All platers			
	Obs	E	SMR	95% CI	Obs	E	SMR	95% CI	Obs	E	SMR	95% CI
All causes	250	271.6	0.92	0.81–1.04	261	272.6	0.96	0.85–1.07	511	544.2	0.94	0.86–1.02
All cancers (C00–C97)	97	92.2	1.05	0.86–1.27	88	87.6	1.00	0.81–1.22	185	179.8	1.03	0.89–1.18
Stomach (C16)	14	20.9	0.67	0.37–1.06	19	20.3	0.94	0.57–1.39	33	41.2	0.80	0.56–1.09
Colon (C18)	3	5.5	0.55	0.11–1.32	8	5.2	1.54	0.67–2.77	11	10.7	1.03	0.52–1.72
Rectum (C20)	5	3.8	1.31	0.43–2.68	5	3.6	1.39	0.45–2.85	10	7.4	1.35	0.66–2.30
Liver (C22)	11	13.2	0.84	0.42–1.39	16	11.8	1.36	0.78–2.09	27	25.0	1.08	0.72–1.52
Gallbladder & biliary tract (C23–C24)	6	3.5	1.72	0.64–3.34	3	3.4	0.88	0.18–2.14	9	6.9	1.31	0.60–2.28
Lung (C33–C34)	28	19.2	1.46	0.98–2.04	20	18.4	1.09	0.67–1.60	48	37.6	1.28	0.95–1.66
Brain (C70–C72, C751–C753)	3	0.3	9.14	1.81–22.09	1	0.3	3.40	1.00–13.07	4	0.6	6.43	1.74–14.09
Malignant lymphoma (C81–C85)	6	2.1	2.84	1.05–5.51	2	2.0	1.01	0.10–2.84	8	4.1	1.95	0.85–3.51
Ischemic heart diseases (I20–I25)	22	19.3	1.14	0.72–1.65	21	19.6	1.07	0.67–1.57	43	38.9	1.10	0.80–1.45
Cerebrovascular diseases (I60–I69)	43	39.4	1.09	0.80–1.43	51	41.2	1.24	0.93–1.59	94	80.6	1.17	0.95–1.41
Pneumonia (J12–J18)	16	20.7	0.77	0.45–1.19	18	22.8	0.79	0.47–1.18	34	43.5	0.78	0.55–1.06
Chronic liver diseases & liver cirrhosis (K70–K77)	10	7.5	1.33	0.65–2.26	11	6.8	1.62	0.82–2.69	21	14.3	1.47	0.92–2.15

^a Cause of death coded according to the International Classification of Disease, 10th revision (ICD-10).

Mortality risk of lung cancer

Although the cohort studied was originally designed to comprise two subgroups, the SMR should not be directly compared as they refer independently to a standard group (ie, the national population), except when one can assume no interaction between exposure effect and age (6).

Higher lung cancer risk was evident among those experiencing earlier exposure but not among subjects with longer exposure. It was not possible, however, to calculate SMR by estimated cumulative exposure to chromium (7). In Japan, the Ordinance on Prevention of Hazards due to Specified Chemical Substances, including chromium, was first enacted in 1972 (5). In addition, technologies to limit exposure, such as containment, local exhaust systems, and ventilation, as well as the use of protective masks, have tended to improve over time. It is thus plausible that exposure levels to chromium mist were higher before the relevant legislation was introduced, particularly before 1970, which was our cut-off point for early exposure. The interpretation of findings on the length of exposure warrant caution, however, as our window of observation for exposure is truncated at 1976, the year of cohort assembly. Any exposure after 1976 could not be accounted for in our study, which lacked the means to update exposure status. Moreover, duration effects are difficult to interpret in the context of exposure levels declining over time.

Sorahan and colleagues conducted studies on two cohorts of UK chromium platers (8–10). An exposure duration-dependent risk of lung cancer mortality was observed in one of the cohorts (9), but not in the other

(10). The authors also acknowledged improvements in exposure levels since 1973; exposure levels of chromic acid had almost always been $<0.05 \text{ mg/m}^3$ [about 0.025 mg/m^3 of chromium(VI)] since that time (9). Although the exposure of the Japanese cohort may not have been similar to that of the UK platers, some common features would exist in the industrial technologies applied and hence in an overall decreasing trend of exposure (11). Interestingly, both the Japanese and UK studies showed that exposure to chromium mist in earlier years was the most important factor for an increased risk of lung cancer.

Smoking histories were not obtained when the cohort was assembled in 1976, and their absence will always remain a limitation of this cohort study. However, smoking prevalence among the general population (Japanese adult males) always exceeded 75% before 1976 (12). Based on the formula of Axelson (13), and assuming a 100% smoking prevalence in the studied cohort and a relative risk of 20 for smoking, the hypothetical SMR for lung cancer in our cohort would be 1.3. These assumed numbers are likely to be overestimates, and the risk observed in the current analysis cannot, therefore, be explained by smoking only. Moreover, it is highly unlikely that smoking prevalence differed between the chromium and non-chromium subgroups.

Mortality risks of brain tumor and lymphoma

The elevated mortality risks observed for brain tumor in both the chromium and non-chromium subgroups and for malignant lymphoma in the chromium subgroup

Table 3. Mortality from lung cancer, brain tumor, and malignant lymphoma among the chromium platers according to observation period, duration of exposure, and year of first exposure (males only, 1976–2003). (Obs = observed; E = expected; SMR = standardized mortality rate; 95% CI = 95% confidence interval)

	Lung cancer (C33–C34) ^a				Brain tumor (C70–C72, C751–C753) ^a				Malignant lymphoma (C81–C85) ^a			
	Obs	E	SMR	95% CI	Obs	E	SMR	95% CI	Obs	E	SMR	95% CI
Follow-up period												
October 1976–December 1989	11	5.6	1.98	1.00–3.29	1	0.1	7.85	0.01–30.16	2	0.7	2.80	0.29–7.89
January 1990–December 2003	17	13.6	1.25	0.74–1.90	2	0.2	9.96	1.03–28.09	4	1.4	2.87	0.77–6.28
Duration of exposure ^b												
1–10 years	15	10.0	1.50	0.85–2.34	1	0.2	5.61	0.01–21.57	3	1.1	2.69	0.53–6.49
11–20 years	7	4.7	1.50	0.61–2.79	2	0.1	25.22	2.60–71.11	2	0.5	3.91	0.40–11.01
≥21 years	6	4.5	1.32	0.49–2.56	·	0.1	·	·	1	0.5	2.07	0.00–7.96
Year of first exposure												
1929–1959	11	7.2	1.52	0.77–2.53	·	0.1	·	·	1	0.8	1.28	0.00–4.90
1960–1969	12	7.3	1.65	0.86–2.69	2	0.1	16.00	1.65–45.11	5	0.8	6.22	2.03–12.72
1970–1976	5	4.7	1.07	0.35–2.19	1	0.1	11.80	0.02–45.35	·	0.5	·	·
Total	28	19.2	1.46	0.98–2.04	3	0.3	9.14	1.81–22.09	6	2.1	2.84	1.05–5.51

^a Cause of death coded according to the International Classification of Disease, 10th revision (ICD-10).

^b Duration of exposure observed as of 1976, the year of cohort assembly. Note that exposures could have continued after 1976 but are not accounted for in the current study.

were unexpected. Earlier, several reports suggested that exposure to chromium(VI) might increase the risk of non-pulmonary cancers, including those of the central nervous system, lymphoma, and Hodgkin's disease (14–16). In our study, the risks observed for brain tumor were based on small numbers (three subjects in the chromium group and one in the non-chromium subcohort), and a detailed discussion is thus inappropriate. However, the observed risk for malignant lymphoma in the chromium subgroup was based on six observed cases and associated exclusively with earlier exposure to chromium. The high level of chromium exposure in earlier years may be the cause of this cancer. In Italy, risks for lymphoma have been reported among chromium tanning workers, although exposure situations were unclear (15, 17). Given that the scientific consensus for carcinogenic risk of chromium plating is currently limited to cancers of the lung and sinonasal cavity (1, 18, 19), close attention is warranted in a further follow-up of this and other studies.

Strengths and limitations of this study

This was a prospective cohort study comprising over 1000 Japanese platers and a follow-up period of 27 years. The cohort was designed to include two comparable subgroups: platers with documented exposure to chromium (ie, chromium platers) and platers with no exposure to chromium (ie, non-chromium platers). The *Koseki* system, a permanent family registration system under the jurisdiction of the Japanese Ministry of Justice, was utilized to achieve an extremely high follow-up rate with a drop-out of only three original members. There is virtually no ambiguity in vital status within this registration system. The limitations of our study included an absence of quantitative data on the level of chromium exposure or working conditions; rather we relied on self-reporting combined with management records of work content and duration, as well as death certificates for causes of death. The most serious limitation of our study was the fact that we lacked the means to update work histories after 1976. Thus, there was no way to detect changes in the status of exposure since that time, which may have led to misclassification of exposure status. Finally, smoking and drinking habits were not documented at the study's inception, although researchers at the time assumed, probably correctly, that little difference existed between the two subgroups within the same plater cohort.

View of the future

After a follow-up period of 27 years, with almost perfect tracing of cohort members, the proportion of subjects who have died is still less than half of the original cohort members (ie, 511 or 42.8%). We will continue to survey

this occupational cohort to utilize the rare opportunity for a thorough follow-up of risk among chromium platers, which may even permit the complete profile of mortality risk to be revealed.

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