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Occupational exposure to metals and risk of meningioma – a multinational case-control study

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Abstract

The aim of the study was to examine associations between occupational exposure to metals and meningioma risk in the international INTEROCC study.

INTEROCC is a seven-country population-based case-control study including 1,906 adult meningioma cases and 5,565 population controls. Incident cases were recruited between 2000 and 2004. A detailed occupational history was completed and job titles were coded into standard international occupational classifications. Estimates of mean workday exposure to individual metals and to welding fumes were assigned based on a job-exposure-matrix. Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were estimated using conditional logistic regression.

Although more controls than cases were ever exposed to metals (14% vs. 11%, respectively), cases had higher median cumulative exposure levels. The ORs for ever vs. never exposure to any metal and to individual metals were mostly greater than 1.0, with the strongest association for exposure to iron (OR=1.26, 95%CI 1.0-1.58). In women, an increased OR of 1.70 (95%CI 1.0-2.89) was seen for ever vs never exposure to iron (OR in men 1.19 (95% CI 0.91-1.54), with positive trends in relation with both cumulative and duration of exposure. These results remained after consideration of other occupational metal or chemical co-exposures.

In conclusion, an apparent positive association between occupational exposure to iron and meningioma risk was observed, particularly among women. Considering the fact that meningioma is a hormone dependent tumor, the hypothesis that an interaction between iron and estrogen metabolism may be a potential mechanism for a carcinogenic effect of iron should be further investigated.

Introduction

Meningiomas are commonly diagnosed benign brain tumors, accounting for approximately 36% of all primary brain tumors [1].

Ionizing radiation is the only environmental factor that has been shown unequivocally to be a risk factor for meningioma development [2-4]. Data is globally concordant with the biologic hypothesis assuming that female sex hormones may increase the risk of meningioma [5]. This is supported by the increased incidence of the disease in women compared to men, the presence of progesterone receptors in most tumors, and reports of modestly increased risk associated with the use of endogenous/exogenous hormones and body mass index [6].

While occupational exposures to some chemical and physical agents are known to be risk factors for several cancer types [7-11], little is known regarding the role of occupational factors in the development of meningioma [3]. Some studies have shown associations between specific works (e.g. cooks or automobile body painters) and meningioma risk [12, 13]. However, results from the German INTERPHONE study group, which included 381 meningioma cases and 762 controls, reported no association between ever having worked in the chemical, metal, agricultural, construction, electrical/electronic, or transport sectors and meningioma [14].

The large-scale INTEROCC consortium, including 1,906 meningioma cases and 5,565 controls, provided a unique opportunity to study the possible association between specific occupational exposures and meningioma risk [15, 16]. Occupational exposure to solvents, metals, and a number of other chemicals (including oils and dusts) was assessed on the basis of a job-exposure matrix applied to occupational histories [17]. Analyses focusing on organic solvents or specific solvents (e.g. benzene and gasoline) have been previously published [16]. Overall, no association was observed between exposure to any organic solvent and meningioma risk (OR = 1.05, 95% CI 0.82-1.36) or to any specific solvent. Analyses of selected combustion products, dusts and other chemical agents showed no association in general, though an increased risk of meningioma was seen in association with exposure to oil mist (manuscript in preparation).

Exposure to metals, some of which have been classified as ‘carcinogenic to humans’ (Group 1) by the International Agency for Research on Cancer (IARC), may occur in occupational settings in many industries [18]. The major route of absorption of metals in industrial workplaces is by inhalation of fumes, powdered material or dust, though some ingestion or skin contact can also occur [19-21]. Cadmium (Cd), Chromium (Cr)-6 and Nickel (Ni) compounds were classified as human carcinogens [18]. Occupational exposure during iron and steel founding was also classified as carcinogenic to humans [22]. Iron (Fe)-dextran complex, which is indicated for intravenous or intramuscular use in patients with Fe deficiency was classified as ‘possibly carcinogenic to humans’, while inorganic lead (Pb) was classified as ‘probably carcinogenic’ [22].

The current paper examines associations between occupational metal exposure and meningioma risk in the international INTEROCC study.

Methods

INTEROCC is a seven country (Australia, Canada, France, Germany, Israel, New Zealand, United Kingdom) population-based case-control study formed from the parent INTERPHONE study. Detailed study methods have been published elsewhere [15]. Incident cases of primary meningioma were recruited between 2000 and 2004. The age range for INTEROCC was 30-59 years for most countries, up to 69 in

Germany, 18-69 in the UK, and 18+ in Israel. In all centers, controls were randomly selected and originally either frequency- or individually-matched to cases by sex and year of birth (15, 23). According to the INTEROCC study protocol and in order to maximize statistical power all available controls in the participating INTERPHONE countries (including those collected for other tumors), were used here. A post-hoc individual matching was conducted using a matching algorithm that included age (5 year groups), sex, region, and country of birth (Israel only) [16, 24]. Using this procedure, no cases and 346 controls, (275 unexposed and 71 exposed) were not successfully matched.

The reference date for controls was calculated as the interview date minus the median difference between dates of diagnosis and interview of cases in each country. Out of 2,382 eligible meningioma cases and 11,112 controls, 1,924 and 5,601 were interviewed respectively. Written informed consent was obtained from all study participants. In a small number of instances where the case participant had died or could not be interviewed, proxy interviews were conducted. Ethics approval from all appropriate national and regional research ethics boards was obtained, including the Ethical Review Board of the IARC (Lyon) for INTERPHONE and the Municipal Institute for Medical Investigation (IMIM) Barcelona for INTEROCC.

A detailed occupational history was completed for all jobs held for at least six months (including job title, company name and description, and start and stop year of each job). Trained occupational hygienists coded job titles using the International Standard Classification of Occupations 1968 (ISCO68) [25] and 1988 (ISCO88) [26], and the International Standard Industrial Classification 1971 edition (ISIC71) [27]. To ensure consistency in coding between countries, guidelines were developed and coding trials were conducted [28]. Eighteen meningioma cases and 36 controls were excluded due to erroneous job start and stop dates in the occupational section.

A total of 29 occupational chemical agents including metals were identified. An updated version of the Finnish Job Exposure Matrix (FINJEM) was used [17, 29]. A crosswalk was also developed to link the updated FINJEM with the international occupational coding systems applied here. FINJEM provides two exposure estimates for each combination of occupation, calendar sub-period, and agent: the proportion of workers in that occupation who were considered to be exposed to the agent (P) and the mean level of exposure among the exposed (L) expressed in concentration units. The current paper focuses on associations between exposures to Cd, Cr, Fe, Ni, Pb, and welding fumes individually, and due to their correlated nature in combinations of Fe, Cr and Ni and meningioma risk.

Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were estimated using conditional logistic regression stratified by sex, five-year age groups, and country-region and adjusted for education. Analyses were conducted overall and by sex (including a test for homogeneity). Exposure to metals was defined as having had an occupation where the estimated probability of exposure $P \geq 25\%$ for at least 1 year, with a 5-year lag. Categorical indicators of ever/never metal exposure, quartiles of cumulative control exposure (calculated as the sum over all jobs of the product of duration of job and concentration), and duration of exposure (1-4, 5-14 and 15+ years) were examined. When $P<5\%$, the exposure level in FINJEM was set to zero. The reference group consisted of those never exposed to any metal or welding fumes. Participants with $5\% \leq P < 25\%$ and exposure duration less than 1 year (n=333, 75 cases and 258 controls) were excluded from analyses. Tests for linear trend across quartiles of exposure were performed.

Sensitivity analyses for different scenarios (e.g. excluding proxy respondents, participants older than 69 years) were conducted as presented in Supplementary Table 2. Potential confounding by socioeconomic status (expressed by SIOPS (Standard International Occupation Prestige Scale) [30], marital status, cigarette smoking, proxy responses, allergy history, age at first exposure and exposure to oil mist were examined. Analyses were also performed according to different lag times (1 year and 10 years) and cut-points for the estimated probability of exposure (P≥5% and 50%). Potential effect modification by sex, age at reference date, age at first exposure, smoking status and country was assessed by entering multiplicative interaction terms into logistic regression models and assessing their significance according to the likelihood ratio test. Analyses were conducted using Stata Version 12.

Results

The study population for the present analysis included 1,906 meningioma cases and 5,565 controls. The female to male ratio was 2.8 and 1.2 among cases and controls, respectively. The mean age at diagnosis of cases was 55 years, with the mean age of controls at the reference date being 3 years less. The number of cases varied among countries ranging from 50 in New Zealand to 737 in Israel. Cases were of lower socio-economic status than controls, as expressed by a lower level of educational attainment and by a larger proportion of cases in the 1st quartile of SIOPS. About 46% of cases reported ever smoking compared to 51% of controls. A history of any allergic condition was less prevalent among meningioma cases than controls (Table 1). More than 75% of the study participants were married; 4.6% of the interviews of the cases were made by a proxy, and 15 cases (0.8%) had malignant meningioma (data not shown).

Eleven percent of cases and 14% of controls were exposed to any metal, ranging from 1.7% for Cd (among cases) to 10.3% for Fe (among controls). Although a greater proportion of controls were exposed to specific metal agents overall, cases tended to have higher median cumulative exposure levels of Cr, Fe, Ni, Pb and welding fumes (Table 2). The top 5 occupations that had the highest cumulative exposures to iron in our study were electric arc welder (hand), sheet-metal worker, general, solderer (hand), welders and flame-cutters, metal smelting, converting and refining furnacemen and to chrome were metal smelting, converting and refining furnacemen, orthopaedic appliance maker and repairer, other metal smelting, converting and refining furnacemen, hot-dip plater and tool and die maker.

The ORs for ever vs. never exposure to any metal and to the various specific agents were mostly greater than 1.0 for the total study population, as well as for men and women separately, although the only estimate that attained near statistical significance was that for Fe (OR=1.26, 95% CI 1.00-1.58), particularly among women (OR=1.70, 95% CI 1.00-2.89). For men, a non-significantly elevated risk estimate (OR= 1.19) was shown (Table 3). Interaction between exposure to the various specific agents and gender was not statistically significant (data not shown).

A significant positive linear trend between lifetime cumulative exposure to Fe and to Cr and meningioma risk was seen (p=0.03 for both). Among women, this trend was significant for Fe (p=0.01) and of borderline significance for Cr (p=0.08). There was a tendency towards increasing risk with increasing number of years of exposure to Cr (p=0.07), with a significantly increased risk in the highest exposure duration category among women (OR = 2.58, 95% CI 1.03-6.47). For Fe, this trend was shown among women only (p=0.03). ORs among women were higher for first exposure before age

18 years compared to exposure later in life: OR 3.06 (95% CI 1.15-8.17) for Fe and 2.00 (95% CI 0.42-9.48) for Cr (Table 4). There were no significant trends according to categories of cumulative exposure to Cd, Ni, Pb or welding fumes, either overall or among men and women separately (Supplementary Table 1).

Sensitivity analyses using different participant exclusions resulted in similar ORs for Fe and Cr (Supplementary Table 2). Results were similar when adjusting for age at reference date, age at first exposure, marital status, SIOPS, smoking status, asthma, hay fever or eczema, proxy used and using different cut off points for exposure (5% and 50%). However, results for ever exposure to any metal, but not for individual metals, varied significantly by country ($p = 0.02$), with a significantly reduced OR in the UK (0.63, 95% CI 0.40-0.99, based on 28 exposed cases) and ORs above 1 in all other countries (ranging from 1.05 95% CI 0.74- 1.50 to 2.44 95% CI 1.16- 5.12 in Israel and Canada respectively), (not shown). Analyses of different time windows of exposure, revealed a positive trend in exposure to Cr or Fe and the risk of meningioma, in both the exposure time windows 5-14 and 15-24 years before the reference date. No significant trend was seen in the 25+ year time window (Supplementary Table 3).

A stratified analysis of exposure to Fe and meningioma risk by menopausal status among women (expressed by average menopausal age of 50 years), showed elevated risks in both pre and post-menopausal women which reached statistical significance only in the postmenopausal group (OR= 1.32 95% CI= 0.43-4.05 and OR= 1.91 95% CI= 1.02-3.58 in women $\leq$50 and >50 years respectively) (data not shown).

There was a high degree of co-exposure to different metals (Table 5). Among participants ever exposed to Cr and to welding fumes, 100% were also exposed to Fe; among those exposed to Ni, 96% were also exposed to Fe. Among those exposed to

Fe, only 66.5% were exposed to Cr. The correlation coefficients between cumulative exposures of the various metals and welding fumes ranged from 0.81 between Pb and Cd to 0.99 between Fe and welding fumes (not shown). ORs for exposure to any of the three metals (Fe, Cr or Ni) were 1.21 (95% CI 0.96-1.51) overall and 1.13 (95% CI 0.88-1.46) and 1.61 (95% CI 0.98-2.64) for men and women, respectively. In analysis of exposure to Fe alone, the corresponding ORs were 1.59 (95% CI 1.03-2.45) overall and 1.44 (95% CI 0.88-2.37) and 2.32 (95% CI 0.93-5.83) for men and women, respectively. The positive trend with increasing category of cumulative Fe exposure remained significant, both overall ($p = 0.03$) and among women ($p = 0.01$), although results within specific categories of exposure were imprecise due to the small number of subjects exposed to Fe alone (Supplementary Table 4).

When analyses were adjusted for exposure to oil mist (Supplementary Table 5), the positive associations between Cr, Fe, and Ni and meningioma risk remained in women.

Discussion

In this study, a positive association was observed between exposure to iron, and possibly chromium, and meningioma risk. These results were based on data on occupational histories of about 1,900 meningioma cases and 5,500 controls, of which 1,000 were classified as ever occupationally exposed to metals. No clear associations between exposure to cadmium, nickel, inorganic lead, and welding fumes and meningioma were shown.

In women, an increased risk of 70% was seen for ever vs never exposure to Fe, with a positive trend in relation to both cumulative exposure and duration of exposure. The risk was higher for women first exposed before the age of 18 years (OR = 3.06, 95% CI 1.15-8.17). Results of sensitivity analyses were generally similar.

For Cr, a non-significant increased risk was observed for ever vs never exposure (23% overall and 45% in women). This risk was significantly elevated in the highest quartile of cumulative exposure (OR=1.60, 95% CI= 1.01-2.53, overall and 5.06, 95% CI 1.25-20.55, in women), and showed a significant linear trend with cumulative exposure overall.

Among the metals which have been shown to have biological effects on the human body as a result of occupational exposure are Cd, Cr, Fe, Ni, and Pb [18]. Following inhalation, ingestion or dermal penetration, these metals are distributed to multiple organs and may affect processes such as cell proliferation, differentiation, and apoptosis (as occurs, for example, with Cd [31]); be involved in regulating blood glucose levels through insulin (e.g., Cr [32]); or activate enzymes (e.g., Ni [33]). Fe is involved in oxygen transport in the blood and may therefore impact all organs, including the meninges. Proteins needed for DNA synthesis and cell division are also dependent on Fe [34].

Further mechanisms for explaining the involvement of Fe in cancer formation include iron auto-oxidation, activation of oxidative responsive transcription factors and pro-inflammatory cytokines, and iron-induced hypoxia signaling [35]. These mechanisms provide some biological plausibility for a possible association between deviation from optimal doses of metals and cancer risk.

Further support for a possible role of these mechanisms in meningioma formation is the association between a functional polymorphism in the heme synthesis pathway and meningioma risk, shown in the study by Rajaraman et al [36]. The results of this casecontrol study showed that the ALAD2 allele of the G177C polymorphism (which catalyzes the second step of heme synthesis) was associated with increased risk of meningioma but not of glioma or acoustic neuroma. The authors suggested further evaluation of the joint effect of exposure and ALAD genotype in their or another study population.

While for many years iron deficiency has been the focus surrounding iron intake, iron excess is gaining more relevance in recent research of chronic diseases including cancer. Carcinogenicity of iron has been clearly shown in animal models. The oldest reported experiment of iron induced carcinogenesis showed pulmonary tumors in mice exposed to iron oxide dust. Subsequent studies showed soft tissue sarcoma induced by injection of iron dextran and renal cell carcinoma that were produced by intraperitoneal injections of iron chelates [37].

Based on 37 publications (56 studies; 39 prospective and 17 case-control), a meta-analysis shows increased risks between dietary iron, total iron, heme iron and iron biomarkers and colorectal, colon, breast and lung cancers (OR=1.08, 95% CI 1.0-1.17; OR=1.12, 95% CI 1.03-1.22; OR=1.03, 95% CI 0.97-1.09 and OR=1.12, 95% CI 0.98-1.29; respectively) [38].

It is noteworthy that a randomized controlled clinical trial shows a decreased cancer risk following iron reduction (by phlebotomy) in patients with peripheral arterial disease, suggesting that control of body iron stores might constitute a strategy for cancer prevention [39, 37]. To the best of our knowledge, no previous reports found a possible association between occupational exposure to Fe and meningioma. However, considering the low prevalence of the exposure and the disease, most previous studies did not have the ability to characterize such an association, even if it exists.

The association found in the present study was mainly seen among women. It is interesting to note that the incidence rates of meningioma show female predominance, with a female: male ratio of approximately 2:1 [40]. In a review of 20 papers an increase in risk for meningioma was observed with the use of HRT and having reached menopause, the increased risk seen for current HRT use declined with cessation of use [5].

In a study of the role of smoking in radiation- and non–radiation- related meningiomas, an interaction between radiation and smoking was seen among women. Whereas among women who were irradiated the OR for smokers compared to nonsmokers was 1.23 (95% CI, 0.68-2.23), a significant protective effect was seen among non-irradiated women, with an OR of 0.32 (95% CI, 0.14-0.77) and a strong dose-response relationship ($P < 0.01$). The authors suggested that host factors such as hormones may modify the effect of smoking on meningioma development [41].

It is also noteworthy that concurrent but inverse changes occur between iron and estrogen levels in healthy women during menopausal transition. While estrogen decreases with declining ovarian functioning, iron increases with declining menstruation [42, 43]. Considering the proposed role of iron in the pathogenesis of many chronic diseases including cancer, we evaluated the risk of developing meningioma following occupational exposure to Fe in women stratified by post and pre-menopausal status. However, considering the relatively low sample size of women occupationally exposed to Fe in the pre-menopausal group, no firm conclusions could be drawn about this issue here.

Metals including Fe have also been associated with hormonal function. There are various possible mechanisms by which chemical interactions between Fe and estrogen metabolism can cause cancer. For example, catecholestrogen metabolites are capable of metabolic redox cycling. Free radicals generated by this process may be converted to highly reactive hydroxy radicals by iron catalyzed reactions, which in turn generate

DNA damage, lipid peroxidation, and a perpetuation of the redox cycling [44, 45]. Tumors may therefore arise in cells which are damaged by such processes and which, at the same time, are stimulated to proliferate by hormone receptor-mediated mechanisms. Since meningioma is a hormone dependent tumor [46], the influence of increased blood levels of Fe might affect meningioma development in women. Our observation of increased risk for meningioma among women who were exposed to Fe is consistent with these observations.

Our study also showed some association between occupational exposure to Cr and meningioma risk. Cr-6 is able to cross cell membranes, be transformed to Cr-3, and interacts directly with DNA, causing mutations and carcinogenesis [47]. In an assessment of health risks in a population exposed to Cr, blood levels of Cr-3 were significantly higher in comparison to an unexposed population [48]. In addition, levels of DNA damage and oxidative stress were significantly increased, particularly among exposed compared to unexposed women. An ecological study of the association between exposure to environmental chemicals and incidence of breast cancer in Texas showed a higher rate of breast cancer in counties in which Cr was released in the environment from industry, in comparison with other counties. In addition, the mean elemental contents of scalp hair of breast cancer patients showed higher levels of Cr compared to controls [49].

Our study population is relatively large, especially compared to previous studies of meningioma. Nevertheless, only 210 cases (148 males and 62 females) in our study were classified as ever occupationally exposed to metals, restricting our ability to find an association if it exists. Sample sizes for the analysis for specific metals were even more limited. The largest exposed groups in our study were subjects exposed to Fe (139 cases), followed by Ni (106 cases), and Cr (89 cases) while the smallest exposed group was exposed to Cd (30 cases only). The number of exposed female cases in our study is even smaller (26, 16 and 20 cases exposed to Fe, Cr and Ni respectively). As mentioned above, the high correlations among the different metals also makes it difficult to isolate the impact of each metal separately.

While the indication for a role of Fe and Cr in the etiology of meningioma seen in our study might result from chance and should be interpreted with caution, the risk estimates remained invariant in sensitivity analyses. The specificity of the association that was observed mainly in women and the possible biological plausibility (2 criteria for causality [50]) add to the importance of these findings. Further studies are therefore needed to clarify the nature of these associations, and the possible role of occupational exposure to metals in the etiology of meningioma.

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Conflict of interest

The authors declare that they have no conflict of interest.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent

Informed consent was obtained from all individual participants included in the study.

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Table 1: Description of selected characteristics of the study population, by study group

Characteristic	**Cases**		**Controls**	
	N	**%**	**N**	**%**
Total	1,906	100	5,565	100
Gender				
Men	507	26.6	2,484	44.6
Women	1,399	73.4	3,081	55.4
Age (years)				
<40	182	9.5	892	16.2
40-49	448	23.5	1,394	25.0
50-59	708	37.2	2,019	36.3
60-69	370	19.4	959	17.4
70+	198	10.4	291	5.2
Mean±SD	55.0±11.8		52.0±11.5	
Country				
Australia	254	13.3	666	12.0
Canada	94	4.9	653	11.7
France	145	7.6	472	8.5
Germany	379	19.9	1,535	27.6
Israel	737	38.7	987	17.7
New Zealand	50	2.6	160	2.9
UK	247	13.0	1,092	19.6
Education				
Primary-Secondary	1,146	60.1	2,998	53.9
Intermediate College	361	18.9	1,045	18.8
Tertiary	392	20.6	1,511	27.2
SIOPS (SES in quartiles)*				
<35	550	28.9	1,369	24.6
35-	439	23.0	1,369	24.6
42.9-	417	21.9	1,369	24.6
52.1+	421	22.1	1,368	24.6
Unknown	79	4.1	90	1.6
Smoking status				
Current	486	25.5	1,501	27.0
Ex	397	20.8	1,319	23.7
Never	1,023	53.7	2,745	49.3
Asthma/Hay Fever/Eczema**				
No	1,500	78.7	4,099	73.7
Yes	400	21.0	1,464	26.3

* SIOPS Standard International Occupation Prestige Scale scores ranging from "most deprived" to "least deprived"

**Six cases (0.3%) and 2 controls had missing data

Table 2: Exposure profiles of metals (P≥25% in JEM) with at least 1y of exposure and 5-yr lag, by study group

		Cases					Controls				
Metal*	**Unit**	**Total**	**Ever**		**Lifetime cumulative exposure**	**Number of years exposed**	**Total**	**Ever**		**Lifetime cumulative exposure**	**Number of years exposed**
			N	**%**	**Median (25%;75%)**	**Median (25%;75%)**		**N**	**%**	**Median (25%;75%)**	**Median (25%;75%)**
Any		1,906	210	11.0	-	-	5,565	778	14.0	-	-
Cd	**ug/m^3**	1,726	30	1.7	172 (62;503)	5.8 (2;13.7)	4,887	100	2.0	184 (93;395)	5 (3;11.8)
Cr	**ug/m^3**	1,785	89	5.0	2,925 (575;7,750)	10 (5.1;18.5)	5,155	368	7.1	776 (347;5,775)	10 (4.5;18.5)
Fe	**mg/m^3**	1,835	139	7.6	165 (60;594)	9.5 (4;20.8)	5,335	548	10.3	141 (48;375)	10 (4.3;21.5)
Ni	**ug/m^3**	1,802	106	5.9	697 (300;1,801)	10 (4.5;18.5)	5,246	459	8.7	600 (225;1,309)	9 (4;19.1)
Pb	**µmol/l (blood)**	1,791	95	5.3	282 (86;554)	8 (3;17.4)	5,190	403	7.8	234 (90;588)	7.1 (3;18)
Welding fumes	**mg/m^3**	1,790	94	5.3	553 (144;2,103)	9.3 (3.3;24.6)	5,187	400	7.7	324 (120;1,120)	10 (4;21.5)

* Cadmium (Cd), Chromium (Cr), Iron (Fe), Nickel (Ni), Lead (Pb)

Table 3: ORs* for Ever/Never (P>=25% in JEM) with at least 1 year of exposure and 5-yr lag, by gender**

	ALL					MEN					WOMEN				
Metal***	**Cases**	**Cont.**	**OR**	**95%CI**		**Cases**	**Cont.**	**OR**	**95%CI**		**Cases**	**Cont.**	**OR**	**95%CI**	
Any	210	707	1.16	0.96	1.40	148	592	1.19	0.94	1.,51	62	115	1.11	0.80	1.55
Never exposed	1,621	4,254	1.00	-	-	316	1,452	1.00	-	-	1,305	2,802	1.00	-	-
Cd	30	83	0.94	0.60	1.46	14	50	0.88	0.46	1.66	16	33	1.01	0.54	1.87
Cr	89	321	1.23	0.93	1.62	73	299	1.21	0.89	1.64	16	22	1.45	0.74	2.83
Fe	139	493	1.26	1.00	1.58	113	458	1.19	0.91	1.54	26	35	1.70	1.00	2.89
Ni	106	413	1.14	0.88	1.47	86	381	1.11	0.83	1.47	20	32	1.37	0.76	2.46
Pb	95	353	1.02	0.79	1.32	64	286	1.09	0.80	1.50	31	67	0.90	0.58	1.41
Welding fumes	94	355	1.19	0.91	1.56	82	342	1.15	0.86	1.54	12	13	1.79	0.78	4.10

* Adjusted ORs and 95% CIs were estimated using conditional logistic regression stratified by sex, five-year age groups, and country-region and adjusted for education.
** P value for interaction between metals and gender were: 0.80, 0.74, 0.59, 0.21, 0.48, 0.52 and 0.30 for any, Cd, Cr, Fe, Ni, Pb and welding fumes respectively.
*** Cadmium (Cd), Chromium (Cr), Iron (Fe), Nickel (Ni), Lead (Pb)

Table 4: ORs* for chromium (Cr) and iron (Fe), for lifetime cumulative exposure, duration of exposure and age at first exposure, (P>=25% in JEM) with at least 1 year of exposure and 5-yr lag, by gender

	ALL					MEN					WOMEN				
METAL	**Cases**	**Cont.**	**OR**	**95%CI**		**Cases**	**Cont.**	**OR**	**95%CI**		**Cases**	**Cont.**	**OR**	**95%CI**	
Cr															
Lifetime cumulative exposures (in quartiles among controls) (in **ug/m^3**)															
Never exposed	1,621	4,169	1.00			316	1,385	1.00			1,305	2,784	1.00		
<346.5	14	76	0.88	0.48	1.63	13	74	0.91	0.48	1.71	1	2	0.72	0.06	8.45
346.5-	15	80	0.90	0.50	1.62	14	73	1.08	0.59	2.00	1	7	0.24	0.03	1.99
776.4-	29	82	1.42	0.90	2.24	22	72	1.40	0.83	2.34	7	10	1.57	0.58	4.26
5775+	31	83	1.60	1.01	2.53	24	80	1.40	0.84	2.32	7	3	5.06	1.25	20.55
	Test for linear trend p-value = 0.03					Test for linear trend p-value =0.10					Test for linear trend p-value = 0.08				
Duration of exposure in years (in fixed categories)															
Never exposed	1,621	4,169	1.00			316	1,385	1.00			1,305	2,784	1.00		
1-4	21	85	0.96	0.58	1.60	16	72	1.05	0.59	1.88	5	13	0.73	0.25	2.10
5-14	34	115	1.29	0.85	1.96	26	106	1.19	0.75	1.91	11	9	2.58	1.03	6.47
15+	34	121	1.41	0.92	2.15	31	121	1.33	0.85	2.06					
	Test for linear trend p-value = 0.07					Test for linear trend p-value = 0.17					Test for linear trend p-value = 0.11				
Age at first exposure (years)															
Never exposed	1,621	4,169	1.00			316	1,385	1.00			1,305	2,784	1.00		
<18	22	107	1.21	0.73	1.99	19	103	1.16	0.68	1.97	3	4	2.00	0.42	9.48
18+	67	214	1.24	0.90	1.69	54	196	1.23	0.87	1.75	13	18	1.35	0.64	2.83
	Test for linear trend p-value =0.15					Test for linear trend p-value =0.22					Test for linear trend p-value =0.33				
Fe															
Lifetime cumulative exposures (in quartiles among controls) (in **mg/m^3**)															
Never exposed	1,621	4,204	1.00			316	1,420	1.00			1,305	2,784	1.00		
<48.1	27	118	1.00	0.64	1.57	25	105	1.11	0.69	1.79	2	13	0.41	0.09	1.84
48.1-	33	121	1.35	0.89	2.06	27	116	1.26	0.80	2.00	6	5	2.08	0.63	6.93
140.8-	34	127	1.29	0.85	1.95	26	119	1.10	0.69	1.74	8	8	3.08	1.12	8.42
374.6+	45	127	1.38	0.94	2.02	35	118	1.27	0.83	1.94	10	9	2.10	0.82	5.34
	Test for linear trend p-value = 0.03					Test for linear trend p-value =0.20					Test for linear trend p-value = 0.01				

	ALL					MEN					WOMEN				
METAL	**Cases**	**Cont.**	**OR**	**95%CI**		**Cases**	**Cont.**	**OR**	**95%CI**		**Cases**	**Cont.**	**OR**	**95%CI**	
Fe															
Duration of exposure in years (in fixed categories)															
Never exposed	1,621	4,204	1.00			316	1,420	1.00			1,305	2,784	1.00		
1-4	38	129	1.16	0.78	1.71	26	108	1.07	0.67	1.71	12	21	1.4	0.67	2.92
5-14	50	160	1.47	1.03	2.09	40	148	1.38	0.94	2.05	10	12	1.95	0.82	4.64
15+	51	204	1.16	0.82	1.65	47	202	1.11	0.77	1.60	4	2	2.97	0.52	17.07
	Test for linear trend p-value = 0.08					Test for linear trend p-value = 0.24					Test for linear trend p-value = 0.03				
Age at first exposure (years)															
Never exposed	1,621	4,204	1.00			316	1,420	1.00			1,305	2,784	1.00		
<18	58	258	1.18	0.85	1.64	49	250	1.06	0.74	1.51	9	8	3.06	1.15	8.17
18+	81	235	1.32	0.99	1.76	64	208	1.30	0.94	1.81	17	27	1.34	0.71	2.53
	Test for linear trend p-value =0.04					Test for linear trend p-value =0.12					Test for linear trend p-value =0.13				

* Adjusted ORs and 95% CIs were estimated using conditional logistic regression stratified by sex, five-year age groups, and country-region and adjusted for education.

Table 5: Joint exposure to metals* and welding fumes in the INTEROCC study**

	Cd	Cr	Fe	Ni	Pb	Welding fumes
n	130	457	687	565	498	494
Cd	-	7.2	6.7	8	9	2.6
Cr	25.4	-	66.5	79.1	37.6	62.1
Fe	35.4	100	-	96.1	61.6	100
Ni	34.6	97.8	79	-	49.8	80
Pb	34.6	40.9	44.7	43.9	-	53.8
Welding fumes	10	67.2	71.9	69.9	53.4	-

* Cadmium (Cd), Chromium (Cr), Iron (Fe), Nickel (Ni), Lead (Pb)

** Values of cells in each column represent the % of participants with exposure to metal A (column header) co-exposed to metal B (row). For example of the 494 participants exposed to welding fumes, all (100%) were also exposed to Fe.