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Occupational exposures and risk of pancreatic cancer

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Abbreviations:

Chlorinated Hydrocarbon Solvents (CHC)

Confidence Intervals (CI)

Exocrine Pancreatic Cancer (EPC)

Finnish job-exposure matrix (FINJEM)

Odds ratio (OR)

Odds ratio for the highest level of exposure (OR_h)

Odds ratio restricted to men (OR men)

Odds ratio restricted to women (OR women)

Polycyclic Aromatic Hydrocarbons (PAH)

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ABSTRACT

The objective was to analyze the relationship between occupation (and specific occupational exposures) and risk of exocrine pancreatic cancer (EPC). We conducted a multicenter hospital-based case-control study in Eastern Spain. We included 161 incident cases of EPC (59.6% men, 94 with histological confirmation, of whom 80% had ductal adenocarcinoma). Cases were frequency-matched with 455 controls by sex, age and province of residence. Information was elicited using structured questionnaires. Occupations were coded according to the Spanish version of the International Standard Classification of Occupations 1988. Occupational exposure to a selection of carcinogenic substances was assessed with the Finnish Job-Exposure Matrix (FINJEM). Odds ratios (OR) and 95% confidence intervals (CI) were estimated by multiple logistic regression, adjusting for sex, age, province, education, alcohol and smoking. A higher risk of EPC was associated with having worked as 'Miners, shotfirers, stone cutters and carvers', 'Machinery mechanics and fitters', 'Building trades workers' and 'Motor vehicle drivers' in men, 'Office Clerks' in women, and 'Waiters' in both sexes. Cases with ductal adenocarcinomas were more likely to have been exposed to chlorinated hydrocarbon solvents (OR = 4.1, 95% CI: 1.1-15.2, p-trend = 0.04). We also observed significant associations with exposure to 'synthetic polymer dust exposure' and 'ionizing radiation'. Suggestive increases in risk were observed for 'pesticides', 'diesel and gasoline engine exhaust', and 'hydrocarbon solvents'. Results support the hypothesis that occupational exposure to chlorinated hydrocarbon solvents is associated with exocrine pancreatic cancer.

INTRODUCTION

The etiology of exocrine pancreatic cancer (EPC) remains largely unknown. The only firmly established and modifiable risk factor is smoking, but it explains only a fraction of cases [1], and the association seems somewhat weaker in Mediterranean countries [2, 3]. Factors that probably cause moderate increases in risk include age, diabetes, chronic pancreatitis, and obesity [1].

The highest incidence and mortality rates of pancreatic cancer are found in developed countries [4]. Pancreatic cancer is the fourth leading cause of cancer death in the United States [5], and the sixth leading cause of cancer death in Europe [6]. Although mortality rates had been low in Spain, mortality increased in both sexes over the past 40 years [7], most likely due to a combination of an improvement in death certification and changes in lifestyle and environmental factors.

A wide spectrum of occupational exposures has been related to an increased risk of EPC [1,9]. A meta-analysis on occupation and EPC suggested that some occupational exposures –like chlorinated hydrocarbon solvents, other organic solvents, chromium, nickel, silica, and organochlorine insecticides– may increase the risk [9, 10]. Other specific agents that might increase EPC risk include asbestos and ionising radiations [1]. Among the specific agents assessed in epidemiologic studies, chlorinated hydrocarbon solvents is probably the exposure that has been most consistently associated with EPC [11]. In Spain, the association between occupation and EPC has been addressed by one study, which suggested increased risks for pesticides, aniline derivatives, dyes and organic pigments, and benzo[a]pyrene [12-14].

In this study we evaluated the association between risk of EPC and occupational exposures in Spain. We also explored the association between specific agents and exposures through the Finnish job-exposure matrix (FINJEM).

MATERIAL AND METHODS

Subjects

This research was part of the PANESOES study, a hospital-based case-control study designed to explore the influence of major lifestyles and diet on the risk of three gastrointestinal cancers: pancreas, oesophagus and stomach. Details of this study have been published elsewhere [15, 16]. The PANESOES Study planned to recruit approximately 200 cases for oesophagus cancer, 200 for pancreatic cancer, 400 cases for stomach cancer, and 450 controls frequency matched to the expected distribution of case subjects of the overall PANEOES study by sex, age and province (Alicante, Valencia). Eligible subjects were Spanish-speaking men and women, 30-80 years old, and hospitalized between January 1995 and March 1999 in any of nine participant hospitals in the provinces of Alicante and Valencia, in the Mediterranean part of Spain. All subjects were informed of the study objectives and gave their informed consent prior to their inclusion in the study. Research protocols were approved by the local ethics and/or research committees of the participating Hospitals and the University.

One-hundred and sixty-one incident cases were finally included (96 men and 65 women) out of the 199 cases initially diagnosed as EPC. Twelve cases (ten men and 2 women) could not be interviewed due to their poor health status or refusal to participate in the study. Twenty five cases were excluded for lack of diagnosis consensus by a panel of clinical experts on pancreatic diseases, and one case did not answer the occupational exposure section of the questionnaire. Diagnosis was obtained by histological confirmation in 95 cases (76 ductal adenocarcinoma and 19 other histologies) and consensus from clinical evidence by an expert group (AC, EMO, JV) in the remaining 67 cases. Cases and controls were recruited concurrently. A wide inclusion criterion was used to select controls from diseases not related a priori to the main exposures of interest (tobacco, alcohol and diet). The overall participation rate of the 457 eligible controls was 99.6%, leaving 455 control subjects with completed interviews for analyses. The distribution of the main diagnostic groups for controls was: hernias (28.3%), fractures or injuries (35.2%), appendicitis (6.4%), eventrations (5.5%), acute cholecystitis (2.6%), and other diagnoses (21.9%).

Exposure assessment

Face-to-face interviews were conducted in-hospital for all participants by trained interviewers, using a structured questionnaire. Eighty-eight percent of the interviews with cases were conducted with the patient (62% with the patient alone and 26% with the patient receiving help from a relative) whereas in controls, 70% were performed alone and 26% with help. Proxies provided information

for the other cases and controls. While interviewers could not be blinded to the case/control status, they were unaware of the main study hypothesis and were trained to administer strictly the structured questionnaires in an equal manner to cases and controls alike.

We collected information on demographic characteristics, tobacco and alcohol use, medical history, other lifestyle factors and occupational history. The interview elicited details on usual tobacco use including tobacco type and the age at which the habit started and stopped. A “never smoker” was defined as someone who had smoked fewer than 100 cigarettes or less than one cigarette per day for one year. A “former smoker” was defined as someone having stopped smoking 1 or more years before the interview. Alcohol consumption patterns were assessed through inquiries into the usual intake of alcoholic beverages. A “never drinker” was someone having consumed less than one drink per month. A “former drinker” was defined as having stopped drinking at least one year before the interview.

Information was elicited for the two main occupations for each person: job title, number of years worked and the products and/or substances that were used in each occupation. Where there was any doubt about the two main occupations, information on a third occupation was collected. Main occupations were defined as those occupations in which a subject had worked longest. All reported occupations were coded according to the Spanish National Classification of Occupations of 1994 (CNO94), which is based on the European Union version of the International Standard Classification of Occupations, ISCO 88 (COM). The coding process was carried out by an occupational physician (MS) who was blinded to the case-control status of the study subjects. The proportions of cases and controls reporting one, two or three occupations were very similar ($p = 0.57$). The median of the total number of worked years was 39.9 (SD = 15.7) in cases and 38.4 (SD = 14.8) in controls ($p = 0.29$).

In addition, we used the FINJEM job exposure matrix [17] to explore occupational exposure to 21 chemical agents, four physical exposures, and two ergonomic exposures. Exposure in FINJEM is characterised by two metrics: the prevalence (probability) of exposure (range 0.06-1) and the average level of exposure (intensity) for each analysed agent (mostly in mg/m^3 or in ppm). We used their product as the exposure metric to classify exposure to each agent in three categories: substantial (high), low, and unexposed. The cut-off points between low and substantial were set as close as possible to the 75th percentile of the distribution of the product of the probability and the intensity of exposure in controls.

Statistical analyses

We only estimated the risk of EPC for occupations held for at least one year. In addition, we only estimated the effects of job titles with at least 10 exposed subjects, combining cases and controls (5 subjects for *a priori* high risk occupational groups), ascending from the more general one-digit classification of major occupational groups to the more specific four-digit classification of occupations (subcategories). The reference group comprised subjects who had never been in the occupation of interest [12]. We performed analyses for all types of EPC combined, and for ductal adenocarcinoma. We also repeated the analyses for exposures of at least 15 years.

Adjusted odds ratios (OR) and 95% confidence intervals (CI) were calculated using unconditional logistic regression [18, 19]. All regression models were built to include categorical covariates for the three frequency matched factors: sex (men, women), age (<60 years, 60-70 and >70 years), and hospital origin (Valencia/Alicante). We also forced the inclusion of categorical covariates for known risk factors of pancreatic cancer: educational level (<primary, primary completed, and high school or higher), tobacco smoking, and alcohol consumption. Other possible confounding variables were also retained in the models when they materially altered the estimates. Final models were chosen coherently with the nature of the variables and the study objectives. Tests for trend in the ORs across exposure strata were calculated through logistic models that included categorical terms as continuous variables, with each model including all potential confounders. For trend-tests, we used the likelihood ratio test statistic with one degree of freedom. The level of statistical significance was set at 0.05 and all tests were two-tailed. All analyses were performed with SPSS v.13.0.

RESULTS

EPC cases were on average 2.5 years older than controls ($p=0.01$), presented a similar distribution by sex and educational level, and reported a higher prevalence of cigarette smoking ($p=0.009$) and a slightly higher prevalence of alcohol consumption ($p=0.12$) than controls.

Table 1 shows risk estimates for a selection of job-titles by gender. Most associations were stronger after restricting the analyses to cases with histologically confirmed adenocarcinoma: 'building finishers and related trades workers (CNO94 code 72)' (OR men = 3.58; 95% CI: 1.03-12.44), 'miners, shotfirers, stone cutters and carvers (code 742)' (OR men = 8.14; 95% CI: 1.55-42.68), 'machinery and electrical and electronic equipment mechanics and fitters (code 76)' (OR men = 3.61; 95% CI: 1.24-10.47) and 'heavy truck and lorry drivers (code 863)' (OR men = 3.46; 95% CI: 1.01-11.83). Although they were not statistically significant, in men suggestive associations were also found for 'employed skilled workers in agricultural activities (code 602)' (OR men = 2.35; 95% CI: 0.51-10.92), 'fibre preparers (code 7931)' (OR men = 3.42; 95% CI: 0.62-18.71), 'wood-processing-plant operators (code 8141)' (OR men = 2.38; 95% CI: 0.35-16.17), and 'metal and mineral products machine operators (code 831)' (OR men = 3.20; 95% CI: 0.78-13.01). In women, an increase of risk was observed among 'other office clerks (code 43)' (OR women = 14.20; 95% CI: 1.16-173.67). In all of these job-titles, associations were similar or increased slightly when analyses were restricted to occupations held for at least 15 years (data not shown).

Table 2 shows risk estimates for specific occupational exposures evaluated by FINJEM in both sexes. A positive association was apparent for high exposure to chlorinated hydrocarbon solvents: the odds ratio for the highest level of exposure (OR_h) was 1.99 (95% CI: 0.62-6.42); it became statistically significant when the analysis was restricted to ductal adenocarcinomas (OR_h = 4.11; 95% CI: 1.11-15.23, $p_{\text{trend}} = 0.04$). Other significant associations were apparent among ductal adenocarcinomas, specially in men, for asbestos (OR_h men = 7.54; 95% CI: 1.61-35.19; $p_{\text{trend}} = 0.001$), and for synthetic polymer dust exposure (OR_h men = 5.40; 95% CI: 1.04-28.11). There was also evidence of an association for ionizing radiation (OR men = 16.73; 95% CI: 2.32-120),

high exposure to pesticides (ORh men = 3.54; 95% CI: 0.83-15.21), diesel engine exhaust (ORh men= 1.88; 95% CI: 0.72-4.90), and gasoline engine exhaust (ORh men= 1.85; 95% CI: 0.71-4.80).

Finally, when analyses were restricted to occupational exposures with a duration of 15 years or longer, associations were not statistically significant, but for the agents mentioned above (e.g., chlorinated hydrocarbon solvents) point estimates were similar or slightly higher (data not shown).

DISCUSSION

We found a significant increase in EPC risk in men among the occupational job-titles 'machinery mechanics and fitters', 'miners', 'building trades workers' and 'motor vehicle drivers'; and among 'office clerks', in women. With respect to occupational exposure to specific agents or groups of agents, we observed significant associations with dose-response trends for 'chlorinated hydrocarbon solvents', and 'asbestos'; and significant increases in risk for 'synthetic polymer dust exposure' and 'ionizing radiation'. A suggestion of association was apparent for 'pesticides', and for 'diesel and gasoline engine exhaust'. Most associations became stronger when analyses were restricted to histologically confirmed ductal adenocarcinomas.

Occupational exposure to chlorinated hydrocarbon solvents (CHC) seems the most consistent occupational association with EPC observed in epidemiological studies. Our results are consistent with the meta-analysis by Ojajärvi et al., based on 20 populations from Europe, North America, and Asia during 1969-1998, in which a statistically significant meta-relative risk of 1.4 (95% CI: 1.0-1.8) was found for CHC and related compounds [9]. In a more comprehensive and detailed meta-analysis for CHC published by the same authors one year later, significant excesses of EPC were found for metal degreasing and related jobs and dry cleaning [11]. Among specific CHC solvents with known or suspected human carcinogenicity [20], evidence of weak associations was found for trichloroethylene, tetrachloroethylene, methylene chloride, vinyl chloride, PCBs, and chlorohydrin manufacture, but not for carbon tetrachloride [11]. Nevertheless, evidence from animal studies for the association between CHC compounds and EPC is scant. It was not feasible to collect information on specific chlorinated organic solvents from our cases, most of whom had severe EPC at the time of the interview, as usual. However, our results support the hypothesis that the association between CHC and EPC is real: first, because it was strengthened when the analysis was restricted to histologically confirmed cases; and second, because there was a significant dose-response trend for long duration exposures of 15 years or more.

The associations found among miners, shotfirers and stone cutters and carvers in men are based on just a few exposed cases and controls; furthermore, they involve a wide range of activities and exposures, such as ionizing radiation, asbestos, oil mist, carbon monoxide, silica dust and other mineral dust and fibres. Although a Finnish study reported an increased risk among quarry miners [21], and the Ojajärvi meta-analysis found in a significant excess risk for silica dust [9], the evidence of an association among miners is scarce.

The association found for ductal adenocarcinoma in men highly exposed to asbestos according to FINJEM was based on three cases and seven controls. The job titles of these cases were miners (n = 1) and shotfirers (n = 2). As there was no asbestos exposure in Spanish mines, the association is likely to be due to overassignment of exposure to asbestos from FINJEM to Spanish workers. In a previous study on pancreatic cancer in Spain, industrial hygienists considered only 1 case and 2 controls as exposed to asbestos (none of them miners), while FINJEM identified 15 cases and 23 controls in the highly exposed category [13].

The significant association between ionizing radiation and ductal adenocarcinoma was based on the three cases and two controls. Although a Finnish population based case-control study that assigned occupational exposure to ionizing radiations by job-exposure matrix also found an elevated odds ratio for ionizing radiation (OR = 4.3 (95% CI:1.6-11.4) [22]), results from studies in other exposed workers are contradictory [23-25]. A collaborative analysis of 11 cohorts of underground miners found an association between cumulative exposure to radon and pancreatic cancer [26]. No clear evidence of a link between EPC and occupational exposure to radiation was identified after a comprehensive review up to 1990 [27]. The associations for 'fibre preparers' and 'synthetic polymer dust' are not supported by previous epidemiological studies.

Although we found a significant association among clerks in women, we did not find an association for sedentary work assessed through FINJEM. Clerical occupations are commonly found to convey a small elevation in risk of EPC [12, 28-30]. Physical activity may play a modest role on EPC [31].

Associations in wide occupational groups such as ‘machinery mechanics and fitters’, ‘machine operators’ and ‘building trades workers’ are supported by previous studies [12, 32-39]. Possible responsible agents might be chlorinated solvents, used while cleaning, as well as mineral oils with PAHs and nitrosamines [40]. The increased risk in men in the group of vehicle drivers –and particularly, heavy truck and lorry drivers– is consistent with other studies [21, 35, 41, 42], and with the suggestive increased risk for diesel and gasoline engine exhaust also found in this study.

While a number of case-control studies examining pesticides observed elevated risks similar to our study [13, 43-46], other studies have not [47-50]. Certain types of pesticides seem to be more related to EPC than others. The organochlorine insecticide DDT has been positively linked in some studies [45, 51, 52]; also, the Ojajärvi meta-analysis found a significant elevated risk with organochlorine insecticide exposure [9]. Ongoing studies should help clarify the potential relationship between organochlorine compounds and risk of EPC [53].

Similarly to other hospital based case-control studies exploring occupational exposures, this study has some limitations, such as low numbers of exposed subjects for uncommon occupational exposures or the high number of comparisons. To increase the statistical power in our study –with only 3 cases less than the largest case-control study on occupation published in Spain [12, 13]–, we used about 3 controls per case, resulting in 80% power to identify two-fold associations at the 5% significant level for exposures with a 12% prevalence among controls. Other caveats relate to the lack of a real adaptation of FINJEM to the specific exposure circumstances in Spain, and to the lack of a control for other putative risk factors of EPC, such as diabetes mellitus, obesity or dietary factors. In contrast, we compared the effect for every job title and occupational exposure to the remaining ones; thus, it may be possible that the effect for some exposures was underestimated because of the inclusion in the reference category of other occupations and substances that also showed an increase in risk of EPC.

Strengths of the study include the high percentage of subjects with data on occupational history (81% of cases and 95% of controls), and the high percentage of interviews performed directly with

the study subjects (88%). These figures are seldom achieved in pancreatic cancer, and are a consequence of the rapid identification of cases in our study [52-58].

In summary, results lend support to the hypothesis of an association between occupational exposure to chlorinated hydrocarbon solvents and EPC risk, which is probably the most consistent occupational association with EPC in the literature. A few other occupations and occupational exposures also appeared to increase risk and are likewise in accordance with some previous studies.

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Table 1 Adjusted Odds Ratio (OR) for Exocrine Pancreatic Cancer and for Ductal Adenocarcinoma subtype separately, according to occupations* in Spanish men and women (at least 1 year worked in the occupation)

Sex	CNO94 Code ^{a,b}	CNO94 Job Titles ^b	Controls		All Pancreatic Cancer		Ductal Adenocarcinoma	
			N ^c	N ^c	OR (95% CI) ^d	N ^c	OR (95% CI) ^d	
Both sexes	50	Housekeeping and restaurant services workers	15/455	6/161	1.15 (0.42-3.11)	3/76	1.23 (0.33-4.62)	
Both sexes	502	Waiters, waitresses and bartenders	7/455	5/162	2.38 (0.70-8.00)	3/76	2.90 (0.67-12.39)	
Men	60	Skilled workers in agricultural activities	70/285	27/96	1.13 (0.63-2.01)	8/47	0.85 (0.35-2.06)	
Men	601	Self-employed skilled workers in agricultural activities	66/285	24/96	1.04 (0.58-1.88)	7/47	0.76 (0.30-1.92)	
Men	602	Employed skilled workers in agricultural activities	4/285	4/96	2.35 (0.51-10.92)	1/47	2.28 (0.22-23.83)	
Men	6022	Employed skilled workers in gardens, nurseries and vegetable or market gardens	1/285	3/96	5.62 (0.48-66.10)	1/47	8.98 (0.38-210.26)	
Men	72	Building finishers and related trades workers	13/285	8/96	2.66 (0.99-7.17)	5/47	3.58 (1.03-12.44)	
Men	723	Building and related electricians	3/285	3/96	3.98 (0.71-22.12)	1/47	1.78 (0.12-24.75)	
Men	724	Painters and related workers	4/285	3/96	2.77 (0.56-13.68)	2/47	4.77 (0.71-32.03)	
Men	742	Miners, shottfirs, stone cutters and carvers	4/285	3/96	2.77 (0.57-13.53)	3/47	8.14 (1.55-42.68)	
Men	7421	Miners and quarry workers	2/285	1/96	1.98 (0.16-23.39)	1/47	6.32 (0.49-81.22)	
Men	7422	shottfirs	0/285	2/96	Ind	2/47	Ind	
Men	76	Machinery and Electrical and electronic equipment mechanics and fitters	15/285	11/96	2.84 (1.18-6.83)	7/47	3.61 (1.24-10.47)	
Men	761	Machinery mechanics and fitters	15/285	8/96	1.75 (0.68-4.5)	4/47	1.68 (0.48-5.86)	
Men	7611	Motor vehicle mechanics and fitters	5/285	2/96	0.87 (0.15-5.07)	1/47	1.08 (0.11-10.52)	
Men	7613	Agricultural- or industrial-machinery mechanics and fitters	10/285	6/96	2.42 (0.79-7.35)	3/47	2.17 (0.49-9.65)	
Men	793	Textile, garment and related trades workers	7/285	4/96	1.57 (0.42-5.91)	1/47	0.79 (0.08-7.80)	
Men	7931	Fibre preparers	3/285	3/96	3.42 (0.62-18.71)	1/47	1.77 (0.12-24.63)	
Men	81	Stationary plant and related operators	17/285	6/96	1.22 (0.43-3.41)	1/47	0.38 (0.04-3.16)	
Men	812	Metal-processing plant operators	8/285	3/96	1.90 (0.46-7.90)	1/47	1.16 (0.12-11.00)	
Men	814	Wood-processing- and papermaking-plant operators	4/285	2/96	1.94 (0.31-11.99)	0/47	Ind	
Men	8141	Wood-processing-plant operators	3/285	2/96	2.38 (0.35-16.17)	0/47	Ind	
Men	831	Metal- and mineral-products machine operators	5/285	4/96	3.20 (0.78-13.01)	3/47	4.22 (0.84-21.04)	
Men	8311	Machine-tool operators	4/285	2/96	1.86 (0.31-11.05)	1/47	1.57 (0.15-16.54)	
Men	86	Motor vehicle drivers	26/285	12/96	1.47 (0.68-3.20)	7/47	1.56 (0.58-4.14)	
Men	863	Heavy truck and lorry drivers	10/285	7/96	2.45 (0.84-7.09)	5/47	3.46 (1.01-11.83)	
Women	4	Office Clerks	3/170	4/65	4.39 (0.65-29.26)	3/29	6.95 (0.78-61.58)	
Women	43	Other Office Clerks	1/170	4/65	14.20 (1.16-173.67)	3/29	17.46 (1.17-259.27)	
Women	601	Self-employed skilled workers in agricultural activities	6/170	3/65	0.85 (0.17-4.33)	2/29	1.38 (0.21-9.27)	
Women	836	Textile-, fur- and leather-products machine operators	10/170	5/65	1.32 (0.40-4.36)	4/29	2.10 (0.55-7.98)	
Women	8366	Shoemaking- and related machine operators	4/170	2/65	1.24 (0.16-9.45)	2/29	2.43 (0.31-18.63)	
Women	9110	Domestic helpers and cleaners	4/170	1/65	0.93 (0.09-9.12)	1/29	1.85 (0.19-17.70)	
Women	912	Helpers and cleaners in offices, hotels and other establishments	6/170	2/65	0.76 (0.13-4.34)	2/29	1.97 (0.33-11.72)	

^a Selected occupations were those with at least 10 exposed subjects at one digit of CNO94 (see text in methods), or those reported as possible risk factors in published studies, provided that there were at least five exposed subjects;

^b The Spanish National Classification of Occupations 1994. One person can be included in more than one occupation.

^c N=Number of exposed controls and cases. Numerator denotes the number of controls & cases who have worked in the mentioned occupation and the denominator denotes the total number of controls & cases according to sex respectively.

^d Odds ratio adjusted for sex, age, province, educational level, alcohol drinking and tobacco smoking. The reference category included all remaining Job-Titles. CI: confidence interval. Ind: Indeterminate

Table 2 Adjusted Odds Ratio (OR) for all exocrine pancreatic cancer and for ductal adenocarcinoma subtype, according to occupational exposures by FINJEM in both sexes

Agents	Exposure level ^a	Controls		All Pancreatic Cancer			Ductal Adenocarcinoma			
		N ^b 455	N ^b 161	OR ^c	(95% CI)		N ^b 76	OR ^c	(95% CI)	
<i>CHEMICAL AGENTS</i>										
Any pesticide ^d	Low ($\leq 0.018 \text{ mg/m}^3$) ^a	72	25	0.99	0.57	1.72	9	0.87	0.39	1.97
	High ($> 0.018 \text{ mg/m}^3$) ^a	4	5	3.54	0.83	15.21	1	2.16	0.21	22.32
Hydrocarbon solvents [¶]	Low ($\leq 12.58 \text{ ppm}$)	33	15	1.44	0.73	2.84	10	2.27	1.00	5.12
	High ($> 12.58 \text{ ppm}$)	10	2	0.77	0.16	3.72	1	0.62	0.07	5.41
Hydrocarbon solvents_recode [°]	Low (lows in any of the subtypes below)	17	8	1.42	0.56	3.62	4	1.56	0.46	5.31
	High (highs in any of the subtypes below)	26	9	1.22	0.54	2.75	7	2.04	0.80	5.18
Aliphatic hydrocarbon solvents	Low ($\leq 9.10 \text{ ppm}$)	23	12	1.65	0.76	3.59	7	2.19	0.83	5.79
	High ($> 9.10 \text{ ppm}$)	13	3	0.87	0.23	3.28	3	1.69	0.42	6.70
Aromatic hydrocarbon solvents.	Low ($\leq 17.65 \text{ ppm}$)	18	7	1.27	0.49	3.29	6	2.70	0.95	7.64
	High ($> 17.65 \text{ ppm}$)	8	1	0.41	0.05	3.46	0	Ind		
Chlorinated hydrocarbon solvents	Low ($\leq 0.83 \text{ ppm}$)	5	1	0.86	0.09	7.84	1	1.17	0.11	12.26
	High ($> 0.83 \text{ ppm}$)	8	5	1.99	0.62	6.42	4	4.11	1.11	15.23
Other organic solvents	Low ($\leq 11.49 \text{ ppm}$)	10	4	1.06	0.31	3.65	3	1.94	0.46	8.17
	High ($> 11.49 \text{ ppm}$)	11	2	0.60	0.12	2.90	2	1.13	0.22	5.79
Formaldehyde	Low ($\leq 0.014 \text{ ppm}$)	79	27	0.90	0.53	1.55	9	0.75	0.34	1.70
	High ($> 0.014 \text{ ppm}$)	24	6	0.79	0.30	2.08	3	0.88	0.24	3.23
Polycyclic aromatic hydrocarbons (PAH)	Low ($\leq 0.15 \text{ } \mu\text{g/m}^3$)	10	6	1.63	0.55	4.81	3	1.43	0.34	6.02
	High ($> 0.15 \text{ } \mu\text{g/m}^3$)	16	8	1.73	0.67	4.42	4	1.71	0.49	5.95
Benzo(a)pyrene	Low ($\leq 0.012 \text{ } \mu\text{g/m}^3$)	11	6	1.53	0.53	4.44	3	1.39	0.33	5.78
	High ($> 0.012 \text{ } \mu\text{g/m}^3$)	15	8	1.82	0.70	4.71	4	1.76	0.50	6.15
Oil mist	Low ($\leq 1.79 \text{ mg/m}^3$)	7	8	2.87	0.98	8.35	5	3.26	0.91	11.65
	High ($> 1.79 \text{ mg/m}^3$)	10	3	0.89	0.23	3.50	1	0.39	0.04	3.49
Diesel engine exhaust	Low ($\leq 0.46 \text{ mg/m}^3$ nitrogen dioxide)	31	14	1.49	0.72	3.08	10	2.40	1.00	5.73
	High ($> 0.46 \text{ mg/m}^3$ nitrogen dioxide)	15	8	1.88	0.72	4.90	4	2.08	0.58	7.38
Gasoline engine exhaust	Low ($\leq 6.92 \text{ mg/m}^3$ carbon monoxide)	26	11	1.38	0.62	3.07	7	1.66	0.63	4.43
	High ($> 6.92 \text{ mg/m}^3$ carbon monoxide)	15	8	1.85	0.71	4.80	4	1.88	0.53	6.62
Gasoline	--	15	8	1.78	0.69	4.60	4/	1.73	0.50	6.02
Bitumen fumes	--	4	0	Ind			0	Ind		
Environmental tobacco smoke	Low (≤ 0.119 [based on a score 0-2])	145	38	0.72	0.44	1.15	20	0.76	0.40	1.45
	High (> 0.119 [based on a score 0-2])	38	21	1.60	0.84	3.06	10	1.39	0.58	3.31
Asbestos	Low ($\leq 0.26 \text{ fibers/cm}^3$)	75	31	1.30	0.77	2.18	18	2.09	1.05	4.13
	High ($> 0.26 \text{ fibers/cm}^3$)	11	3	0.84	0.22	3.20	3	2.33	0.57	9.47
Cadmium	--	6	1	0.48	0.05	4.31	0	Ind		
	--									

(Table 2, Continued)

<i>Agents</i>	<i>Exposure level^a</i>	Controls		All Pancreatic Cancer		Ductal Adenocarcinoma				
		N^b 455	N^b 161	OR^c	(95% CI)		N^b 76	OR^c	(95% CI)	
Nickel	Low ($\leq 0.99 \mu\text{g}/\text{m}^3$)	27	11	1.40	0.64	3.08	4	1.01	0.31	3.26
	High ($>0.99 \mu\text{g}/\text{m}^3$)	13	4	0.93	0.28	3.08	1	0.30	0.04	2.61
Lead	Low ($\leq 0.237 \mu\text{mol}/\text{l}$)	49	17	1.02	0.54	1.90	7	0.76	0.31	1.86
	High ($>0.237 \mu\text{mol}/\text{l}$)	12	4	1.54	0.46	5.17	2	1.24	0.24	6.46
Chromium compounds	Low ($\leq 4.35 \mu\text{g}/\text{m}^3$)	29	13	1.62	0.77	3.41	4	0.89	0.28	2.85
	High ($>4.35 \mu\text{g}/\text{m}^3$)	11	4	1.10	0.32	3.71	1	0.34	0.04	2.93
Volatile sulphur compounds	Low ($\leq 0.025 \text{ ppm}$)	67	27	1.06	0.61	1.84	9	0.86	0.38	1.94
	High ($>0.025 \text{ ppm}$)	27	5	0.55	0.20	1.54	1	0.26	0.03	2.03
Leather dust	--	12	2	0.49	0.10	2.34	2	1.07	0.22	5.22
	--									
Textile dust	--	20	4	0.45	0.15	1.40	2	0.51	0.11	2.36
	--									
Wood dust	Low ($\leq 0.99 \text{ mg}/\text{m}^3$)	10	2	0.58	0.12	2.82	0	Ind		
	High ($>0.99 \text{ mg}/\text{m}^3$)	6	0	Ind			0	Ind		
Synthetic polymer dust	Low ($\leq 0.52 \text{ mg}/\text{m}^3$)	16	5	0.79	0.27	2.33	3	0.89	0.23	3.42
	High ($>0.52 \text{ mg}/\text{m}^3$)	6	4	2.22	0.58	8.48	3	4.00	0.86	18.62
<i>PHYSICAL AGENTS</i>										
Cold	Low ($\leq 16\%$ of working hours)	196	69	0.89	0.55	1.43	33	1.01	0.53	1.91
	High ($>16\%$ of working hours)	20	3	0.37	0.10	1.40	0	Ind		
Heat	Low ($\leq 2.5\%$ of working hours)	103	35	0.96	0.59	1.56	10	0.58	0.28	1.24
	High ($>2.5\%$ of working hours)	17	8	1.32	0.52	3.34	5	2.23	0.73	6.78
Ionizing radiation	--	2	3	4.73	0.72	30.88	3	15.19	2.12	109.15
	--									
Low-frequency magnetic fields	Low ($\leq 0.52 \mu\text{T}/24\text{h}$)	74	24	0.98	0.57	1.68	11	0.85	0.41	1.79
	High ($>0.52 \mu\text{T}/24\text{h}$)	12	1	0.27	0.03	2.16	0	Ind		
<i>ERGONOMIC AGENTS</i>										
Perceived physical workload	Low (≤ 0.56 [based on a score 0-2])	159	54	0.97	0.60	1.57	29	1.17	0.62	2.18
	High (>0.56 [based on a score 0-2])	96	32	0.86	0.48	1.54	10	0.73	0.31	1.71
Sedentary work ^f	Low (≤ 0.62 [based on a score 0-2])	10	4	1.08	0.31	3.77	3	1.28	0.30	5.40
	High (>0.62 [based on a score 0-2])	28	12	1.36	0.64	2.92	7	1.44	0.56	3.74

^a Low and high exposure levels were based on the product of the probability and the intensity of exposure to each agent for at least 1 year (see text for details).

^b N: number of exposed controls and cases respectively.

^c OR were adjusted for: sex, age, province, educational level, alcohol drinking and tobacco smoking. The reference category included all remaining exposures. CI: confidence interval. Ind.: Indeterminate.

^d Includes exposure to any of the following types of pesticides: insecticides, herbicides and fungicides.

^e The "Hydrocarbon solvents" includes "Aliphatic hydrocarbon solvents", "Aromatic hydrocarbon solvents" and "Chlorinated hydrocarbon solvents". Hydrocarbon solvents recode denotes a recode by felling the cut point by considering as highly exposure to Hydrocarbon solvents all the subjects highly exposed in any of these subtypes.

^f Work done mostly in sitting position, as reported by subjects