

Occupational exposure and cancer of the pancreas: a review

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Abstract

Many hypotheses have been proposed about the aetiology of cancer of the pancreas, especially concerning the effects of tobacco, coffee, alcohol, diet, and pancreatic pathology. Results of numerous epidemiological studies are, however, inconsistent. Chemical carcinogens have been implicated as possible risk factors. Animal studies have been carried out to determine the role of these chemical factors but, except for nitrosamines and their derivatives (components of tobacco), chemicals have not been proved carcinogenic for the pancreas. Many studies have also been conducted among occupational groups. Several of them showed an excess risk of cancer of the pancreas, especially in the chemical and petroleum industries. The lack of accuracy about the nature of products used, however, does not permit a definitive conclusion as to their carcinogenic role.

This paper is a review of publications about occupational exposures and cancer of the pancreas.

Among various hypotheses, it has been postulated that chemical carcinogens play a part in pancreatic carcinogenesis. This hypothesis led to many animal studies, especially in rodents.

Among the various chemical products investigated nitrosamines and their derivatives, mainly found in tobacco, have been shown to exhibit carcinogenic properties. Other chemical products have not been proved to be carcinogenic for the pancreas. Although results from animal studies cannot be extrapolated with impunity to man, several chemical agents could be implicated in cancer of the human pancreas.

The potential carcinogenic effects of these agents have been studied in occupational epidemiological cohort and case-control studies.

Cohort studies

Most cohort studies (table 1) have been carried out among cohorts of workers, alive or dead, who were employed in various occupational branches. Many of them concerned people who had died after working in various industries. They compared proportions of deaths from different causes in these industries with those of a reference population (proportionate mortality ratio method). Others concerned a group of workers followed up during a specific period and compared the number of deaths from different causes in this group with the number expected from a reference population (standardised mortality ratio method).

CHEMICAL AND PETROLEUM INDUSTRIES

Most studies have been carried out in the chemical and petroleum industries. Many show an excess of cancer of the pancreas among exposed workers, but the results are significant in only four of them:

Mancuso and El-Attar¹ showed an excess of deaths from cancer of the pancreas among workers exposed to β -naphthylamine and benzidine. Li *et al*² found an over-representation of deaths from cancer of the pancreas among a cohort of chemical industry workers but this result was significant among 20-64 year olds only. It was confirmed by Thomas *et al*³ among workers employed in petroleum refining, but only in the petroleum refining and production of petrochemicals group with less than 10 years of exposure. The authors confirmed these results in a later study⁴ that concerned active and retired workers of the three petroleum refineries where an excess risk of cancer of the pancreas had been shown in the first study.

Others, however, did not confirm these findings. Rushton and Alderson⁵ did not find any excess risk among workers in oil refineries in Britain. Norell *et al*⁶ found a significant excess risk among petrol station workers, but no significant excess among workers in refineries. According to Bond *et al*⁷ and Hanis *et al*,⁸ the excess risk associated with exposure in the chemical industry was not significant.

EXPOSURE TO METALS

Redmond *et al* in two studies,^{9,10} found an increased risk among coke byproduct workers in the steel

Table 1 Cohort studies

<i>Authors, date</i>	<i>Industry</i>	<i>Duration of follow up</i>	<i>No exposed</i>	<i>Exposure</i>	<i>Risk of CP</i>	<i>p Value</i>
Mancuso and El-Attar 1967 ¹	Chemical	1938-65	216	β -Naphthylamine/benzidine	Three observed deaths; No expected deaths	
Li <i>et al</i> 1969 ²	Chemical	1948-67	3637	Death cases; various	1.6 (men aged 20-64)	< 0.01
Bond <i>et al</i> 1985 ⁷	Chemical	After 1977	1666	Various	2.3	NS
Thomas <i>et al</i> 1980 ³	Petroleum	1947-77	3105	Death cases; petrol refining and production of petrochemicals	empl < 10 years 3.4 empl > 10 years 1.1	< 0.05 NS
Rushton <i>et al</i> 1981 ⁵	Petroleum	Before 1975	34781	At least 1 year between 1950-76; refinery workers	0.9	NS
Thomas <i>et al</i> 1982 ⁴	Petroleum	1943-79	2509	Death cases; refinery workers	1.4	< 0.05
Hanis <i>et al</i> 1982 ⁸	Chemical and petroleum	Before 1977	8666	At least 1 year between 1970-77; various	1.5	NS
Vena <i>et al</i> 1985 ¹⁸	Car	1970-9	769	Death cases; at least 10 years	1.9 (engine plant)	< 0.05
Redmond <i>et al</i> 1976 ⁹	Steel	1953-66	2543	Coke byproduct workers; hired before 1953	4.5 (non-coke oven workers)	< 0.01
Redmond 1983 ¹⁰	Steel	1953-70 Former study extended to 1970			3.7 (non-coke oven workers)	< 0.01
Rockette and Arena 1983 ¹²	Aluminium	Before 1977	21829	Al reduction; at least 5 years between 1946-77	1.7 (potroom workers)	< 0.01
Milham 1979 ¹¹	Aluminium	Before 1976	2103	Al reduction; at least 3 years with 1 year between 1946-62	1.8	NS
Sheffet <i>et al</i> 1982 ¹³	Pigment plant (lead and zinc chromates)	Before 1979	1946	Hired between 1940-69; at least 1 month	Increased	NS
Selikoff and Seidman 1981 ¹⁷	Asbestos	1967-76	17800	Hired before 1967	1.3	NS
Newhouse <i>et al</i> 1988 ¹⁶	Acetylene	1935-84	981	Crocidolite	Bilston (n = 370) 4.70 Expo > 20 years 6.7 Other plants (n = 611) Copper/tin 1.3	< 0.01 < 0.005 NS NS
Milham 1976 ¹⁴	Metallurgy	1950-71	2697	Death cases; 10 groups of type of metal	Al 2.0	< 0.05
Silverstein <i>et al</i> 1988 ¹⁵	Metallurgy	1950-82	1532	Died 1950-1982; at least 5 years	1.43 expo > 10 years to oil cutting 4.67	NS 0.06
Monson and Fine 1978 ¹⁹	Rubber	1940-76	13570	Hired before 1971; at least 5 years	3.0 (tyre curing)	NR
Delzell <i>et al</i> 1981 ²⁰	Tyre	1954-77	1792	Hired between 1947-54; At least 2 years	1.9	NR
Delzell and Monson 1985 ²¹	Rubber tyre curing	1940-71	1150	At least 2 years	1.5	NS
Lloyd <i>et al</i> 1977 ²²	Printing	1966-8	2604	Died 1966-1968; newspaper printing, commercial, handling	Increased risk all categories and commercial 20-54 years old	< 0.05 0.05 < 0.05
Zoloth <i>et al</i> 1986 ²³	Printing Commercial pressmen	1958-81	1401	Died 1958-1981; at least 5 years	1.6 (expo > 20 years)	< 0.05 < 0.05
Sparks and Wegman 1980 ²⁴	Jewellery	1956-75	931	Died 1956-1975; various	1.8	< 0.05
Costantini <i>et al</i> 1989 ²⁵	Leather	1950-83	2926	Work in tanneries; at least 6 months	1.46 No trend with duration	NS

industry compared with other steel workers; however, this result was significant in non-coke oven workers only. Milham¹¹ showed an increased risk among aluminium reduction plant workers. In the study by Rockette and Arena,¹² the increased risk was significant only in potroom workers with more than five years of exposure. Sheffet *et al*¹³ found a non-significant excess risk in a pigment plant utilising lead and zinc chromates. Milham,¹⁴ in a study of patterns

of cancer mortality associated with exposure to metals, found an excess risk among sheet metal workers, including coppersmiths and tinsmiths, and among aluminium workers. In their study of mortality among workers exposed to metal working fluids and abrasives, Silverstein *et al*¹⁵ found an excess of deaths from cancer of the pancreas with borderline significance among workers with exposure of 10 or more years of oil cutting.

ASBESTOS

Newhouse *et al*¹⁶ found a significant excess of deaths from cancer of the pancreas among workers at acetylene production plants exposed to crocidolite asbestos (used to top off cylinders containing acetylene). Most of the deaths were seen among workers employed as cylinder examiners, who handled crocidolite asbestos, after at least 20 years of follow up. The number of cases were too small, however, to allow definite conclusions. According to Selikoff and Seidman¹⁷ the risk of cancer of the pancreas associated with exposure to asbestos is slightly increased but non-significant.

AUTOMOBILE INDUSTRY

Vena *et al*¹⁸ found a significant excess risk among

workers in the engine plant of an automobile engine and parts manufacturing complex but only for those with 20 or more years of employment. The risk was not increased in the other plants.

RUBBER INDUSTRY

In a cohort study of rubber workers, Monson and Fine¹⁹ found an excess risk of pancreatic cancer among elevators and tyre curers with five or more years of exposure. Delzell *et al* confirmed this result in the rubber tyre industry,²⁰ especially in curing workers.²¹

PRINTING

Lloyd *et al*²² showed an increased risk among printing pressmen. This was only significant, however, for

Table 2 Case control studies

Authors	Industry	Cases	Controls	No cases/ controls	Pairing factors	Risk of CP	p Value
Edling <i>et al</i> 1986	Leather tanning (Sweden)	Deaths from 6 cancer sites	Deaths from non-malignant disease	464/464 (men)	Stratified on age at death and parish	3.1	p < 0.05
Norell <i>et al</i> 1986 ⁶ (case-control study)	Various (Sweden)	CP	Hospital controls (inguinal hernia) + population controls	99/301	Sex, age, parish	Welding 2.0 Petrochemical 2.0 Exp to paint thinners, detergents, floor cleaning agents, polish, refuse Petroleum refineries/ petrol stations SMR = 1.3/1.6 Painting, paint and varnish factories, floor polishing, window cleaning, refuse disposal works increased SMR Paper, printing 2.4 Food, tobacco 2.0	NS NS NS excess risk NS NS NS
Norell <i>et al</i> 1986 ⁶ (cohort study)	Various	Employed men, 1960 census and Swedish cancer register; comparison between obs and exp cases in various occupational groups					
Magnani <i>et al</i> 1987 ²⁶	49 various (England)	Deaths from 5 cancer sites 1959-79	Death from non-malignant disease	343/1315 (men)	Age at death, county of residence		NS NS NS
Maruchi <i>et al</i> 1979 ²⁸	Various	116 cases of CP 1935-74 Comparison with Minnesota population for occupations				Overrepresentation of metal workers (incl sheetmetal workers, welders, tanners, plumbers) under risk of CP	
Pickle and Gottlieb 1980 ²⁹	Various	Death from CP Louisiana 1960-75	Death from non-malignant disease	876/876	Age, sex, race, year of death, parish	Paper industry 1.77 Oil refining 2.11	NS NS
Mack <i>et al</i> 1985 ³⁰	46 professional occupations and industries	CP 1976-81 residents of Los Angeles county	Neighbours of residence	490/490	Age, sex, race, neighbourhood of residence		NS (all)
Mallin <i>et al</i> 1989 ²⁷	Various (Illinois)	Deaths from 7 cancer sites	Non-cancer deaths	7861/2099 (white men)	Adj on age at death, Stratified by race and socioeconomic group	White men Photoengravers and lithographers 4.2 Brick and stonemasons 3.8 Material moving equip 3.8 Sheetmetal workers 3.7 Food 1.86 Textile 1.87 Leather 1.63 Subgroup of manual workers: food 4.83 Subgroup of French nationals: textile 2.30	p < 0.05 NS 0.07 NS p = 0.08 p = 0.03
Pietri <i>et al</i> 1990 ³²	Various (France)	CP 1982-85 in 7 hospitals	Non-cancer control + 1 cancer control	171/317	Adj on age, sex, origin, education, coffee, tobacco, alcohol		

CP = Cancer of the pancreas; NS = non significant.

pressmen aged 20–54 and in the subgroup of commercial pressmen; it was confirmed by Zoloth *et al*²³ among commercial pressmen with 20 years or more of employment.

JEWELLERY

Sparks and Wegman²⁴ found a significant excess risk in jewellery workers, but they did not pinpoint any specific exposure among the various categories found in this occupational branch.

LEATHER INDUSTRY

Costantini *et al*²⁵ studied cancer mortality among workers in the Tuscan tanning industry. They showed a non-significant excess risk of death from cancer of the pancreas.

Case-control studies

Case-control studies are less numerous than cohort studies (table 2). Most of them have attempted to show a risk factor among multiple occupational exposures in cases with pancreatic cancer compared with controls. Magnani *et al*²⁶ found a borderline significant excess risk in the paper industry, printing, and food and tobacco industries. Mallin *et al*,²⁷ in a mortality study for seven cancer sites among workers in Illinois, found a significantly increased odds ratio in several occupations and several industrial branches; among white men, the risk was significantly increased for photoengravers and lithographers, brickmasons and stonemasons, operators of material moving equipment, and sheet metal workers. Blue collar workers in the electric power industry and in electrical machinery manufacturing also had a significant excess risk of cancer of the pancreas. For black workers, the limited usefulness of death certificates due to a high percentage of missing or erroneous information made findings difficult to interpret. Maruchi *et al*,²⁸ in a study in Minnesota, found an over-representation of metal workers among cases of cancer of the pancreas, including sheet metal workers, welders, tanners, and plumbers. Conversely, in two other reports, Pickle and Gottlieb²⁹ and Mack *et al*³⁰ did not single out any occupational branch as a risk factor for this cancer, although Pickle and Gottlieb²⁹ found a non-significant excess risk in the paper industry and petroleum refineries. Edling *et al*³¹ showed a significantly increased odds ratio among leather tanners.

In a case-control study, which we carried out on 171 cases of cancer of the pancreas in France,³² we confirmed some of these findings. We found a borderline significant excess risk among manual workers in the food industry, but only four cases and two controls were concerned. We also found a non-significant excess risk among workers in the leather industry. Part of our analysis was carried out among French nationals only, and a significant excess risk

was found in this subgroup among workers in the textile industry.

Discussion

From this review, it seems that the most consistent results are in the chemical and petroleum industries and in metallurgy, especially for aluminium workers.

A variety of exposures may exist, however, in one professional branch, and the results of the studies do not permit the incrimination of one chemical or physical factor in particular. The most frequently evoked are petroleum and petrochemicals in the petroleum industry, fluoride fumes, sulphur dioxide, carbon dioxide, and polycyclic aromatic hydrocarbons next to potrooms in aluminium reduction plants, solvents in the tyre industry, pigments and solvents in printing, photoengraving, and lithography, abrasives and acid fumes in the jewellery industry, cutting oils, welding fumes, and solvents in metal working, lubrication oils in engine plants of the automobile industry, asbestos in acetylene production plants, dyes, pigments, and chromates in leather tanning, diesel fumes in material moving equipment operating, and textile dust in the textile industry. No particular compound has been singled out for the food industry.

Results based on death certificates may be difficult to interpret as the accuracy of these data varies according to countries, occupation, duration of employment, and other factors.^{27 33 34} The accuracy of these data also varies according to the cause of death, particularly for cancers diagnosed at death or autopsy.^{35 36} Cancer of the pancreas is a rapidly fatal disease, often diagnosed late during the course of the illness, and histological evidence may not be needed to confirm the diagnosis, so death certificates are particularly inaccurate for this disease.

Although most studies were carried out separately according to ethnic origin (especially among white and black people), other potential confounding factors such as consumption of tobacco were often not taken into account. This can bias the results. Indeed, consumption of tobacco is known to vary between socio-occupational groups³⁷ and smoking is the most consistent risk factor, with roughly a doubling of the risk for pancreatic cancer in heavy smokers.

Many studies have taken into account various causes of death in cohort studies and various occupational exposures in case-control studies. Because of this multiplicity of comparisons, some results can be expected to be significant by chance.

Cohort studies using the proportionate mortality ratio method may overestimate (or underestimate) one of the causes of death if an under-representation (or over-representation) of deaths from another cause occurs in the studied group.

Lastly, because cancer of the pancreas does not

occur often, only a few cases occur in cohort studies; this limits statistical power.

From this review, it is possible to identify a risk, and confirm the carcinogenic role, for the pancreas, of some groups of chemical agents found in various occupations. The simultaneous existence of a variety of agents in a single occupation makes it difficult, however, to attribute a carcinogenic role to any one chemical in particular. Further studies are warranted to clarify which of them are specifically involved in the aetiology of cancer of the pancreas.

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