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Exposure to environmental chemicals and heavy metals, and risk of pancreatic cancer

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Abstract

Purpose—Exposure to various chemicals and heavy metals has been associated with risk of different cancers; however, data on whether such exposures may increase the risk of pancreatic cancer (PC) are very limited and inconclusive. We examined PC risk with self-reported exposures to chemicals and heavy metals.

Methods—The design was a clinic-based, case–control study of data collected from 2000 to 2014 at Mayo Clinic in Rochester, Minnesota, USA. Cases were rapidly ascertained patients diagnosed with pancreatic ductal adenocarcinoma ($n = 2,092$). Controls were cancer-free patients in primary care clinics ($n = 2,353$), frequency-matched to cases on age, race, sex, and state/region of residence. Cases and controls completed identical risk factor questionnaires, which included yes/no questions about regular exposure to pesticides, asbestos, benzene, chlorinated hydrocarbons, chromium, and nickel. Unconditional logistic regression was used to estimate odds ratios (ORs) and 95 % confidence intervals (CI) comparing those who affirmed exposure to each of the chemicals/heavy metals to those who reported no regular exposure, adjusting for potential confounders.

Results—Self-reported regular exposure to pesticides was associated with increased odds of PC (OR 1.21, 95 % CI 1.02–1.44). Regular exposure to asbestos (OR 1.54, 95 % CI 1.23–1.92), benzene (OR 1.70, 95 % CI 1.23–2.35), and chlorinated hydrocarbons (OR 1.63, 95 % CI 1.32–

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Compliance with ethical standards

Conflict of interest The authors have no conflict of interest to disclose. Written informed consent was obtained from all participants. This study was approved by the Mayo Clinic Institutional Review Board.

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 was obtained from all individual participants included in the study.

2.02) also was associated with higher odds of PC. Chromium and nickel exposures were not significantly associated with PC.

Conclusions—These findings add to the limited data suggesting that exposure to pesticides, asbestos, benzene, and chlorinated hydrocarbons may increase PC risk. They further support the importance of implementing strategies that reduce exposure to these substances.

Keywords

Pancreatic cancer; Pesticides; Chlorinated hydrocarbons; Asbestos; Benzene

Introduction

Pancreatic cancer (PC) is the eleventh most commonly diagnosed cancer among men and ranks eighth among women in the USA, yet it is the fourth most common cause of cancer-related death in each sex and in both groups combined [1]. Typical of solid tumors, the incidence of this rapidly fatal malignancy increases with age. Most PC cases are diagnosed between the sixth and eighth decades of life and have a dismal 5-year survival rate of 7 % [1]. The majority of pancreatic tumors (>90 %) are ductal adenocarcinomas that arise from high-grade pancreatic intraepithelial neoplasia and are associated with worse prognosis [2, 3]. Though the etiology of PC is not well understood, genetic factors are thought to account for ~ 10 % of all PC cases [4]. The remaining 90 % has been attributed to nongenetic factors such as cigarette smoking and exposure to chemicals and heavy metals, benign diseases such as long-standing type II diabetes and chronic pancreatitis, and dietary factors [5–9]. Cigarette smoking is the only environmental factor that has been causally linked to PC [4–6]. The role of environmental exposure to chemicals and heavy metals remains unclear.

Several studies have linked PC incidence to work-related exposure of various chemicals and metals, such as pesticides, asbestos, benzene, chlorinated hydrocarbons, chromium, and nickel [10–15]. The mechanisms by which such exposures may lead to PC are not completely understood. It is thought that these substances may reach the pancreas through the bloodstream or via refluxed bile and, in the process, exert genotoxic effects including altered methylation, oncogene activation, inactivation of tumor-suppressor proteins, and formation of DNA adducts [16, 17]. A meta-analysis of occupational exposures and PC risk covering 92 studies [10] reported excess risk of PC associated with exposure to chlorinated hydrocarbon solvents and nickel, as well as suggested increased risk of exposure to other substances including chromium and organochlorine pesticides. Occupational studies published since this meta-analysis have also linked chlorinated hydrocarbons, chromium, and nickel exposures to pancreas carcinogenesis [18–20]. Increased PC risk has been reported among agricultural workers exposed to pesticides [14, 21–25], although not consistent [26–28]. Data regarding the relationship between asbestos and benzene exposures and PC are substantially less and equivocal [10, 15, 29].

Occupational exposures may explain only a portion of PC cases attributable to environmental chemicals and heavy metals because these exposures are also prevalent in nonoccupational settings (e.g., residence) [30]. Few studies have examined associations between PC and such environmental exposures in nonoccupational setting [31–33];

however, due to the rarity of PC, these studies have been universally limited by small numbers of PC cases and evaluation of few environmental factors. We therefore examined associations between environmental exposure to pesticides, asbestos, benzene, chlorinated hydrocarbons, chromium, and nickel and PC risk in a large, clinic-based, case-control study in Rochester, MN.

Materials and methods

Study population

This study was approved by the Mayo Clinic Institutional Review Board. The study population has been described in detail [8]. In brief, patients with a histologically confirmed pancreatic ductal adenocarcinoma evaluated at Mayo Clinic between 6 October 2000 and 29 December 2014 were approached to participate in a prospective PC registry using an ultra-rapid case ascertainment system described previously [34]. Controls were healthy patients from Mayo Clinic Primary Care clinics who did not have a personal history of cancer (except nonmelanoma skin cancer) and were recruited between 25 May 2004 and 20 March 2012. Controls were frequency-matched to cases based on age (± 5 years), race, sex, and state/region of residence [within Olmsted County in Rochester, MN; within one of the three states (IA, MN, WI); or outside region]. Written informed consent was obtained from all participants. Consenting cases ($n = 2,092$) and controls ($n = 2,353$) completed comprehensive questionnaires that included demographic information, self-report of usual adult weight and height, health behaviors such as cigarette smoking history, and self-reported diagnosis of diabetes mellitus (type II). Body mass index (BMI) was estimated from usual adult weight and height as kg/m^2 .

Chemicals/heavy metals exposure ascertainment

Participants completed identical risk factor questionnaires that solicited information on various environmental exposures. The participants were asked the following question: *Are/Were you ever regularly exposed to any of the following substances?* Formatted as a list with “Yes” and “No” check boxes: asbestos; chlorinated hydrocarbons, solvents or related compounds; chromium/chromium compounds; nickel/nickel compounds; insecticides/pesticides; benzene or derivative; or other (open-ended). These questions were designed to capture both work-related and nonwork-related exposures. Participants were also asked whether they usually worked indoors, outdoors, or spent about an equal amount of time indoors and outdoors (i.e., *In your work, where do/did you spend more time?*). Responses were used to categorize participant work exposure status.

Analytic sample

Of the total sample of 4,445 participants, 234 ($n = 199$ cases; $n = 35$ controls) had missing data on all of the exposures under study and three participants had missing data on smoking history or education level (cases: $n = 1$; and controls: $n = 2$). These participants were excluded (Supplemental Table 1), leaving a final sample of 4,208 for analysis (cases: $n = 1,892$; controls: $n = 2,316$). Two participants had missing data on race; however, because the study consisted of individuals of mainly European descent ($\sim 98\%$), we imputed their race as “White” and they were retained in the analysis. In the analytic sample, 413 participants

(~10 %; $n = 247$ cases, $n = 166$ controls) had missing data on at least one of the exposures of interest. Of the 413 participants, 364 ($n = 217$ cases; $n = 147$ controls) responded “yes” to at least one other exposure of interest, and 49 ($n = 30$ cases; $n = 19$ controls) did not have a “yes” response to any of the exposures on the list. To maximize sample size, we imputed a “no” response for the exposure(s) with missing response only for the 364 participants with a “yes” response to another exposure under study. This decision was based on the assumption that participants did not provide affirmative responses for the chemicals and heavy metals to which they were uncertain of being regularly exposed, and were likely not regularly exposed to the respective agent(s). Sensitivity analysis was conducted to evaluate the impact of this imputation. Missing information on the remaining 49 participants was retained as “missing” in all analyses.

Statistical methods

Unconditional logistic regression was used to estimate odds ratios (ORs) and 95 % confidence intervals (CIs) in age-and multivariable-adjusted models. The multivariable models adjusted for the following known or suggested risk factors for PC: age, sex, smoking status, personal history of diabetes, BMI and education, measured as continuous or categorical variables as presented in Table 1. In each model, patients who reported no regular exposure to asbestos, chlorinated hydrocarbons, chromium, nickel, insecticides/pesticides (hereafter referred to generally as pesticides), and benzene were used as the referent group to estimate the odds of PC for those affirming exposure to the respective substance. We also explored associations between usual working environment [i.e., indoor (referent group), outdoor, about equal] and PC. Stratified analysis by working environment was performed to examine whether associations between chemicals/heavy metals exposure and PC varied by usual working environment, including evaluation of the interaction between working environment and exposure status in multivariable-adjusted models. All statistical analyses were performed using SAS[®] version 9.3, with statistical significance set at $\alpha = 0.05$ (two-sided).

Results

Characteristics of the 1,892 pancreatic ductal adenocarcinoma cases and 2,316 controls are presented in Table 1. While cases were approximately 1 year older than controls (65.7 vs. 64.7 years), they were similar in race and sex. A greater proportion of cases reported a physician-diagnosed diabetes history, ever-smoking (defined by ≥ 100 cigarettes in a lifetime), and lower levels of education compared to controls. Cases had also marginally higher BMI than controls.

Table 2 presents associations between self-reported regular exposure to chemicals/heavy metals and risk of PC. After adjusting for age, sex, smoking, diabetes, BMI, and education, self-reported regular exposure to pesticides (including insecticides, fungicides and herbicides) was associated with a 21 % increased odds of PC (OR 1.21, 95 % CI 1.02–1.44). The odds of being diagnosed with PC were also higher among patients who reported regular exposure to asbestos (OR 1.54, 95 % CI 1.23–1.92), benzene (OR 1.70, 95 % CI 1.23–2.35), and chlorinated hydrocarbons (OR 1.63, 95 % CI 1.32–2.02). There was a suggestive,

although not statistically significant, association between affirmation of regular exposure to chromium and nickel and PC with ORs of 1.42 (95 % CI 0.89–2.26) and 1.55 (95 % CI 0.95–2.52), respectively. No association was observed between usual working environment (indoor/ outdoor) and PC risk.

We further examined whether the associations between reported exposures to chemicals/ heavy metals and PC differed by working environment. No compelling evidence of effect modification was observed, except for the association between pesticides exposure and PC, which was confined to those who reported that they usually worked indoors (OR 1.48, 95 % CI 1.17–1.89, $p_{\text{interaction}} = 0.01$) (Table 3).

A sensitivity analysis was performed to evaluate the impact of the strategy for dealing with missing exposure data. Instead of imputing “no” regular exposure response for patients with at least one affirmative response to a question on chemicals and heavy metals, but who were missing data on other exposures, the missing information was retained as “missing,” and consequently those patients were eliminated from the analysis. Conclusions from this analysis (Supplemental Table 2) were similar to those reported in Table 2, though the imputation of no regular exposure response for the patients with missing data resulted in attenuated OR estimates.

Discussion

The results from this clinic-based, case–control study suggest that regular exposure to pesticides, asbestos, benzene, and chlorinated hydrocarbons may be associated with PC risk. Suggestions of an increased risk of PC also were observed among patients who affirmed regular exposure to chromium and nickel, though not statistically significant. There was no apparent association between usual working environment (indoor/outdoor) and PC risk.

These results support earlier observations linking environmental chemicals and heavy metals exposure to PC [10–15]. In a hospital-based case–control study conducted in Egypt, Lo et al. [31] observed a suggestive increased risk of PC among patients who had been ever exposed to pesticides (OR 2.6, 95 % CI 0.97–7.2). Excess risk of PC has also been associated with self-reported exposure to organochlorine pesticides, including ethylan and dichlorodiphenyltrichloroethane (DDT), in a case–control study in Michigan [32] and with occupational exposure to pesticides in a multicenter US population-based study [25]. In a case–control study nested in the Agricultural Health Study cohort in Iowa and North Carolina, Andreotti et al. [14] reported a null association between exposure to pesticides in general and PC risk. However, when specific types of pesticides were examined among licensed pesticides applicators, increased risks of PC were observed among those exposed to pendimethalin (OR 3.0, 95 % CI 1.3–7.2) and S-ethyl dipropylthiocarbamate (EPTC) (OR 2.6, 95 % CI 1.1–5.4) compared to those who had never been exposed to either of these pesticides [14]. There are other reports of increased risk of PC among agricultural pesticides users [10, 13] and workers handling pesticides [23, 24, 35], as well as higher risk of death from PC among aerial pesticides applicators (mortality rate ratio 2.7, 95 % CI 1.4–5.3) when compared to flight instructors [36]. Although others have found no association between pesticides exposure and PC [26, 28, 37], most of these studies were limited by small

numbers of PC cases. While we observed no association between usual working environment and PC, the association between pesticides exposure and PC was confined to patients reporting that they mostly work indoors. Given that the study participants were asked about pesticides exposure in general, which includes insecticides, herbicides, and fungicides, it is possible that this finding may reflect exposure to insecticides rather than herbicides or fungicides. Alternatively, it could be a function of sample size, since the majority of participants (74 %) reported that they mostly worked indoors.

Chlorinated hydrocarbons, a group of organic compounds consisting of chlorine, hydrogen, and carbon molecules found in a broad spectrum of pesticides, industrial chemicals, and plastics, have been associated with a number of malignancies, including PC [11, 15, 38]. Consistent with our finding, exposure to chlorinated hydrocarbons has been associated with an increased risk of pancreatic ductal adenocarcinoma (OR 4.1, 95 % CI 1.1–15.2), with a positive linear trend for increasing duration of exposure (p trend = 0.04) in a hospital-based case-control study in Spain [18]. A meta-analysis involving five studies also observed significant association between exposure to chlorinated hydrocarbons and PC risk [39]. Results from three other meta-analyses covering studies published from 1969 to 1998 performed by the same group [10–12] also demonstrated associations between chlorinated hydrocarbons and PC. The first reported a marginally significant association between chlorinated hydrocarbons exposure and PC [meta-risk ratio (MRR) 1.4, 95 % CI 1.0–1.80] [10]. The second, which examined specific chlorinated hydrocarbon solvents, found suggestive increased risks of PC for exposure to poly-chlorinated biphenyls, vinyl chloride, methylene chloride, trichloroethylene, and tetrachloroethylene [11]. The most recent analysis, which adopted a Bayesian hierarchical modeling approach, observed an over twofold increased risk of PC among subjects with occupational exposure to chlorinated hydrocarbon solvents (MRR 2.21, 95 % CI 1.2–3.6). A more recent review of the literature that covered studies published between 1998 and 2010 also suggests that chlorinated hydrocarbons may be important modifiable risk factors for PC [15].

Increased risks of PC have been associated with exposure to chromium and nickel [10, 15, 20], although study results have varied [19, 40]. The current study suggests that regular exposure to these heavy metals may increase the risk of pancreatic ductal adenocarcinoma, but these associations were not statistically significant—possibly due to the relatively low prevalence of these exposures in this study. However, we observed significant associations between reported exposure to asbestos and benzene and PC. The International Agency for Research on Cancer (IARC) classifies asbestos and benzene as “carcinogenic to humans,” but indicates that there is no sufficient evidence in humans to show that they are site-specific carcinogens for the pancreas [41]. It is worth noting that while asbestos has been studied extensively in relation to other malignancies, particularly lung cancer and mesothelioma [42, 43], relatively little is known about its relation to PC. Some [44, 45], but not all [10, 46], studies have demonstrated association between asbestos exposure and PC. Similarly, benzene, a volatile aromatic compound ubiquitous in tobacco smoke, coal tar, and petroleum products [47], has been studied less in relation to PC. Exposure to benzene has been associated with a higher frequency of *K-ras* mutations in pancreatic tumors [48]. Higher levels of benzene have also been found in bile aspirates of PC patients than in patients with

benign biliary conditions [49]. Nonetheless, the data relating to benzene exposure and PC are not entirely consistent [10, 15, 29]. Thus, despite the significant association reported here, additional work is needed to help clarify the role of asbestos and benzene in PC, optimally involving evaluation of dose–response relationships and assessment of latency between exposure and onset of clinical symptoms of PC.

Inherent to all case–control studies, recall bias is a limitation of this study. Two methods were used to minimize recall bias in this study. First, a standardized risk factor questionnaire was utilized to solicit exposure information from both the cases and controls. This ensured that the cases and controls had comparable opportunity for recall of the exposures of interest. Second, cases and controls were recruited from sectors of the same health system with similar referral pattern [34]. The cancer-free control patients were unaware of the outcome of interest, and thus differential recall bias is less likely; nondifferential exposure misclassification might have occurred, biasing ORs toward null [50]. Additionally, we examined the pattern of responses to the open-ended question on chemicals and heavy metals exposure: other (open-ended). While the frequency of the list of exposures provided by respondents was too few for independent evaluation of their association with PC, no significant differences were observed between case and controls ($p > 0.05$). Nonetheless, the use of clinic-based cases and controls precludes generalizability of findings to the broad population outside the clinic setting. Another limitation of concern is the potential for selection bias resulting from the exclusion of approximately five percent ($n = 234$) of the study participants (after frequency matching) who had missing data on exposure history. Compared to those included in the analysis, the excluded participants consisted of a greater proportion PC cases, females, ever-smokers, and they tended to have lower levels of education (Supplemental Table 1). Depending on the nature of exposure distribution in this group, the exclusion of these subjects may have biased the study results somewhat, either toward or away from null [50]. The study questionnaire did not provide a lay explanation of exposures such as chlorinated hydrocarbons. Participant lack of understanding could have biased the results toward null to some extent. It is also worth noting that we imputed a “no” regular exposure response for missing information on approximately 9 % ($n = 364$) of the research subjects who had missing data on one or more of the chemicals or heavy metals under study. Sensitivity analysis subsequently indicated that the assignment of “no” exposure response for these subjects may have resulted in more conservative OR estimates. Even though it would have been desirable to examine occupational exposures, the data needed for such analysis, which requires job titles, detailed description of job functions, and duration, was not available. The available data (based on broad job categories) did not permit such analyses.

Major strengths of the study include its large sample size, particularly the large number of PC cases. The use of an ultra-rapid case ascertainment system to recruit PC cases during or shortly after their initial clinic visit for evaluation [34] also minimizes the potential effect of survival bias and allowed solicitation of information directly from patients rather than from proxy respondents. Adjusting for several known or suspected risk factors for PC, including diabetes, smoking status, and BMI, also adds to the study strengths. Future work that accounts for exposure–response associations, latency between exposure and clinical

diagnosis, and evaluation of environment exposures in tandem with genetic variation in carcinogen-metabolizing genes would help unravel how these exposures may be influencing PC risk.

In summary, we observed significant associations between self-reported regular exposure to pesticides, asbestos, benzene, and chlorinated hydrocarbons and risk of PC. There also were suggestions toward increased risk of PC among patients affirming regular exposure to chromium and nickel. These findings lend support for a role of environmental chemicals and heavy metals in the etiology of PC and further support the need for strategies to reduce exposure to these substances.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

BMI	Body mass index
CI	Confidence interval
DDT	Dichlorodiphenyltrichloroethane
EPTC	S-ethyl dipropylthiocarbamate
MRR	Meta-risk ratio
NSAIDS	Nonsteroidal anti-inflammatory drugs
OR	Odds ratio
PC	Pancreatic cancer

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Table 1

Characteristics of pancreatic ductal adenocarcinoma cases and controls included in the final analysis

	Cases <i>n</i> = 1,892	Controls <i>n</i> = 2,316
Age (years) ^a		
Mean (SD)	65.7 (10.4)	64.7 (10.5)
Median	66.0	65.0
Q1, Q3	59.0, 74.0	58.0, 73.0
Range	(20.0–91.0)	(29.0–94.0)
Race		
White	1,855 (98.0 %)	2,275 (98.2 %)
Other	37 (2.0 %)	41 (1.8 %)
Sex		
Female	841 (44.5 %)	1,084 (46.8 %)
Male	1,051 (55.5 %)	1,232 (53.2 %)
Diabetes mellitus type II		
No	1,326 (70.1 %)	2,060 (88.9 %)
Yes	566 (29.9 %)	256 (11.1 %)
Smoking ^b		
Never	813 (43.0 %)	1,287 (55.6 %)
Ever	1,079 (57.0 %)	1,029 (44.4 %)
Education level		
Less than high school education	114 (6.0%)	68 (2.9 %)
High school graduate	584 (30.9 %)	538 (23.2 %)
Some college	459 (24.3 %)	552 (23.8 %)
College graduate	404 (21.4 %)	543 (23.4 %)
Postgraduate education	331 (17.5 %)	615 (26.6 %)
BMI (kg/m ²)		
Mean (SD)	28.3 (5.3)	27.4 (5.0)
Median	27.5	26.6
Q1, Q3	24.7, 31.1	24.2, 29.7
Range	(16.5–56.1)	(16.9–75.9)

BMI, body mass index; SD, standard deviation; Q1, 25th percentile; Q3, 75th percentile; range, (minimum–maximum)

^a Age at diagnosis (cases) or at the time of consent/recruitment (controls)^b Never defined as <100 cigarettes in lifetime; ever, 100 cigarettes in lifetime

Table 2

Odds ratio (OR) and 95 % confidence intervals (CI) for associations between chemicals/heavy metals exposure and risk of pancreatic ductal adenocarcinoma

	Cases <i>n</i> = 1,892	Controls <i>n</i> = 2,316	Age-adjusted OR (95 % CI)	Multivariable-adjusted OR (95 % CI) ^a
Pesticides				
No	1,497	1,934	1.00 (ref)	1.00 (ref)
Yes	381	374	1.29 (1.11–1.52)	1.21 (1.02–1.44)
Missing	14	8		
Asbestos				
No	1,643	2,127	1.00 (ref)	1.00 (ref)
Yes	240	178	1.75 (1.42–2.14)	1.54 (1.23–1.92)
Missing	9	11		
Benzene				
No	1,770	2,236	1.00 (ref)	1.00 (ref)
Yes	105	76	1.75 (1.29–2.37)	1.70 (1.23–2.35)
Missing	17	4		
Chlorinated hydrocarbons				
No	1,599	2,113	1.00 (ref)	1.00 (ref)
Yes	279	199	1.86 (1.54–2.26)	1.63 (1.32–2.02)
Missing	14	4		
Chromium				
No	1,830	2,274	1.00 (ref)	1.00 (ref)
Yes	49	37	1.68 (1.09–2.58)	1.42 (0.89–2.26)
Missing	13	5		
Nickel				
No	1,832	2,276	1.00 (ref)	1.00 (ref)
Yes	46	34	1.72 (1.10–2.70)	1.55 (0.95–2.52)
Missing	14	6		
Where spent most time during work				
Indoor	1,334	1,744	1.00 (ref)	1.00 (ref)
Outdoor	225	213	1.36(1.11–1.66)	1.16 (0.92–1.47)
About equal	307	323	1.22 (1.02–1.44)	1.06 (0.87–1.28)
Missing	26	36		

^a Adjusted for age, sex, smoking, diabetes, body mass index, and education

Table 3

Associations between chemicals/heavy metals exposure and pancreatic cancer risk, stratified by working environment

	Indoor n = 3,078			Outdoor n = 438			About equal n = 630			Interaction* p value
	Cases	Controls	OR (95 % CI) ^a	Cases	Controls	OR (95 % CI) ^a	Cases	Controls	OR (95 % CI) ^a	
Pesticides										
No	1,144	1,580	1.00 (ref)	104	87	1.00 (ref)	223	234	1.00 (ref)	0.01
Yes	182	159	1.48 (1.17–1.89)	117	125	0.77 (0.50–1.17)	82	87	1.07 (0.73–1.58)	
Missing	8	5		4	1		2	2		
Asbestos										
No	1,192	1,629	1.00 (ref)	194	188	1.00 (ref)	231	275	1.00 (ref)	0.54
Yes	135	105	1.55 (1.16–2.06)	31	24	1.15 (0.62–2.15)	74	48	1.83 (1.17–2.86)	
Missing	7	10		0	1		2	0		
Benzene										
No	1,263	1,692	1.00 (ref)	207	202	1.00 (ref)	274	306	1.00 (ref)	0.40
Yes	59	49	1.61 (1.07–2.43)	16	11	1.23 (0.52–2.91)	30	16	2.34 (1.17–1.68)	
Missing	12	3		2	0		3	1		
Chlorinated hydrocarbons										
No	1,159	1,620	1.00 (ref)	183	182	1.00 (ref)	232	275	1.00 (ref)	0.41
Yes	164	120	1.77 (1.35–2.32)	41	31	1.08 (0.62–1.89)	73	48	1.64 (1.05–2.57)	
Missing	11	4		1	0		2	0		
Chromium										
No	1,294	1,717	1.00 (ref)	218	210	1.00 (ref)	292	311	1.00 (ref)	0.67
Yes	30	23	1.48 (0.81–2.69)	6	3	2.28 (0.52–10.00)	13	11	0.98 (0.40–2.41)	
Missing	10	4		1	0		2	1		
Nickel										
No	1,293	1,717	1.00 (ref)	220	211	1.00 (ref)	293	312	1.00 (ref)	0.70
Yes	31	22	1.77 (0.96–3.24)	3	2	1.86 (0.29–11.97)	12	10	1.03 (0.40–2.64)	
Missing	10	5		2	0		2	1		

^a Adjusted for age, sex, smoking, diabetes, body mass index, and education

* Interaction between exposure variable and working environment in multivariable-adjusted models