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Mortality for Pancreatic Cancer Among Aluminium Smelter Workers in Sardinia, Italy

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RIASSUNTO. In una coorte di 1152 lavoratori di una fonderia di alluminio primario della Sardegna basata sulla tecnologia dell'elettrolisi ad anodi precotti è stata valutata la relazione tra esposizione professionale agli Idrocarburi Policiclici Aromatici (IPA) e la mortalità per cause specifiche. I decessi osservati tra il 1972, anno d'inizio dell'attività produttiva della fonderia, e il Dicembre 2001 sono stati rapportati a quelli attesi calcolati sulla base dei tassi regionali età-specifici per anno di calendario. L'esposizione individuale ad IPA è stata valutata sulla base delle numerose misure di esposizione ambientale e individuale disponibili fin dal 1979 per ogni mansione nei differenti reparti della fonderia. Dalle cartelle cliniche individuali sono state raccolte le informazioni sul fumo di tabacco, sulle attività lavorative svolte prima dell'assunzione nella fonderia di alluminio e sulle principali manifestazioni cliniche osservate in ogni lavoratore nel corso del follow-up. Lo studio non ha mostrato un incremento di mortalità per neoplasie polmonari e vescicali associato all'esposizione ad IPA. La mortalità per neoplasie pancreatiche, basata su 6 decessi, è risultata significativamente più elevata rispetto all'atteso sia nel complesso della coorte (SMR 2.4; IC 95% 1.1-5.2) che in particolare tra i lavoratori impiegati nella fabbrica anodi (Mescola, Forni di cottura e Rodding) (N° 4, SMR 5.0, IC 95% 2.1-12.1), caratterizzata da relativamente elevata esposizione ad IPA. Lo studio caso-controllo approntato per le neoplasie pancreatiche ha confermato che, anche dopo aver tenuto conto del fumo di tabacco, l'esposizione ad IPA legata all'attività lavorativa svolta nella fabbrica anodi risultava associata con un significativo incremento del rischio di cancro del pancreas. In tale rischio significative covariate sono risultate anche l'evidenza di diabete mellito e una potenziale esposizione a pesticidi legata a pregresse attività lavorative svolte in agricoltura.

In conclusione, appare evidente come la relativamente elevata esposizione ad IPA associata all'attività lavorativa svolta nella fabbrica anodi e in particolare nel reparto mescola sia da considerare fattore di rischio rilevante nell'eziologia multifattoriale delle neoplasie pancreatiche osservate in questa fonderia di alluminio primario.

Parole chiave: industria dell'alluminio, idrocarburi policiclici aromatici, cancro del pancreas, diabete.

ABSTRACT. www.gimle.fsm.it

To investigate the relationship between exposure to polycyclic aromatic hydrocarbons (PAHs) and mortality for specific cancer sites, 1152 men, employed for at least 1 year at a prebake aluminium smelter, were followed-up from 1972 until 31 December 2001. Exposure to PAHs was estimated from a detailed reconstruction of the working history experienced in the plant by each cohort member and from several environmental and personal shift-sampling measurements available, by task and working department, since 1979. Furthermore, information on smoking habits, previous jobs before engagement in the smelter

and main clinical findings observed during the follow-up were collected from the personal medical files.

This study showed no increased mortality for lung cancer or bladder cancer associated to exposure to PAHs. Mortality for pancreatic cancer, based on 6 observed deaths, was significantly higher than expected in the whole cohort (SMR 2.4; 95%CI 1.1-5.2) and particularly among workers employed in the anodes factory of the plant (SMR 5.0, 95%CI 2.1-12.1), where a relatively consistent exposure to PAHs has been estimated. The nested case-control study planned for pancreatic cancer cases, confirmed that, also after controlling for cigarette smoking, PAH exposure experienced in the anodes factory was associated with a significant increased risk of pancreatic cancer. A pre-existent diabetes mellitus and a potential occupational exposure to pesticides experienced in previous agricultural jobs were found as concurrent significant covariates increasing the risk. In conclusion, the relatively high exposure to PAHs, experienced in the anodes factory and particularly in the green-mill department of this prebake aluminium reduction plant, cannot be ruled out as one of the main factors in the multifactorial aetiology of the pancreatic cancers observed in this study.

Key words: aluminium industry, polycyclic aromatic hydrocarbons, pancreatic cancer, diabetes.

Introduction

In the primary aluminium industry, rows of electrolytic cells called "pots" are used in wide potrooms for reduction of alumina (Al₂O₃). Two different types of anodes are used: continuous Söderberg, and prebaked. In both technologies the anode is a mixture of granular petroleum-coke and hot, liquid or granular, coal-tar pitch, mixed and pressed to form a semisolid paste. In potrooms using the Söderberg technology the "green" anodes are continuously baked in uncovered pots by heat produced by low-voltage and high-intensity electric current applied to metallic studs fitted to the anodes, and new fresh paste is regularly supplied during the electrolytic process. This implies very high tar exposure of potroom-workers due to evaporation of coal tar peach volatiles (CTPV) from the anode top. In the prebake technology, the big green-carbon blocks, formed in the green-mill section of the anodes factory, are slowly pre-baked in the oven department before their use in the electrolytic pots, where electric current flows through metallic rods previously fitted to the prebaked anodes in the

“rodding” department. As the anodes are almost completely consumed they are replaced by new ones and the exhausted anodes recycled. Finally, the liquid aluminium derived from the electrolytic process is removed by siphoning from the bottom of the pots and transported to the casting department for further processing.

All these working phases expose the workers, by respiratory and skin route of body entry, to CTPV and more specifically to polycyclic aromatic hydrocarbons (PAHs), with potential risk of cancer. The highest tar exposure, usually estimated as airborne Benzene Soluble Matter (BSM) and benzo- α -pyrene (BaP) concentrations, occurs in the Söderberg potrooms, while it is significantly much lower (1-2 orders less) in the prebake electrolytic potrooms, particularly if covered pots are used. Workers in the green-mill area of the anode factory have relatively relevant exposure to tars and pitch and coke dusts during mixing and forming the anode past. Tar exposure in the baking furnaces and rodding departments of the prebake plants is intermediate. As in potrooms, the exposure to CTPV is generally very low also in the casting department (1-7).

Several experimental studies have pointed out significant evidences of carcinogenic effects in animals of complex mixture of PAHs and particularly of some selected compounds with four or more condensed benzene rings (4, 8). Moreover it has been shown that in the primary aluminium industry certain exposures, as working in carbon-plants or in Söderberg potrooms, are associated with an increased risk of lung and bladder cancer with a significant exposure-response trend with cumulative tar exposures (4, 9, 10).

In 1987 the International Agency on Research on Cancer (IARC) classified the primary aluminium industry into the group 1 of carcinogens (11). For lymphomas, leukaemias and pancreatic cancer the evidence to humans was considered as inadequate. However, other humans studies are not conclusive for an increased risk of lung, bladder and hemato-lymphopoietic cancers (7, 12, 13), particularly in the prebake electrolytic potrooms (14).

In 1992 Rönneberg (15) reviewed the main epidemiological studies concerning about 51,000 workers from 35 aluminium plants and 9 carbon plants not in the aluminium industry and concluded for a clear association between bladder cancer and work in Söderberg pots, but a limited one between lung cancer risk and cumulative tar exposure. Furthermore, this review suggested also an increased risk of leukemias and pancreatic cancer but without any clear association with specific exposures or working areas. The higher cancer risk associated to the Söderberg electrolysis has been confirmed by two wide Canadian studies of Quebec aluminium workers (6, 16) They showed significant association with working in Söderberg pots and both lung and bladder cancer risk, with a significant trend with the time spent in these types of potrooms. The relative risk for both cancer sites was low and without evidence of significant trend for working in the prebake pots, after adjusting for smoking and Söderberg works. Intermediate results were observed for working in the carbon plant.

A previous mortality study of Sardinian aluminium prebake smelter workers (17) showed an all cancer mortality as that expected from the regional rates (SMR 1.05;

95% C.I. 0.8-1.5). Workers who died for lung cancer (7 cases; SMR 0.67) and for bladder cancer (1 death and 1.7 expected) were less than expected. However, an excess of pancreatic cancer deaths was observed, based on 3 cases and 1.63 expected (SMR: 1.84; 95%ci: 0.60-5.60). Two of them had been employed in the carbon area. The present study updates the previous results, adding ten more years of follow-up.

Materials and Methods

The cohort under study refers to 1152 male blue-collar workers with at least one year of employment in the plant, hired in the Portovesme smelter, located in the south-western coast of Sardinia, a region of Italy, between 1972, year of starting of smelter's production, and 1980. More than 95% of cohort members were born in Sardinia and mostly resident in towns near the plant. Vital status as that of 31 December 2001 has been ascertained for all subjects using the mortality register of the local Health Unit (ASL N° 7 of Sardinia). Standardised Mortality Ratios (SMRs) were calculated as the ratio between the observed deaths, coded according to the ICD-IX revision, and the expected numbers based on age-specific regional rates, available for specific causes for each calendar-year since 1972.

The 95% confidence intervals (95%CI) were calculated assuming a Poisson distribution for the observed numbers. Furthermore, a nested case-control study has been planned for the pancreatic cancer deaths based on 6 cases and 12 controls for each cancer case, matched by age and calendar-year at hire, randomly selected, irrespective of their disease status, from the whole cohort. Odds Ratios (ORs) by conditional logistic regression analysis have been calculated for different occupational and non occupational variables.

Plant description

The plant has a production of about 130,000 tons of aluminium a year in two wide potrooms with 164 prebaked-type cells each one. Sixteen prebaked anodes are assembled in each pot with a renewal frequency of 14-28 days. Since the mid of 80's all pots have been covered and fumes directly picked up from the cells and sent to the central dry scrubber. The aluminium sinks to the cathode at the bottom of the pot from where it is periodically removed by siphoning and then transported by means of ladles to the casting department. The green-carbon blocks are produced continuously in the green-mill section of the anodes factory. Crude anodes are moved to the ovens department where they are baked into deep brick-lined pits for about 220 hours at 1200°C and then cooled in the same ovens by forced ventilation for 280 hours more. About 200 prebaked anodes are produced daily in two wide baking rooms. Volatile and particulate emissions are kept directly from the ovens and burned in situ or sent by forced ventilation to a dry filter system or to a pipeline where they are abated with a forced stream of alumina dust. The prebaked

anodes, after being fitted onto metallic rods, are then inserted in the pots by means of a special tractor. The exhausted anodes, removed from the pots and milled in granular shape in the rodding section of the plant, are sent back to the green-mill department, where they are mixed with new fresh paste. All sections of the plant are semi-automated and several free steered diesel vehicles are used for material transportation. Direct manual interventions are usually necessary only for maintenance or special duties. A part from the covering of electrolytic pots, no substantial main changes in the operating process have been done in the other departments since the start of production.

Exposure estimates

A detailed reconstruction of the length and calendar-years of each task performed by the cohort members since their engagement in the smelter has been done using administrative duty rosters and individual clinical records collected during the yearly medical examinations scheduled by specific health surveillance protocols. Through this way it was also possible to have information on individual smoking habits for 93% of all cohort members. For each case and control included in the nested case-control study, more detailed information on cigarette smoking, previous jobs experienced before the engagement in the smelter and main clinical findings during the follow-up were also collected from the personal medical files. Exposure to CTPV was estimated using several environmental and biological measurements available since 1979 for almost all tasks of the main departments of the plant. Until 1990, only data of airborne dusts and BSM concentrations derived from static samplings were available for the main working departments. After this year, findings of airborne BSM and PAHs concentrations derived from periodic personal shift-samplings, as well as, measurements of the after-shift urinary 1-hydroxypyrene (1-OHP) excretion, became widely available for the main tasks of each working area. The rating of tar exposure of different tasks and departments has been estimated from results of about 180 different work-shifts periodically surveyed (18). Airborne PAHs were sampled and analysed according to the NIOSH method 5506 using a teflon filter for the particulate-phase and a solid adsorbent Amberlite XAD-2 for the vapour-phase (19). Nineteen single compounds were determined by HPLC and spectrofluorimetric detection. The urinary 1-OHP excretion was measured by HPLC and corrected for urinary creatinine (20). Furthermore, in a sub-sample of 86 workers from the main departments, PAHs-DNA adducts in peripheral lymphocytes were also measured by ³²P-postlabelling assay in 1998 (21).

Results

PAH exposure

As reported elsewhere (18), the profile of airborne PAHs mixture did not differ between the working areas: compounds with 2 or 3 rings accounted in average for mo-

re than 70% of the total PAH concentrations. The relative proportion of pyrene in air was in average 2-5% of total PAHs, that of BaP 0.5-1%. Pyrene was significantly correlated to the total PAH and BaP levels. Workers employed in the green-mill department were the most exposed: total PAHs ranged up to 41.8 µg/m³ (Geometric Mean = 8.7 µg/m³), BaP ranged up to 1.9 µg/m³ (GM = 0.8 µg/m³) and the after-shift 1-OHP excretion ranged up to 20.1 µg/g creatinine (GM = 6.1 µg/g creatinine). Airborne exposure to PAHs and the after-shift 1-OHP concentration in urine were significantly lower for workers of the other departments, being the 1-OHP of potroom and foundry workers quite similar to that found among a reference group of non occupationally exposed subjects, randomly selected from the local general population. Also the PAHs-DNA adduct levels were significantly higher among workers of the green-mill department than those found among workers of the other areas.

So, data from both the environmental and the biological monitoring show a consistent exposure to PAHs only for the green-mill plant workers. In the other sections of the anodes factory, baking furnaces and rodding department, tar exposure has been found relatively a bit lower. Tar exposure resulted significantly much lower for workers employed in electrolysis and in casting departments and in general maintenance, and absolutely not relevant for workers employed in the general services.

Mortality study

As reported in table I, age, job duration and smoking habits were comparable between the three main groups of workers categorized according to increasing ranks of estimated PAH exposure (group A, B and C). The ascertainment of vital status was completed for all cohort members, as well as detailed death certificates were available for all subjects deceased during the follow-up (N° 138). Overall mortality was significantly lower than expected in the whole cohort, while all cancer mortality was within the expected numbers (51 observed against 48.5 expected). Workers who died for lung cancer (11 cases; SMR 0.70) and for bladder cancer (3 cases; SMR 0.79) were less than expected (table II).

A statistically significant excess was observed for the pancreatic cancer deaths (6 cases and 2.49 expected; SMR: 2.41; 95%CI: 1.11-5.23) and for cancers of the hematopoietic system (SMR 2.03; 95%CI: 1.03-4.00) based on 8 cases (4 NH-lymphomas, 1 multiple myeloma, 1 Hodgkin lymphoma and 2 myeloid leukemias). Deaths for non-tumoral diseases were all within the expected numbers.

Table III shows SMRs for specific neoplasms observed among the three groups of workers categorized by increasing ranks of exposure to PAHs. No substantial differences in lung or bladder cancer SMRs was observed between the groups, while a statistically significant positive trend for pancreatic cancer mortality was found by rank of exposure to PAHs. The excess of pancreatic cancer mortality was particularly concentrated in the group C which included the 252 workers employed for at least 2 years in the anodes departments (4 observed against 0.80 expected; SMR 5.00, 95%CI 2.07-12.08). A borderline significant excess

Table I. Main characteristics of the cohort members

	N°	Mean and (SD)			Smoking habit %	
		Age at entry	Age at follow-up	Length of employment		
All	1152	30.0 (7)	56.2 (7)	19.2 (8)	NS	46.7
Group A) workers ever employed in general services	311	32.2 (8)	57.4 (8)	15.8 (9)	NS	52.2
Group B) workers ever employed in potrooms, foundry or general maintenance	589	29.7 (7)	55.7 (87)	20.3 (8)	FS	8.0
Group C) workers employed for at least 2 years in the anodes factory (green-mill, baking furnaces, rodding departments)	252	30.7 (7)	56.4 (7)	21.0 (7)	CS	45.0

NS = Never smokers; FS = Former smokers; CS = Current smokers

Table II. Observed (Obs) and expected (Exp) numbers of cause-specific deaths and Standardized Mortality Ratio (SMR) among 1152 aluminium workers in the follow up period 1972-2001 (29 010.8 person-years)

	Obs	Exp	SMR	95% CI
All causes	138	169.6	0.81	0.69 - 0.96 *
All neoplasms	51	48.5	1.05	0.80 - 1.38
– Pancreas	6	2.5	2.41	1.11 - 5.23 *
– Lung	11	15.8	0.70	0.39 - 1.26
– Bladder	3	3.8	0.79	0.26 - 2.44
– Lymphomas-Leukemias	8	3.9	2.03	1.03 - 4.00 *
– Other cancers	23	22.5	1.02	0.68 - 1.54
Non neoplastic diseases				
Cardiovascular	42	37.0	1.13	0.84 - 1.53
Respiratory	12	12.5	0.96	0.55 - 1.70
Digestive	14	18.1	0.77	0.46 - 1.30
Urinary	2	1.9	1.03	0.26 - 4.12
All accidents	17	23.6	0.72	0.45 - 1.16

* p < 0.05

Table III. Observed (Obs) and expected (Exp) numbers of deaths and Standardized Mortality Ratio (SMR) for selected cancer sites among working groups categorized by increasing rank of PAH exposure

	Group A [^]			Group B [§]			Group C [£]		
	Obs	SMR	95% CI	Obs	SMR	95% CI	Obs	SMR	95% CI
All neoplasms	15	0.94	0.57-1.55	24	1.07	0.72-1.60	13	1.27	0.74-2.19
– Pancreas	0	–		2	1.72	0.44-6.78	4	5.00	2.07-12.08*
– Lung	3	0.69	0.22-2.11	6	0.72	0.32-1.60	2	0.65	0.16-2.55
– Bladder	0	–		2	1.06	0.27-4.25	1	1.14	0.16-8.06
– Lymphomas and Leukemias	2	1.83	0.47-7.18	3	1.69	0.55-5.19	3	2.88	0.98-8.50

* P for trend < 0.05

[^] Group A = workers employed in general services [N° 321, person-years 7941.7][§] Group B = workers employed in potrooms, foundry or general maintenance [N° 589, person-years 14704.3][£] Group C = workers employed for at least 2 years in the anodes factory [N° 252, person-years 6364.8]

of mortality for lymphomas and leukemias (SMR 2.88, 95%CI 0.98-8.50) was also observed in this last group, without evidence of significant trend by groups with increasing PAH exposure.

Case-control study of pancreatic cancer

Age and calendar-year at engagement in the aluminium smelter, as well as, the year of dismissal from the plant and the length of employment in the smelter and in previous jobs, experienced before the engagement in the aluminium industry, were comparable between cases and controls. A non-significant higher prevalence of ever smokers was observed among cases (5 subjects on 6; 83.3%) than among controls (44 subjects on 72; 61.1%), but the average number of cigarettes smoked per day was comparable between cases and referents. Two cases on 6 (33.3%) and 11 controls on 72 (15.3%) with first evidence in the personal medical files of repeated values of glycemia above 120 mg/dl, dated back to at least 5 years before the end of their individual follow-up, were identified as affected by a long-standing diabetes mellitus. Among several job titles experienced by cases and controls before their engagement in the smelter, only farming jobs resulted significantly associated with the pancreatic cancer risk (crude OR = 6.7; 95% CI: 1.2-37.7).

Almost all cases and controls had worked in the same department since their first hire in the Portovesme plant, with only marginal changes in the prevalent task. Four of the 6 pancreatic cancer cases (66.6%) had worked in the anodes factory (2 in the green-mill and 2 in the rodding department), while only 10 subjects among controls (13.9%) had worked there (1 in the green-mill plant, 5 in the baking furnaces, 2 in the rodding department and 2 as maintenance operators in the carbon area). This distribution leads to a statistically significant association between pancreatic cancer deaths and working in the anodes factory (crude OR: 12.4; 95% CI: 2.7-57.5). The logistic regression, performed including all variables in the model as categorical covariates (dummy variables 1/0), shows that, even after controlling for smoking habits, pancreatic cancer deaths were strongly associated with working in the anodes factory, and, at the same time, even if at a lesser extent, also with elevated values of glycemia, suggesting a pre-existent diabetes, and with an history of previous agricul-

tural jobs, which, in this context, can be considered as a surrogate of exposure to pesticides (table IV). Results of regression analysis did not change including individual BaP exposure, values of glycemia and cigarette smoking as continuous variables.

Discussion

Bladder cancer is the main cancer site strongly associated with cumulative exposure to CTPV and PAHs in the primary aluminium industry. Despite some negative studies (22, 23), several large epidemiological investigations from USA, Canada and Norway have shown significant excess in mortality or incidence rate, with significant positive dose-response relationship with CPTV exposure, particularly in Södeberg potrooms (5, 7, 10, 14, 16, 24-26). Results on lung cancer risk, although well defined in some studies of Södeberg workers (6, 10) are less or not consistent between studies (13, 15, 27). Four recent wide Norwegian studies (23-26) and a French one (22) did not find any increased risk of lung cancer incidence or mortality among workers of aluminium reduction plants. As in our previous study (17), the current investigation of Sardinian prebake aluminium workers showed no excess of mortality for bladder and lung cancer in the whole cohort, nor significant trend with increasing exposure to PAHs as estimated in the different departments of the plant. Exposure to CPTV of our aluminium workers was found significantly much lower than that estimated in Canadian studies where lung and bladder cancer excess had been documented (6, 16). Exposure to PAHs in this study was found relevant only for workers of the green-mill department (18), where values of BaP concentration above 0.2 µg/m³, the action level applied in the ALCOA plants, were documented in more than fifty percent of surveyed working shifts, maximal values being up to 2.0 µg/m³. Furthermore, the studied cohort is relatively young in age, being the 93% of cumulative person-years at follow-up included in age categories below 60 years, without significant differences between exposure groups. However, we did not have sufficiently detailed personal shift measurements to calculate accurate individual cumulative exposure for all cohort members, but environmental estimates and data of biolo-

Table IV. Nested case-control study: best-fit model for pancreatic cancer deaths from logistic regression (pancreatic cancer cases N° 6, matched controls N° 72)

Dependent variable:	Model Chi-Square 15.7; df 4; p 0.003				
Pancreatic Cancer (1/0)	<i>b</i>	<i>SE</i>	<i>Wald</i>	<i>p</i>	<i>Exp (b)</i>
<i>Categorical variables (1/0)</i>					
Employment in the anodes factory	1.511	0.607	6.19	0.013	4.53
Previous job as a farmer	1.478	0.781	4.23	0.039	4.38
Glycemia > 120 mg/dl	1.023	0.499	2.89	0.045	2.64
Ever smokers	0.567	0.64	0.78	0.376	1.76
Constant	-0.988	0.501	1.86	0.056	

gical monitoring, as well as the individual working history experienced in the plant were detailed enough to well categorize workers by ranks of increasing exposure to PAHs. The prevalence of ever smokers in the whole cohort (53.3%) was found to be lower than that of Sardinian males in 1980 (61.9%), due to a lower percentage of current smokers (45.0%), as defined from the last medical record of each subject, than that observed (52.3%) in the reference population. This finding suggests that workers under study smoked less than did the regional population, probably due to advice against smoking provided during the periodical clinical examinations by the occupational physician of the plant. Such a tobacco under-consumption may have lowered SMRs for smoking related diseases, as lung, bladder and pancreatic cancer. Using the method proposed by Axelson (28, 29), and assuming different risk ratios for current and former smokers vs. non smokers (28-30), we were able to evaluate the confounding effect of smoking habits in the lung and bladder cancer deficit found in this cohort. For lung cancer we used risk ratios of 20 for current smokers and 10 for former smokers, while for bladder and pancreatic cancer the risk ratios vs. non smokers were assumed to be, respectively, 4 and 2. Smoking-adjusted SMRs in the whole cohort were, respectively, 0.80 (95%CI 0.46-1.39) for lung cancer, 0.86 (95%CI 0.29-2.55) for bladder cancer and 2.64 (95%CI 1.3-5.5) for pancreatic cancer. These results are higher than the observed SMRs reported in table III, but the low differences found between observed and adjusted SMRs suggest that, the negative confounding due to smoking is unlikely to account for the totality of the lung and bladder cancer deficit. Furthermore, the small differences in smoking habits found between the three occupational strata of workers (table I) cannot explain the significant increase of pancreatic SMR observed by groups with increasing exposure to PAHs (table III).

However, results from the cohort and case-control study have shown a significant association between PAH exposure, as that experienced particularly in the green-mill section of the anodes factory, and pancreatic cancer mortality.

Increased mortality for pancreatic cancer has been reported in some earlier studies of aluminium workers (12, 17, 31, 32). Recently an increased incidence of pancreatic cancer, with a potential association with PAH exposure, although non-statistically significant, was suggested in some Norwegian studies cited above (23-25).

A meta-analysis of 92 studies dealing with the relationship between occupational exposures and pancreatic cancer found a meta-risk ratio for PAHs of 1.5 (95%CI 0.6-2.5) (33). More recently, an association between exposure to pesticides and the pancreatic cancer risk was found in two case-control studies performed in Spain and in USA (34, 35). In the Spanish study (34) an increased risk associated to occupational BaP exposure was also described. However, the overall findings in literature did not suggest that occupational exposure is a major contributor to the aetiology of pancreatic cancer (36), even if different occupational exposures, as aluminium production, may increase the risk (33). Many non-occupational, personal, dietary and environmental factors, or specific medical conditions have been associated to the multifactorial aetiology of pan-

creatic cancer (37). The most important established risk factor is cigarette smoking; smokers have roughly double the risk as non smokers. Other factors that are strong suspected are: heavy alcohol consumption, diets relatively high in animal fat and low in fruits and vegetables and an history of chronic pancreatitis or of a pre-existent diabetes mellitus (37).

A meta-analysis (38) of studies that provided relative risk of pancreatic cancer for patients with diabetes diagnosed well before the recognition of the cancer, concluded that, independently from smoking habits and other covariates, pancreatic cancer occurs more frequently among subjects with long-standing diabetes. Considering a duration of diabetes of at least 1 year prior to either pancreatic cancer diagnosis or death, the pooled RR of pancreatic cancer for diabetics relative to non diabetics derived from 11 case-control studies and 9 cohort or nested case-control studies, was 2.1 (95% CI 1.6-2.8). Similar results (RR 2.0; 95%CI 1.2-3.2) were observed restricting the analysis to the six case-control and five cohort studies in which a 5-year duration of diabetes was required as inclusion criteria. Considering that in 80% of patients the death for pancreatic cancer occurs generally within 1 year from the first diagnosis (39), a 5-year duration of diabetes, as we used in our nested case-control study, is to be considered enough to prevent the possible confusion between a true causal association of a pre-existent diabetes with the pancreatic cancer, and the impairment of glucose metabolism due to a local or remote effect of the neoplasm (40), as generally observed in a high proportion of newly diagnosed cases of pancreatic cancer (41). A role of chronic hyperinsulinemia, increasing the local blood flow and cell division in exocrine pancreas (42), could be taken in account also considering the higher RRs for pancreatic cancer observed among patients with non-insulin-dependent-diabetes (38, 43, 44) who generally show high level of insulin for years before and after the diagnosis of diabetes. The increasing prevalence of diabetes, as occurs in Sardinia (45), may become potentially associated with an increasing proportion of pancreatic cancer particularly when cigarette smoking and/or occupational exposure to PAHs or pesticides are concurrent risk factors as found in this study of Sardinian aluminium smelter workers.

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