Toenail concentrations of trace elements and occupational history in pancreatic cancer

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ABSTRACT

Background: Some occupations potentially entailing exposure to cadmium, arsenic, lead, selenium, nickel, and chromium have been associated with an increased risk of exocrine pancreatic cancer (EPC), but no studies have assessed whether body concentrations of such compounds differed among subjects occupationally exposed and unexposed. No studies which found that exposure to such metals increased the risk of EPC assessed whether past occupations were the source of exposure.
Objective: The aim was to analyse the relationship between toenail concentrations of trace elements and occupational history in EPC patients.
Methods: The study included 114 EPC cases personally interviewed on occupational history and lifestyle factors. Occupations were coded according to the International Standard Classification of Occupations 1988. Selected occupational exposures were assessed by two industrial hygienists and with the Finnish job-exposure matrix (Finjem). Concentrations of 12 trace elements were determined in toenail samples by inductively coupled plasma mass spectrometry. Adjusted geometric means (aGMs) and 95% confidence intervals (95% CI) were calculated.
Results: Patients occupationally exposed to aromatic hydrocarbon solvents (AHs) had higher concentrations of cadmium, manganese, lead, iron and vanadium. The aGM of cadmium concentrations for cases exposed to any pesticide was 0.056 μg/g [95% CI: 0.029–0.108], and, for unexposed cases, 0.023 μg/g [0.017–0.031]. Patients occupationally exposed to pesticides had higher concentrations of cadmium and manganese. Higher concentrations of vanadium, lead and arsenic were related to exposure to formaldehyde. Vanadium and lead were also associated with exposure to chlorinated hydrocarbon solvents, and arsenic was related to exposure to polycyclic aromatic hydrocarbons (PAHs).
Conclusions: Patients occupationally exposed to AHs, pesticides, chlorinated hydrocarbon solvents, formaldehyde, volatile sulphur compounds and PAHs had higher concentrations of several metals. These elements may account for some of the occupational risks previously reported for pancreatic cancer.

1. Introduction

Occupational and non-occupational exposures to cadmium, arsenic, lead, selenium, nickel, and chromium have been associated with an increased risk of exocrine pancreatic cancer (EPC) (Alguacil et al., 2003; Amaral et al., 2012; Andreotti and Silverman, 2012; Ojajärvi et al., 2000) and other diseases (McCarty and DiNicolantonio, 2016; Menke et al., 2016). However, evidence is limited and not always

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consistent, and few studies used biomarkers to assess such exposures (Boffetta, 2014; Cheng et al., 2015; Fritschi et al., 2015; Luckett et al., 2012; Maisonneuve and Lowenfels, 2015; Reul et al., 2016). This lack of consistency might partly be explained by unaccounted differences in exposure to specific chemical or physical agents (Ojajärvi et al., 2000). Also, workers are subject to complex chemical mixtures, whose exact composition is seldom fully characterized (Reul et al., 2016; Sexton and Hattis, 2007).

Exposure to chlorinated hydrocarbon solvents and similar compounds is considered a major occupational risk factor for EPC (Amaral et al., 2012; Antwi and Eckert, 2015; Barone et al., 2016; Bosch de Basea et al., 2011) and high levels of cadmium and arsenic have also been associated with an increased risk (Amaral et al., 2012; Andreotti and Silverman, 2012; Antwi and Eckert, 2015; Barone et al., 2016; Luckett et al., 2012). In contrast, levels of selenium may be inversely associated with EPC (Amaral et al., 2012; Barone et al., 2016). An increased incidence of EPC has been identified among metal plating workers, in particular in those exposed to nickel and chromium (Alguacil et al., 2003; Amaral et al., 2012; Antwi and Eckert, 2015; Barone et al., 2016; Maisonneuve and Lowenfels, 2015; Ojajärvi et al., 2000). Lead exposure has also been inconclusively associated with EPC (Amaral et al., 2012; Ojajärvi et al., 2000). Only two previous studies on trace elements as possible etiologic factors of EPC used biomarkers of chromium exposure (Amaral et al., 2012; Lener et al., 2016). Two additional studies measured serum and urinary cadmium concentrations to assess the role of occupational exposure to cadmium in EPC (Luckett et al., 2012; Kriegel et al., 2006). To our knowledge there are no data relating occupational history and biomarkers of exposure to trace elements in EPC. In the present study we analysed toenail concentrations of the following trace elements in EPC cases: cadmium, arsenic, selenium, nickel, lead, chromium, manganese, aluminium, iron, vanadium, copper and zinc (Amaral et al., 2012). Contrary to concentrations in urine and blood –which might reflect more recent exposures–, concentrations of trace elements in hair and nails reflect exposures over several months, and are thus preferable as an estimate of longer exposures (Golasik et al., 2015; Goyer and Clarkson, 2001; Hopps, 1977; Slotnick and Nriagu, 2006).

The aim of the present study was to assess the relationship between concentrations of trace elements and occupational exposures in EPC patients. Knowledge of this relationship may help understand processes through which certain trace elements and occupations influence EPC risk.

2. Methods

2.1. Study population

Methods of the PANKRAS II study have been described in detail elsewhere (Alguacil et al., 2000, 2002, 2003; Amaral et al., 2012; Bosch de Basea et al., 2011; Crous-Bou et al., 2007; Gasull et al., 2010; Mendez et al., 2006; Morales et al., 2007; Porta et al., 1999, 2000, 2007, 2008a, 2008b; Soler et al., 1999). Briefly, subject recruitment took place between 1992 and 1995 at five general hospitals in the eastern part of Spain, where 185 incident cases of EPC were prospectively identified. The present report is based on 114 cases (70 men and 44 women, mean age 62.9 and 71.4 years, respectively) with complete data on toenail concentrations of trace elements, occupation and lifestyle. There were no significant differences between these 114 and the remaining cases with respect to a broad range of socio-demographic and clinical variables (including age, sex, occupational history, education and social class, hospital, tumour stage, signs and symptoms of pancreatic cancer, duration of the interview, energy intake, and consumption of coffee, tobacco and alcohol). A structured form was used to collect clinico-pathological information from medical records, including details on diagnostic procedures, laboratory results and follow-up. The primary and secondary discharge diagnoses and the

tumour's clinical stage at diagnosis were also recorded on this form. Clinical stage was classified according to the tumour-node-metastasis (TNM) system, and the histological type was classified according to the International Classification of Diseases for Oncology. All cases were independently reviewed by the study reference pathologists, blinded to the original diagnoses. Furthermore, a panel of clinical and surgical experts in gastrointestinal diseases reviewed the hospital discharge diagnosis of all patients and, based on all clinical and pathological information available, including follow-up, achieved a consensual clinical-pathological diagnosis. The ethics committees of participating hospitals approved the study protocol, and patients gave informed consent to participate.

2.2. Personal interviews and information on occupational history

All 114 EPC cases were interviewed face-to-face by trained monitors during hospital stay, soon after the time of diagnosis (Alguacil et al., 2000, 2002, 2003; Bosch de Basea et al., 2011; Porta et al., 2007, 2008a, 2008b; Soler et al., 1999). The respondent was the patient in 94.7% of cases and a relative in 5.3%. Interviews included questions on past clinical history, signs and symptoms of pancreatic cancer, diet, coffee, alcohol and tobacco consumption, education, and occupation (Alguacil et al., 2000, 2002, 2003; Bosch de Basea et al., 2011; Crous-Bou et al., 2007; Morales et al., 2007; Porta et al., 2000, 2008a, 2008b; Soler et al., 1999). Coffee and alcohol consumption were not related to occupation. To assess the reliability of interviews, a sample of relatives was concurrently and separately interviewed about the same questions and agreement between the two sets of responses was compared (Alguacil et al., 2003; Bosch de Basea et al., 2011; Ojajärvi et al., 2000; Soler et al., 1999).

Participants were asked if they had ever worked in any of 10 activities a priori defined to be potentially related with pancreatic ductal and biliary adenocarcinomas (Alguacil et al., 2000, 2002, 2003; Porta et al., 2008a). These activities were pesticide use, handling of petroleum derivatives, the chemical industry, graphic arts, jewellery making, manufacture or repair of automobiles, leather tanning, and the textile industry. Patients who reported having ever worked in any of these activities were asked about the duration of the employment, specific activity, and products to which they had been exposed. The same information was also requested for any other activities (up to two) that the patient might have performed over their lifetime. Information on occupational history was not available for controls (Amaral et al., 2012). The occupational history of EPC cases collected during the interview was used in three ways.

First, occupations were coded according to the Spanish version of the International Standard of Occupations 1988 (ISCO 88) (Alguacil et al., 2000; Bosch de Basea et al., 2011; Porta et al., 2008a). Occupations classified as ISCO group 1 to 4 (all office-related) were merged into one category, since they were not discriminating factors in a qualitative sense in the occupational classification (Table 1, footnote). When patients had several occupations, the most recent was used in the analyses. There were some differences in the distribution of age and sex among participants belonging to the different ISCO major groups (Table 1). Most occupations were performed by males. Only within elementary occupations (ISCO 9) were participants mostly women (81.5%), all of whom ($N = 22$) were housewives. Among participants in the "skilled agricultural occupations" (ISCO 6 major group), 46.2% were women. There were no significant differences among the major ISCO groups in the time interval between the first symptom of the disease and its diagnosis, the time interval between the first symptom and the collection of the toenail samples in which trace elements were analysed, or in tumour stage at diagnosis (Table 1).

Second, using all information on occupational history available from the interview, two industrial hygienists (IH) assessed exposure to 22 suspected carcinogens: pesticides, aromatic hydrocarbon solvents (AHs), hexavalent and trivalent chromium, lead, nickel compounds,

Table 1
Characteristics of pancreatic cancer patients by last occupation classified by major groups of the International Standard Classification of Occupations 1988 (ISCO 88).

Characteristics	Total	Major ISCO groups[a]						p-Value[b]
		ISCO 1 to 4	ISCO 5	ISCO 6	ISCO 7	ISCO 8	ISCO 9	
	(N = 114)	(N = 16)	(N = 10)	(N = 13)	(N = 27)	(N = 21)	(N = 27)	
Age[c] (years)	66.2 ± 12.4	66.9 ± 14.0	63.0 ± 14.6	70.5 ± 10.2	60.5 ± 10.9	65.1 ± 13.6	71.4 ± 9.9	0.021[d]
Gender (% males)	61.4	81.2	70.0	53.8	85.2	71.4	18.5	< 0.001
Education (%)								0.009
Illiterate/can only read and write	40.7	12.5	30.0	66.7	29.6	42.9	59.3	
Up to 10 years of schooling	51.3	56.3	70.0	33.3	66.7	52.4	33.3	
More than 10 years of schooling	8.0	31.3	0	0	3.7	4.8	7.4	
Years of education[c]	4.7 ± 4.5	8.7 ± 5.0	4.7 ± 3.2	2.3 ± 2.9	4.7 ± 3.7	4.0 ± 3.6	3.9 ± 5.3	0.003[d]
First symptom to diagnosis interval[c] (days)	107.8 ± 122.1	90.3 ± 138.6	116.0 ± 113.6	139.9 ± 99.3	123.2 ± 153.9	138.4 ± 140.2	60.6 ± 43.6	0.217[d]
First symptom to nail sample interval[c] (days)	113.9 ± 125.4	89.3 ± 139.4	113.2 ± 115.6	142.8 ± 114.4	135.0 ± 156.1	144.3 ± 138.0	70.1 ± 58.8	0.254[d]
Occupational social class (%)								< 0.001
Non-manual workers	37.2	87.5	30.0	92.3	3.7	14.3	34.6	
Manual workers	62.8	12.5	70.0	7.7	96.3	85.7	65.4	
Total intake[c] (Kcal)	1735 ± 325.5	1713 ± 332.2	1738 ± 200.1	1462 ± 345.8	1833 ± 293.7	1766 ± 363.7	1758 ± 301.7	0.031[d]
Smoking status (%)								0.011
Non smoker	43.0	25.0	30.0	53.8	25.9	33.3	77.8	
Former	22.8	31.3	20.0	15.4	25.9	33.3	11.1	
Current	34.2	43.8	50.0	30.8	48.1	33.3	11.1	
Alcohol consumption (%)								0.248
No and occasional	27.2	18.8	50.0	23.1	14.8	28.6	37.0	
Moderate and Heavy	72.8	81.3	50.0	76.9	85.2	71.4	63.0	
Tumour stage (%)								0.922
Stage I	21.4	18.8	20.0	16.7	19.2	28.6	22.2	
Stage II	15.2	6.2	10.0	8.3	15.4	9.5	29.6	
Stage III	14.3	18.8	10.0	25.0	15.4	14.3	7.4	
Stage IV	49.1	56.2	60.0	50.0	50.0	47.6	40.7	

ISCO 1: Legislators, senior officials and managers. ISCO 2: Professionals. ISCO 3: Technicians and associate professionals. ISCO 4: Clerks. ISCO 5: Service, shop and market sales workers
ISCO 6: Skilled agricultural and fishery workers. ISCO 7: Craftsmen and related trades workers. ISCO 8: Plant and machine operators and assemblers. ISCO 9: Elementary occupations.
[a] Based on subjects' last occupation.
[b] Unless otherwise specified, p-value derived from Fisher's exact test (two-tailed).
[c] Mean ± standard deviation.
[d] ANOVA.

aluminium and others, and classified subjects as non-exposed or exposed. The "exposed" classification required a substantiated source of exposure (Alguacil et al., 2000, 2002, 2003; Bosch de Basea et al., 2011). If exposure was unsubstantiated but possible, the category 'unknown' was used. The intensity of exposure was coded as high, low, unknown or none. The IH developed algorithms for the exposure assessment. Two occupational epidemiologists evaluated and accepted the algorithms. The IH were also given information about the ages at which subjects started and stopped schooling, and about the calendar year and the place of residence (Alguacil et al., 2000, 2002). Patients exposed to organochlorine pesticides (N = 11) were also exposed to arsenical pesticides by the IH classification. Also according to the IH classification, the total number of patients exposed to any type of pesticide was 13: a) including 11 patients exposed to organochlorine/ arsenical pesticides; b) two of 12 exposed to organophosphorus pesticides and not exposed to organochlorine pesticides; and c) one exposed to other pesticides and not exposed to organochlorine or to organophosphorus pesticides.

And third, we used the Finnish job-exposure matrix (Finjem) to evaluate occupational exposure to 21 chemical agents and 2 physical exposures (Alguacil et al., 2000, 2002, 2003; Bosch de Basea et al., 2011). The exposure categories used were 'substantial', 'low', and 'unexposed'. The cut-off point between exposed and non-exposed was set as close as possible to the median of the distribution of the product of the probability of exposure and the intensity of exposure (most in mg/ m³ or ppm) (Alguacil et al., 2000, 2002, 2003). Exposure to aromatic hydrocarbon solvents by the Finjem matrix was restricted to polycyclic

aromatic hydrocarbons (PAHs).

Patients were asked about the frequency of consumption of food groups during the year before the first symptom of the current illness. For this purpose a brief food frequency questionnaire was administered (Gasull et al., 2010; Mendez et al., 2006; Morales et al., 2007).

2.3. Assessment of trace elements

Trace elements analysed were cadmium, arsenic, selenium, nickel, lead, chromium, manganese, aluminium, iron, vanadium, copper and zinc (Amaral et al., 2012). Toenails were collected during the hospital stay where EPC was diagnosed (Bosch de Basea et al., 2011; Gasull et al., 2010; Porta et al., 1999, 2007). Information on time of treatment onset was available for 73 patients, of whom two started treatment before collection of toenails. Samples were stored at room temperature until the time of analysis. After cleaning and washing to remove external contaminants, trace elements were quantified at the Trace Element Analysis Core (Dartmouth College, NH, USA), using inductively coupled plasma-mass spectrometry (Amaral et al., 2012).

2.4. Statistical analyses

Univariate statistics were computed as customary. Thus, for instance, means and medians of toenail concentrations were compared for levels of ISCO 88 groups, IH-based metrics, and Finjem-based metrics. General linear models were applied to analyse variations in concentrations of trace elements (Bosch de Basea et al., 2011; Porta et al.,

2008a). The main effects of all predictors were independently explored in the base models. Geometric means and their 95% confidence intervals (CIs) were estimated for the occupational exposures by the codes of the IH and by Finjem codes (exposed vs. unexposed). Adjusted models for each trace element included age, gender, and total caloric intake (Kcal) as covariates. Region of residence (Hashemian et al., 2017) and specific diet variables were also considered as potential confounders (NRC, 1989). In models for cadmium and lead concentrations, tobacco smoking was included as a covariate. The level of statistical significance was set at 0.05, and all tests were two-tailed. Statistical analyses were performed using Stata software version·10.1 (StataCorp, College Station, TX) and SPSS version 18.0.0 (SPSS, Chicago, IL, USA, 2009).

3. Results

Median toenail concentrations of cadmium and manganese were significantly higher in EPC patients exposed to aromatic hydrocarbon solvents (AHs), assessed by IH, than in patients unexposed to AHs. Such concentrations were also higher in patients exposed to organochlorine and arsenical pesticides (vs. patients unexposed to these pesticides), to organophosphorus pesticides (again vs. unexposed) and to other pesticides (vs. unexposed); always, as assessed by IH (Table 2). Concentrations of lead, selenium, iron and arsenic, were significantly higher in patients exposed to AHs (again vs. unexposed to AHs) (Table 2 and Supplemental Table 1).

In multivariate models, concentrations of cadmium, lead, manganese, iron and vanadium were higher in patients exposed to AHs than in patients unexposed: e.g., for cadmium, when adjusting for age, sex, tobacco smoking, and intake of fresh vegetables and fruit, the aGM for exposed patients was 0.056 μg/g for exposed patients vs. 0.023 μg/g for unexposed; *p*-value = 0.022 (Table 3). Cadmium and manganese concentrations were also higher in patients exposed to pesticides regardless of the kind of pesticide, even when models were fully adjusted. Concentrations of aluminium were significantly higher in patients exposed to organophosphorus pesticides (vs. non-exposed) and, although not statistically significant, were also higher in patients exposed to other pesticides (vs. non-exposed) (Table 3).

Median concentrations of cadmium in EPC patients whose last occupations were included in ISCO major groups 7 (median of 0.038 μg/g) and 9 (median of 0.034 μg/g) were slightly higher than concentrations of other patients whose last occupation was another major group (range between 0.017 μg/g and 0.025 μg/g) (Supplemental Table 2). Copper concentrations were significantly higher in patients whose last occupation was included in ISCO major group 8 (4.35 μg/g) (plant and machine operators and assemblers) than in patients whose last occupation was another major group (range between 3.20 μg/g and 3.69 μg/g; *p*-value = 0.027). For zinc, median concentrations of cases whose last occupation was included in ISCO major groups 8 and 9 (116.7 μg/g and 115.1 μg/g, respectively) were also higher than concentrations of patients whose last occupation was another major group (range between 101.7 and 112.4; *p*-value = 0.064) (Supplemental Table 2).

Concentrations of aluminium of patients of major group 6 (skilled agricultural and fishery workers) were higher than groups 1 to 4 (all office-related) and group 9, (median concentrations of 19.43 μg/g, 7.24 μg/g and 7.38 μg/g, respectively, both *p*-values ≤ 0.045). For iron, concentrations of patients with a last occupation in ISCO major groups 6 and 8 were higher than concentrations of patients in major groups 1 to 4; median concentrations were 22.63 μg/g, 14.35 μg/g and 11.31 μg/g, respectively; *p*-value = 0.050 for the contrast between concentrations of major groups 6 and 1 to 4, and p-value = 0.083 for the contrast between concentrations of major groups 8 and 1 to 4. Concentrations of nickel were significantly higher in ISCO major group 9 (0.310 μg/g) than in patients whose last occupation was in another group (median range between 0.128 μg/g and 0.219 μg/g; p-value = 0.022) (Supplemental Table 2). When we stratified by gender, differences in copper concentrations remained statistically significant in men, and the

highest concentrations were in patients of ISCO group 8 than in patients of other ISCO groups (data not shown).

When adjusting for age, sex and total caloric intake (Kcal), the aGM of iron concentrations of patients in the major group 8 were higher than concentrations of patients in the majors groups 1 to 4 (aGM = 24.08 [16.86–34.40] and aGM = 11.72 [7.75–17.72], respectively; p-value = 0.010); they only remained statistically significant for men (aGM = 20.76 [13.87–31.10] and aGM = 11.24 [7.31–17.28], respectively; p-value = 0.043). aGM of copper concentrations were higher in patients whose last occupation was in ISCO major group 8 (aGM = 4.51 μg/g [95% CI: 3.77, 5.39]) than in patients whose last occupation was in an ISCO group 1 to 4 (aGM = 3.25 [2.65, 4.00], p-value = 0.018).

Exposure to chlorinated hydrocarbon solvents, formaldehyde and volatile sulphur compounds, assessed through the Finjem, was related to vanadium concentrations, whose median was higher in the corresponding exposed EPC cases (> 0.03 μg/g) than in the non-exposed cases (0.019 μg/g) (p-values < 0.035 for Mann-Whitney's *U* test) (Table 4). aGM of vanadium concentrations of patients exposed to chlorinated hydrocarbon solvents, and of those exposed to formaldehyde, doubled the aGM of the non-exposed when adjusted for age and sex, and also when further adjusted for Kcal (Table 5). aGM of vanadium concentrations for patients exposed to volatile sulphur compounds also was statistically higher than concentrations of patients non-exposed (0.034 μg/g and 0.021 μg/g, respectively, p-value = 0.048). Exposure to chlorinated hydrocarbon solvents according to Finjem was also related with higher copper concentrations, although it was not statistically significant when dietary factors were included in the regression model (Table 5).

Lead concentrations were significantly higher for patients exposed to chlorinated hydrocarbon solvents, and also to formaldehyde, than for the respective non-exposed (Table 5). Levels of arsenic assessed through Finjem were higher in cases exposed to formaldehyde than in the non-exposed (median concentrations of 0.149 μg/g and 0.070 μg/g, respectively, p-value = 0.009) (Supplemental Table 3); in multivariate models, aGMs for the exposed remained significantly higher than for the non-exposed (0.137 μg/g vs. 0.075 μg/g, p-value = 0.017) (Table 5).

Patients exposed to polycyclic aromatic hydrocarbons (PAHs) showed higher arsenic concentrations than the non-exposed (median of 0.121 μg/g and 0.071 μg/g, respectively; p-value = 0.021) (Supplemental Table 3). In adjusted models, the aGM for arsenic of cases exposed to PAHs was significantly higher than that of the unexposed/non-exposed (Table 5).

In cases exposed to cadmium, lead, chromium and nickel (according to IH and Finjem), concentrations of cadmium and nickel were higher than in non-exposed cases (Supplemental Figs. 1 and 2); but in the regression models these differences were not significant (data not shown).

Patients exposed and unexposed to other substances, assessed by IH and Finjem (industrial chromium, lead, cadmium, nickel, organic pigments, benzene and other organic components, gasoline and diesel exhaust, cotton and synthetic polymer dust, and asbestos), did not show significant difference in concentrations of trace elements.

4. Discussion

Higher body concentrations of several trace elements –notably, cadmium, manganese, lead, aluminium, vanadium, copper, iron and arsenic– were found in patients with pancreatic cancer who had been occupationally exposed to AHs, pesticides, chlorinated hydrocarbon solvents, formaldehyde, volatile sulphur compounds and PAHs. Findings thus suggest that these elements may account for some of the occupational risks previously reported for this cancer (Alguacil et al., 2003; Amaral et al., 2012; Andreotti and Silverman, 2012; Ojajärvi et al., 2000).

Table 2
Trace element concentrations (μg/g) by occupational exposure assessed by industrial hygienists in pancreatic cancer patients.

Trace element concentration (μg/g)	Total	Aromatic hydrocarbon solvents			Organochlorine and arsenical pesticides			Organophosphorus pesticides			Other pesticides		
	(N = 114)	Exposed (N = 23)	Non-exposed (N = 91)	p-Value	Exposed (N = 11)	Non-exposed (N = 103)	p-Value	Exposed (N = 12)	Non-exposed (N = 102)	p-Value	Exposed (N = 13)	Non-exposed (N = 101)	p-Value
Cadmium													
Mean ± SD	0.103 ± 0.431	0.089 ± 0.143	0.107 ± 0.477	0.863[a]	0.134 ± 0.183	0.100 ± 0.450	0.806[a]	0.125 ± 0.178	0.101 ± 0.452	0.853[a]	0.129 ± 0.171	0.100 ± 0.454	0.824[a]
Median	0.030	0.036	0.025	0.063[b]	0.067	0.028	0.010[b]	0.068	0.028	0.025[b]	0.069	0.028	0.010[b]
Lead													
Mean ± SD	2.73 ± 14.76	8.26 ± 32.41	1.33 ± 2.66	0.044[a]	1.15 ± 1.14	2.90 ± 15.53	0.711[a]	1.52 ± 1.65	2.87 ± 15.60	0.765[a]	1.48 ± 1.59	2.89 ± 15.68	0.748[a]
Median	0.879	1.12	0.804	0.078[b]	1.33	0.870	0.867[b]	1.34	0.863	0.685[b]	1.33	0.856	0.608[b]
Selenium													
Mean ± SD	0.516 ± 0.113	0.551 ± 0.082	0.507 ± 0.118	0.089[a]	0.527 ± 0.102	0.514 ± 0.114	0.726[a]	0.536 ± 0.095	0.513 ± 0.115	0.510[a]	0.538 ± 0.091	0.513 ± 0.115	0.448[a]
Median	0.513	0.550	0.503	0.075[b]	0.498	0.515	0.981[b]	0.538	0.510	0.592[b]	0.543	0.509	0.473[b]
Chromium													
Mean ± SD	1.13 ± 3.14	1.02 ± 1.85	1.15 ± 3.40	0.860[a]	1.04 ± 1.12	1.14 ± 3.29	0.924[a]	1.63 ± 2.42	1.07 ± 3.22	0.560[a]	1.52 ± 2.35	1.08 ± 3.23	0.634[a]
Median	0.418	0.410	0.425	0.802[b]	0.587	0.394	0.110[b]	0.704	0.400	0.112[b]	0.587	0.406	0.198[b]
Manganese													
Mean ± SD	0.490 ± 0.772	0.688 ± 0.822	0.440 ± 0.756	0.170[a]	0.840 ± 0.848	0.453 ± 0.759	0.115[a]	0.992 ± 1.02	0.431 ± 0.721	0.089[a]	0.939 ± 0.997	0.433 ± 0.725	0.099[a]
Median	0.218	0.289	0.205	0.053[b]	0.387	0.200	0.026[b]	0.426	0.203	0.035[b]	0.387	0.200	0.029[b]
Aluminium													
Mean ± SD	14.47 ± 18.74	21.59 ± 30.91	12.66 ± 13.83	0.189[a]	28.57 ± 40.80	12.96 ± 14.22	0.235[a]	31.49 ± 40.52	12.46 ± 13.26	0.134[a]	29.45 ± 39.48	12.54 ± 13.30	0.150[a]
Median	8.08	11.01	7.57	0.153[b]	12.87	7.42	0.143[b]	12.98	7.49	0.088[b]	12.87	7.57	0.180[b]
Iron													
Mean ± SD	36.18 ± 153.6	33.76 ± 36.15	36.79 ± 171.2	0.933[a]	37.97 ± 44.30	35.98 ± 161.1	0.968[a]	43.25 ± 46.64	35.34 ± 161.7	0.867[a]	40.41 ± 45.81	35.63 ± 162.5	0.916[a]
Median	13.21	22.14	12.68	0.053[b]	18.91	12.69	0.117[b]	19.84	12.68	0.062[b]	17.06	12.69	0.183[b]
Vanadium													
Mean ± SD	0.040 ± 0.082	0.052 ± 0.067	0.037 ± 0.085	0.433[a]	0.064 ± 0.080	0.038 ± 0.082	0.303[a]	0.074 ± 0.087	0.036 ± 0.081	0.134[a]	0.069 ± 0.085	0.036 ± 0.081	0.170[a]
Median	0.020	0.022	0.020	0.149[b]	0.030	0.019	0.082[b]	0.029	0.019	0.095[b]	0.028	0.020	0.114[b]

SD: standard deviation.
[a] Student's t-test (two-tail).
[b] Mann-Whitney's U test (two-tail).

Table 3

Influence on trace element concentrations (µg/g) of occupational exposures assessed by industrial hygienists in pancreatic cancer patients.

Trace element	Exposure	Model I[a]			Model II[b]		
		aGM	(95% CI)	P-value	aGM	(95% CI)	P-value
Cadmium[c] (µg/g)	Aromatic hydrocarbon solvents			0.066			0.022
	Non exposed	0.023	(0.017, 0.033)		0.023	(0.017, 0.031)	
	Exposed	0.049	(0.025, 0.098)		0.056	(0.029, 0.108)	
	Organochlorine pesticides[d]			0.013			0.006
	Non exposed	0.024	(0.018, 0.033)		0.024	(0.018, 0.032)	
	Exposed	0.083	(0.033, 0.209)		0.088	(0.037, 0.211)	
	Organophosphorus pesticides			0.029			0.023
	Non exposed	0.024	(0.018, 0.033)		0.024	(0.018, 0.032)	
	Exposed	0.070	(0.029, 0.170)		0.069	(0.030, 0.159)	
	Other pesticides			0.012			0.005
	Non exposed	0.024	(0.018, 0.032)		0.024	(0.018, 0.031)	
	Exposed	0.077	(0.033, 0.179)		0.081	(0.036, 0.181)	
	Any pesticide			0.010			0.004
	Non exposed	0.024	(0.017, 0.032)		0.023	(0.018, 0.031)	
	Exposed	0.075	(0.033, 0.170)		0.081	(0.038, 0.176)	
Lead[e] (µg/g)	Aromatic hydrocarbon solvents			0.049			0.067
	Non exposed	0.778	(0.626, 0.967)		0.781	(0.628, 0.971)	
	Exposed	1.317	(0.836, 2.09)		1.298	(0.808, 2.084)	
Manganese[f] (µg/g)	Aromatic hydrocarbon solvents			0.073			0.032
	Non exposed	0.233	(0.187, 0.289)		0.228	(0.185, 0.282)	
	Exposed	0.375	(0.237, 0.592)		0.402	(0.256, 0.631)	
	Organochlorine pesticides[d]			0.028			0.062
	Non exposed	0.239	(0.196, 0.291)		0.241	(0.199, 0.293)	
	Exposed	0.491	(0.267, 0.903)		0.445	(0.242, 0.820)	
	Organophosphorus pesticides			0.012			0.030
	Non exposed	0.236	(0.194, 0.287)		0.238	(0.196, 0.290)	
	Exposed	0.519	(0.291, 0.928)		0.470	(0.264, 0.837)	
	Other pesticides			0.013			0.023
	Non exposed	0.235	(0.193, 0.286)		0.237	(0.195, 0.288)	
	Exposed	0.502	(0.287, 0.877)		0.469	(0.270, 0.815)	
	Any pesticide			0.013			0.022
	Non exposed	0.234	(0.192, 0.285)		0.236	(0.194, 0.287)	
	Exposed	0.490	(0.286, 0.841)		0.462	(0.271, 0.788)	
Aluminium[g] (µg/g)	Organochlorine pesticides[d]			0.085			0.141
	Non exposed	9.00	(7.63, 10.63)		9.07	(7.71, 10.66)	
	Exposed	14.44	(8.66, 24.09)		13.53	(8.15, 22.46)	
	Organophosphorus pesticides			0.024			0.054
	Non exposed	8.85	(7.51, 10.44)		8.94	(7.61, 10.51)	
	Exposed	16.04	(9.87, 26.06)		14.75	(9.13, 23.84)	
	Other pesticides			0.050			0.098
	Non exposed	8.90	(7.54, 10.52)		8.99	(7.63, 10.58)	
	Exposed	14.67	(9.17, 23.47)		13.62	(8.57, 21.65)	
	Any pesticide			0.063			0.109
	Non exposed	8.91	(7.53, 10.53)		8.98	(7.71, 10.66)	
	Exposed	14.12	(8.96, 22.25)		13.28	(8.48, 20.78)	
Iron (µg/g)	Aromatic hydrocarbon solvents			0.065			0.018
	Non exposed	14.99	(12.53, 17.93)		14.66	(12.32, 17.45)	
	Exposed	22.52	(15.41, 32.91)		24.57	(16.94, 35.65)	
Vanadium (µg/g)	Aromatic hydrocarbon solvents			0.072			0.040
	Non exposed	0.020	(0.017, 0.025)		0.020	(0.017, 0.025)	
	Exposed	0.032	(0.021, 0.049)		0.034	(0.022, 0.052)	

aGM: Adjusted geometric mean.

[a] Each Model I is adjusted for age and sex.

[b] Each Model II is adjusted for age, sex and total intake (Kcal).

[c] Further adjusted for tobacco smoking (ever/never), and in each Model II also for intake of fresh vegetables and fruit (low, medium and high intake).

[d] The classification includes exposure to organochlorine and arsenical pesticides.

[e] Further adjusted for tobacco smoking (ever/never), and in each Model II also for intake of fish and shellfish (low, medium and high intake).

[f] In each Model II further adjusted for intake of milk, dairy products and butter (low, medium and high intake).

[g] In each Model II further adjusted for intake of fruit (low, middle and high intake).

AHs are found in numerous products (Sexton and Hattis, 2007). In a previous analysis of our study, occupations involving use of solvents included farmers, machine and engine mechanics, sheet-metal workers, service station attendants, machine-tool setters, and painters (Alguacil et al., 2000). In the present report, patients occupationally exposed to AHs had significantly higher concentrations of cadmium, manganese, lead, iron, and vanadium.

Among subjects exposed to pesticides we observed higher levels of cadmium and manganese. Pesticide mixtures can contain different chemical compounds, including trace metals (MacBean, 2012; Sexton and Hattis, 2007). Almost all phosphate fertilisers produced from phosphate rock contain traces of cadmium (Cupit et al., 2002; de Meeûs et al., 2002). However, there are no data about cadmium concentrations in farmers or other exposed populations. Glyphosate-based herbicide mixtures may contain arsenic, chromium, cobalt, lead and nickel (Defarge et al., 2018).

Manganese ethylenebis (maneb) is widely used as fungicide and its toxicity is well known (Houeto et al., 1995). However, there are no

Table 4

Trace element concentrations (µg/g) by occupational exposure assessed by Finnish job-exposure matrix (Finjem).

Trace element concentration (µg/g)	Chlorinated hydrocarbon solvents			Formaldehyde			Volatile sulphur compounds		
	Exposed	Non-exposed		Exposed	Non-exposed		Exposed	Non-exposed	
	(N = 7)	(N = 107)	p-Value	(N = 8)	(N = 106)	p-Value	(N = 18)	(N = 96)	p-Value
Cadmium									
Mean ± standard deviation	0.077 ± 0.119	0.105 ± 0.444	0.870[a]	0.067 ± 0.075	0.106 ± 0.446	0.805[a]	0.072 ± 0.098	0.109 ± 0.468	0.736[a]
Median	0.024	0.031	0.583[b]	0.028	0.030	0.903[b]	0.031	0.029	0.647[b]
Lead									
Mean ± standard deviation	23.68 ± 58.72	1.36 ± 2.52	0.353[a]	20.91 ± 54.92	1.36 ± 2.54	0.348[a]	9.95 ± 36.69	1.38 ± 2.58	0.336[a]
Median	1.13	0.870	0.126[b]	1.52	0.863	0.067[b]	0.778	0.898	0.777[b]
Selenium									
Mean ± standard deviation	0.531 ± 0.093	0.515 ± 0.114	0.712[a]	0.557 ± 0.126	0.513 ± 0.112	0.288[a]	0.543 ± 0.104	0.511 ± 0.114	0.269[a]
Median	0.501	0.515	0.948[b]	0.512	0.513	0.587[b]	0.522	0.513	0.423[b]
Chromium									
Mean ± standard deviation	0.851 ± 0.627	1.15 ± 3.24	0.811[a]	0.830 ± 0.677	1.15 ± 3.25	0.782[a]	1.32 ± 2.02	1.09 ± 3.31	0.781[a]
Median	0.782	0.394	0.222[b]	0.724	0.400	0.399[b]	0.642	0.363	0.071[b]
Manganese									
Mean ± standard deviation	0.510 ± 0.386	0.489 ± 0.792	0.945[a]	0.479 ± 0.384	0.491 ± 0.795	0.965[a]	0.706 ± 0.789	0.450 ± 0.767	0.197[a]
Median	0.375	0.200	0.082[b]	0.318	0.203	0.166[b]	0.381	0.188	0.018[b]
Aluminium									
Mean ± standard deviation	11.15 ± 4.55	14.68 ± 19.30	0.631[a]	11.59 ± 4.46	14.68 ± 19.39	0.655[a]	22.42 ± 30.89	12.97 ± 15.26	0.220[a]
Median	13.43	7.57	0.583[b]	13.47	7.55	0.405[b]	12.54	7.42	0.192[b]
Iron									
Mean ± standard deviation	24.11 ± 10.34	36.97 ± 159	0.831[a]	19.46 ± 9.79	37.44 ± 159	0.751[a]	31.35 ± 34.06	37.08 ± 167	0.885[a]
Median	22.46	12.68	0.076[b]	18.19	12.86	0.351[b]	16.98	12.68	0.181[b]
Vanadium									
Mean ± standard deviation	0.048 ± 0.023	0.040 ± 0.084	0.801[a]	0.045 ± 0.022	0.040 ± 0.084	0.863[a]	0.058 ± 0.070	0.037 ± 0.084	0.300[a]
Median	0.037	0.019	0.013[b]	0.034	0.019	0.014[b]	0.031	0.019	0.033[b]

[a] Student's *t*-test (two-tail).
[b] Mann-Whitney's *U* test (two-tail).

reports on the relationship between maneb exposure and manganese body concentrations. There is a large amount of literature on occupational exposure to aluminium phosphide, but there are no reports of an association between aluminium phosphide exposure and aluminium body concentrations (Sudakin, 2005). Further research should clarify the possible role of manganese and aluminium in EPC risk, mediated and unmediated by exposure to pesticides.

Formaldehyde is used mainly in the production of various resins, as an intermediate in the manufacture of industrial chemicals, and as a disinfectant and preservative in many applications (IARC, 2012). It is an established human carcinogen for cancer of the nasal passages and leukaemia (IARC, 2012), and there is evidence that it also causes a modest increase of EPC risk (Collins et al., 2001; Maisonneuve and Lowenfels, 2015). EPC patients with occupational exposure to formaldehyde had significantly higher levels of arsenic, lead and vanadium. We previously found an association between arsenic and lead and EPC risk (Amaral et al., 2012).

Cases that performed occupations with a risk of exposure to volatile sulphur compounds had significantly higher concentrations of vanadium and manganese. Such compounds are found in a myriad of chemical products. Exposed workers are most common in chemical and metal plating industry plants, where sulphur compounds occur as a by-product; e.g., in the copper smelting industry and in the processing or burning of coal or oil (Amaral et al., 2012). In a previous analysis of our study, an association was apparent for volatile sulphur compounds and EPC (Alguacil et al., 2000).

Significantly higher levels of lead, vanadium and copper were observed in EPC patients who had worked in occupations associated with a risk of exposure to chlorinated hydrocarbon solvents. They are usually released to the environment during the formulation process and through their use in some formulated products such as pesticides. Chlorinated hydrocarbon solvents are considered a major occupational risk factor for EPC (Antwi and Eckert, 2015; Bosch de Basea et al., 2011; Maisonneuve and Lowenfels, 2015; Ojajärvi et al., 2000). To our

knowledge there are no epidemiologic studies showing an association between copper and EPC; thus, there is a need to clarify the role of this trace element in EPC risk, as well as its association with exposure to chlorinated hydrocarbon solvents (Lener et al., 2016; Manousos et al., 1981).

Occupational environments are usually characterized by exposure to complex chemical mixtures rather than to single agents, potentially leading to combined and cumulative toxic exposures. Knowledge on how best monitor complex exposures is limited and, in this sense, the findings here reported suggest possible pathways connecting exposures to chemical mixtures and pathological effects (Silins and Högberg, 2011). The variety of occupational instruments is a strength of the study. ISCO is a standard international classification that allows comparison with past and future similar studies from other countries. It captures exposures related to all tasks performed by a given occupation. Finjem is a job exposure matrix that captures exposure to 21 selected exposures starting with a low probability (5%) of exposure to each agent. Hence, it is a rather sensitive approach. The evaluation by industrial hygienists focused on 22 suspected carcinogens, and the assignment of exposure to each exposure needed high evidence of the presence of the exposure; thus, it can be considered a more specific exposure metric (Alguacil et al., 2000, 2003).

Even though the study sample was small, it adds important information to the body of knowledge on the possible contribution of trace elements to the aetiology of EPC, as previous studies rarely included biomarkers of exposure (Amaral et al., 2012; Collins et al., 2001; Luckett et al., 2012). Only two other studies used an exposure biomarker for cadmium to assess the role of an occupational exposure in EPC (Barone et al., 2016; Kriegel et al., 2006). In contrast, we examined several trace elements. Ours is the first study to analyse the relationship between concentrations of trace elements and occupational history in any human cancer.

An increased risk of EPC has been associated with exposure to chromium and nickel (Antwi and Eckert, 2015; Ojajärvi et al., 2000).

Table 5
Influence on trace element concentrations (µg/g) in pancreatic cancer patients by occupational exposure assessed by the Finnish job-exposure matrix (Finjem).

Trace element	Exposure	Model I[a]			p-Value	Model II[b]			p-Value
		aGM	(95% CI)			aGM	(95% CI)		
Lead[c] (µg/g)	Chlorinated hydrocarbon solvents				0.003				0.004
	Non exposed	0.801	(0.660,	0.973)		0.804	(0.665,	0.973)	
	Exposed	2.80	(1.29	6.08)		2.64	(1.22,	5.72)	
	Formaldehyde				0.002				0.003
	Non exposed	0.794	(0.653,	0.964)		0.797	(0.659	0.964)	
	Exposed	2.72	(1.32,	5.62)		2.58	(1.25,	5.31)	
	Any pesticide				0.060				0.085
	Non exposed	0.835	(0.686,	1.02)		0.838	(0.692,	1.015)	
	Exposed	2.30	(0.816,	6.49)		2.09	(0.751,	5.84)	
Manganese[d] (µg/g)	Volatile sulphur compounds				0.027				0.027
	Non exposed	0.233	(0.190,	0.286)		0.234	(0.191,	0.286)	
	Exposed	0.421	(0.261,	0.678)		0.417	(0.261,	0.667)	
Vanadium (µg/g)	Chlorinated hydrocarbon solvents				0.050				0.039
	Non exposed	0.021	(0.018,	0.026)		0.021	(0.018,	0.026)	
	Exposed	0.045	(0.022,	0.094)		0.047	(0.023,	0.097)	
	Formaldehyde				0.055				0.041
	Non exposed	0.021	(0.018,	0.026)		0.021	(0.018,	0.026)	
	Exposed	0.043	(0.022,	0.084)		0.045	(0.023,	0.088)	
	Volatile sulphur compounds				0.043				0.048
	Non exposed	0.021	(0.017,	0.025)		0.021	(0.017,	0.025)	
	Exposed	0.034	(0.022,	0.054)		0.034	(0.022,	0.053)	
Arsenic[e] (µg/g)	Formaldehyde				0.008				0.017
	Non exposed	0.075	(0.066,	0.085)		0.075	(0.067,	0.085)	
	Exposed	0.143	(0.091,	0.226)		0.137	(0.086,	0.218)	
	Polycyclic aromatic hydrocarbons				0.024				0.024
	Non exposed	0.075	(0.067,	0.085)		0.075	(0.067,	0.085)	
	Exposed	0.128	(0.082,	0.199)		0.128	(0.083,	0.198)	
Copper[f] (µg/g)	Chlorinated hydrocarbon solvents				0.048				0.077
	Non exposed	3.65	(3.37,	3.95)		3.66	(3.38,	3.95)	
	Exposed	5.08	(3.70,	6.98)		4.91	(3.58,	6.74)	
Zinc[g] (µg/g)	Any pesticide				0.003				0.007
	Non exposed	113.4	(107.7,	119.5)		113.6	(107.9,	119.6)	
	Exposed	174.5	(132.7,	229.3)		167.6	(127.2,	220.8)	

aGM: Adjusted geometric mean.
[a] Each Model I is adjusted for age and sex.
[b] Each Model II is adjusted for age, sex and total intake (Kcal).
[c] Further adjusted for tobacco smoking (ever/never), and in each Model II also for intake of fish and shellfish (low, medium and high intake).
[d] In each Model II further adjusted for intake of milk, dairy products and butter (low, medium and high intake).
[e] In each Model II further adjusted for intake of butter (low, medium and high intake).
[f] In each Model II further adjusted for intake of oil in two categories.
[g] In each Model II further adjusted for intake of fish and shellfish (low, middle and high intake).

We did not find differences in toenail concentrations of these elements among subjects with different historical occupational exposures (Supplemental Figs. 1 and 2); e.g., patients with past occupations that potentially entailed exposure to chromium and nickel had similar concentrations of these metals than unexposed patients. One explanation is that no actual exposure to chromium and nickel occurred; hence, exposure to these metals can be misclassified by studies that rely on occupational titles and do not use biomarkers. Another possibility concerns the chemical and oxidative state of the metals, which can affect whether they accumulate inside the body or instead are eliminated (WHO, 2006).

Lipid mobilization and the other metabolic changes that commonly characterize progression of pancreatic cancer (Gasull et al., 2019; Porta et al., 2008b) are unlikely to have had an influence on toenail levels of the trace elements. Unlike blood and urine, hair and nail samples reflect the concentration of elements in the organism over several months, and are thus useful for the evaluation of long term exposure (Golasik et al., 2015). Trace elements in nails are incorporated during their formation (12–18 months) from blood, lymph vessels, body tissues and epidermis; thus, they reflect exposures that have occurred in such months (Goyer and Clarkson, 2001; Hopps, 1977; Slotnick and Nriagu, 2006). However, the rationale for their use in studies on disease aetiology is that the ranking of toenail concentrations in a group of individuals at one point in time will be highly similar to the ranking in the more distant past. Metals in nails come from metabolic processes after formation and thus may be stable markers of past exposure (Hopps, 1977). In our study, a large number of cases were interviewed and had toenail samples drawn soon after their cancer diagnosis. Lack of differences between patients included and excluded in the study further argues against selection bias (Hoppin et al., 2002).

In summary, the present study identifies occupational sources of trace elements; strictly, just in EPC, although the processes may be similar in other diseases. The study also makes a relevant contribution by assessing the extent to which trace elements may explain some occupational risks previously observed for pancreatic cancer.

5. Conclusions

Higher toenail concentrations of several metals were observed in patients occupationally exposed to AHs, pesticides, chlorinated hydrocarbon solvents, formaldehyde, volatile sulphur compounds, and PAHs. The findings suggest that these elements may account for some of the occupational risks previously reported for EPC. Results also show occupations likely to be a source of exposure to metals. Biomarkers of exposure to trace elements may help understand the role of chemical mixtures in the aetiology of EPC and, potentially, of other diseases.

Declarations of interest

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Appendix A. Supplementary data

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