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Occupational Risk Factors and Pancreatic Cancer: A Review of Recent Findings

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Abstract

Several occupational exposures have been linked to excess risk of pancreatic cancer; however, most associations are not well established. The objective of this review article is to report on the more recently published studies (1998–2010), and provide a summary of the most consistently reported occupational risk factors for pancreatic cancer, including exposure to chlorinated hydrocarbon compounds, pesticides, polycyclic aromatic hydrocarbons (PAHs), metals, nitrosamines, radiation, various airborne particles, and employment in sedentary occupations. We conclude that the strongest and most consistent findings linking occupational exposures with pancreatic cancer risk to date are for chlorinated hydrocarbons and PAHs.

Keywords

occupation; pancreatic cancer; epidemiology

INTRODUCTION

Cigarette smoking is the most established risk factor for pancreatic cancer, yet only about 25% of the newly diagnosed cases can be attributed to smoking [1,2]. The proportion of pancreatic cancer that may be attributable to occupational exposures has been estimated to be 12% [3]. While relatively small, occupational risk factors are largely preventable, and thus important to identify and eliminate. Certain occupational exposures have been linked to excess risks of pancreatic cancer; however, few occupational exposures are firmly established pancreatic risk factors since most findings are weak or modest effects, often based on small numbers of participants, and lack consistency across studies [4].

One of the most comprehensive studies of occupational exposures and pancreatic cancer risk to date is a meta-analysis conducted by Ojajärvi et al. which indicated statistically significant associations for chlorinated hydrocarbon compounds and nickel compounds, based on studies published between 1969 and May 1998 [3]. The purpose of our review is to report on the more recently published studies (1998–2010), and provide a summary of the most consistently reported occupational risk factors and those warranting further research.

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Although a discussion of the potential contributing biological mechanisms are beyond the scope of this review, the etiology of pancreatic cancer, which is not completely understood, may be further elucidated by evaluating the occupational exposures that are linked to this rare, yet highly fatal disease [4].

METHODS

Based on previously published studies, we identified the following exposures as the most consistently reported occupational risk factors for pancreatic cancer: chlorinated hydrocarbon compounds, pesticides, polycyclic aromatic hydro-carbons (PAHs) (particularly from aluminum production and diesel exhaust), metals, nitrosamines, radiation, various airborne particles, and employment in sedentary occupations [3,4]. We used PubMED to identify published epidemiologic studies on the occupational exposures listed above and pancreatic cancer that were published between 1998 and 2010; however, some earlier studies of historical importance are also included. The key words we used to search PubMED are: [pancreatic cancer odds ratio (OR) cancer] AND [occupational exposure, occupational risk factors, workers, chlorinated hydrocarbon compounds, organochlorines, pesticides, PAHs, aluminum, diesel, metals, nitrosamines, radiation, silica, dust, sedentary occupations, OR physical activity]. Table 1 lists the studies published between 1998 and 2010 that are included in this review by occupational exposure, and indicates the occupational exposure method used in the study (i.e., job-exposure-matrix (JEM), job or title, self-report, measured in biological sample).

RESULTS

Chlorinated Hydrocarbon Compounds

Chlorinated hydrocarbons are a diverse group of organic molecules used in a variety of applications and products, such as solvents, pesticides, and plastics. Thus, occupational exposure to chlorinated hydrocarbons can occur in different industries via a variety of agents. Three recent meta-analyses of occupational exposures and pancreatic cancer have shown associations for chlorinated hydrocarbons [3,5,6]. These three meta-analyses were conducted by the same investigators and were based on studies conducted between 1969 and 1998 in 20 populations in Europe, North America, and Asia. The first of these analyses examined 32 specific agents and reported that chlorinated hydrocarbon solvents and related compounds had a meta-risk ratio (MRR) of 1.4 (95%CI: 1.0–1.8) [3]. A subsequent and more detailed meta-analysis of chlorinated hydrocarbons found suggestive, but not statistically significant, excess risks for the following types of chlorinated hydrocarbons: trichloroethylene, polychlorinated biphenyl (PCB), methylene chloride, vinyl chloride, and tetrachloroethylene, but not carbon tetrachloride [5]. In addition, based on job title, a significant increased risk was apparent for two occupations linked to chlorinated hydrocarbon exposure, metal degreaser (MRR = 2.0, 95%CI: 1.2–3.6) (based on six populations) and dry cleaner (MRR = 1.4, 95%CI: 1.1–2.4) (based on eight populations) [5]. In the most recent analysis, Ojajärvi et al. applied hierarchical Bayesian methods using both job title and exposure data; they observed roughly double the risk of pancreatic cancer with occupational exposure to chlorinated hydrocarbon compounds (MRR = 2.21, 95%CI: 1.31–

3.68) [6]. A hospital-based case–control in Spain also found a positive, although not statistically significant, association for high exposure to chlorinated hydrocarbon solvents (OR = 1.99, 95%CI: 0.62–6.42), and a statistically significant association when cases were restricted to ductal adenocarcinomas of the pancreas (OR = 4.11, 95%CI: 1.11–15.23), with a significant positive trend in risk with increasing duration of exposure (*P*-trend =0.04) [7]. Chlorinated hydrocarbon exposure is one of the most researched and established occupational risk factors for pancreatic cancer.

Organochlorines

Chlorinated hydrocarbon pesticides encompass the class of insecticides, organochlorines, which were used widely in agriculture and pest control between the 1940s and 1960s throughout the world. Because of reported health concerns and persistence in the environment, use of organochlorines has been restricted [8]. The organochlorine DDT was banned in the United States in 1972 and worldwide for agricultural use in 2004, although it is still used limitedly in vector control and agriculture in some countries such as India and North Korea [8]. In a nested case–control study among chemical manufacturing workers in the United States, ever exposure to DDT was associated with a 4.8-fold risk, and workers with a mean exposure of 47 mo had a 7.4-fold risk of pancreatic cancer compared to those who were never exposed [9]. This study also showed elevated risk for two DDT derivatives, DDD, and ethylan [9]. When this analysis was restricted to cytologically, surgically, or clinically confirmed pancreatic cancer cases the associations with DDT and derivatives became stronger [10]. A population-based case–control study of self-reported environmental and occupational pesticide exposure in Michigan also showed a significant association between ever versus never use of ethylan and pancreatic cancer, and an elevated risk for DDT and any organochlorine (OR = 1.5, 95%CI: 0.8–2.9) [11]. In a cohort study of Australian outdoor workers who applied pesticides, serum level of DDT in exposed workers was five times that of the non-exposed workers, and pancreatic cancer mortality was elevated among those exposed to DDT compared to those not exposed (standardized mortality ratio, SMR = 1.98, 95%CI: 0.79–4.07), although no exposure–response trend was apparent [12]. The meta-analysis of occupational exposures and pancreatic cancer conducted by Ojajärvi et al. also showed a non-significant increased risk for organochlorine exposure (MRR = 1.5, 95%CI: 0.6–3.7) [3]. These findings are supported by two molecular epidemiology studies. In a hospital-based case–control study in Spain, concentrations of DDT were significantly higher for K-*ras* mutated cases than controls ($P < 0.01$), but similar among wild-type cases and controls [13]. This study also reported a significant exposure–response relationship between serum concentrations of DDT and pancreatic cancer among cases with a K-*ras* mutation compared to cases without this mutation (OR = 8.7, 95%CI: 1.6–48.5) [13]. In a population-based case–control study in San Francisco, higher median serum concentrations of organochlorine compounds were detected among pancreatic cancer cases compared to controls [14]. Another recently conducted molecular study examined the relationship between measured concentrations of organochlorines with occupational history [15]. Results of this study indicated significantly higher median serum concentrations of PCBs in exocrine pancreatic cancer patients whose last occupation included “craftsman, manufacturing, construction, or mining” compared to patients not in these occupations, but no considerable differences in other organochlorine compounds (DDT, DDE, HCB, HCH)

by occupational group [15]. Results of a mortality study of male workers in anti-malarial operations in Sardinia, Italy, between 1946 and 1950, indicated that risks of pancreatic cancer were not elevated in the DDT-exposed workers compared to non-exposed workers (risk ratio, RR = 0.8, 95%CI: 0.4–1.8) [16]. In addition, in a nested case–control study in the Agricultural Health Study cohort, exposure to organochlorines was not associated with pancreatic cancer, and exposure to DDT was inversely related to pancreatic cancer (OR = 0.4, 95%CI: 0.2–0.9) [17]. However, these findings may be due to a healthy survivor effect among those who used DDT before it was banned [17]. Thus, there is some evidence that high levels of organochlorines are linked to pancreatic cancer. Future epidemiologic research of this occupational exposure may be warranted in countries that continue to use organochlorines for agricultural and/or vector control.

Other Pesticides

Occupational exposure to pesticides in general has been linked to pancreatic cancer [18–21]. Besides organochlorines, a limited number of studies have examined other types of pesticides. In a hospital-based case–control study in Egypt, ever exposure to agricultural pesticides was associated with an increased risk (OR = 2.6, 0.97–7.2), while ever exposure to natural fertilizers was not linked to an excess risk (OR = 0.1, 0.1–0.4) [22]. In a multicenter population-based case–control study, occupational exposure to fungicides significantly increased pancreatic cancer risk (OR = 1.5) and herbicide exposure non-significantly elevated risk (OR = 1.6) [23]. A case–control study nested in the Agricultural Health Study cohort found significant excess risks of pancreatic cancer among applicators with elevated pendimethalin use (OR = 3.0, 1.3–7.2) and with elevated EPTC use (OR = 2.56, 1.1–5.4) compared to never users of each pesticide [17]. Both of these pesticides are herbicides that contain or can be metabolized to form *N*-nitroso compounds [24,25], which is noteworthy since tobacco-specific nitroso compounds have been implicated as pancreatic carcinogens in cigarette smoke [26,27]. Although limited, studies suggest that certain non-organo-chlorine pesticides may be linked to pancreatic cancer. Further research to identify these pesticides is warranted.

Polycyclic Aromatic Hydrocarbons

PAHs are a class of chemicals that include hundreds of compounds. They are found in crude oils, mineral oils and tar, and can form during the combustion of fossil fuels and oil products. Occupational PAH exposure has been reported in the production of such products as aluminum, coke, carbon black, coal tar, iron, and steel. Epidemiologic studies have reported increased risks of certain cancers in relation to occupational PAH exposure. For pancreatic cancer, the meta-analysis conducted by Ojajärvi et al. showed a nonsignificant elevated risk associated with PAHs (MRR = 1.5, 95%CI: 0.9–2.5) [3]; this association was attenuated in the analysis using hierarchical Bayesian methods (MRR =1.14, 95%CI: 0.89–1.45) [7]. Subsequent studies have also shown positive results for PAH exposure or jobs linked with PAH exposure. A Finnish cohort study of road paving workers, who may likely be exposed to PAHs, reported significant increased mortality among construction workers (SMR = 2.35, 95%CI: 1.08–4.47), and non-significant increased incidence and mortality among bitumen workers [28].

Aluminum production

Studies of the aluminum reduction industry have consistently shown increased pancreatic cancer risks. Three studies of a cohort of male aluminum smelter workers in Norway found suggestive, although not statistically significant, associations for PAH exposure and pancreatic cancer [29–31]. A mortality study of men employed in a prebake aluminum smelter in Italy found statistically significant higher pancreatic cancer mortality rates than expected (SMR = 2.4, 95%CI: 1.1–5.2); the association was higher among workers employed in the anodes factory (SMR = 5.0, 95%CI: 2.1–12.1) and remained significant after adjusting for cigarette smoking [32]. A series of studies in a cohort of aluminum smelter workers in Canada reported a statistically significant excess in pancreatic cancer incidence among workers hired after 1950 [33]. To identify the exposure responsible for the increased risk among aluminum smelter workers, Gibbs et al. examined the relationship between pancreatic cancer and cumulative benozo[a]pyrene exposure, a PAH compound that is a known carcinogens [34], but no exposure-response association was observed [33].

Diesel exhaust

In addition to the aluminum industry, another potential occupational source of PAHs and nitro-PAHs is diesel exhaust. Studies examining the association between diesel exhaust and pancreatic cancer risk are limited, and published results are mixed. In the meta-analysis by Ojajärvi et al., the association between diesel exhaust and pancreatic cancer was null [3]. However, a subsequent study of workers exposed to diesel exhaust in Sweden found a small, but significant, increased risk among men (standardized incidence ratio, SIR = 1.05, 95%CI: 1.00–1.10) [35], and a recent hospital-based case–control in Spain found an approximate twofold risk in relation to diesel engine exhaust (all pancreatic cancer: OR = 1.88, 95%CI: 0.72–4.90; ductal adenocarcinomas of pan creas: OR = 2.08, 95%CI: 0.58–7.38) [7]. This study also reported over a twofold risk among truck drivers (all pancreatic cancer: OR = 2.45, 95%CI: 0.84–7.09; ductal adenocarcinomas of pancreas: OR = 3.46, 95%CI: 1.01–11.83) [7], which is consistent with findings from a case–control study conducted in the 1980s [36].

Metals

Metal work has been repeatedly, although not always consistently, linked to pancreatic cancer [4]. It has been suggested that PAHs, nitrosamine compounds, and chlorinated hydrocarbons, may be among the carcinogenic agents released during production or use of metals and metalworking fluids [4,37]. A systematic review of occupational exposure to metalworking fluids concluded that despite some inconsistencies within and between studies, metalworking fluids may increase the risk of pancreatic cancer [37]. A subsequent study of workers exposed to metalworking fluids in automobile manufacturing plants in Michigan showed elevated SMRs (SMR = 1.44, 95%CI: 1.11–1.83) [38]. Two other recent studies reported increased risks for metal-related jobs among men in Spain [39] and Sweden [40].

Some specific metals that have been linked to increased pancreatic cancer risk include nickel, chromium, and cadmium. The meta-analysis by Ojajärvi et al. found significant elevated risk for nickel exposure (MRR = 1.9, 95%CI: 1.2–2.3) [3]; however, a review of

this analysis reported that two studies with null associations for nickel had been omitted [41]. The same meta-analysis found a non-significant increased risk for exposure to chromium (MRR = 1.9, 95%CI: 0.9–2.3) [3], and a subsequent cohort study of female Finnish workers, observed a significant elevated risk for exposure to chromium (RR = 1.8, 95%CI: 1.0–3.1), with a significant positive trend in risk with increasing exposure (*P*-trend =0.01) [42].

Cadmium is a heavy metal that has been hypothesized to cause pancreatic cancer [43]. It is classified by International Agency for Research on Cancer (IARC) as a known human carcinogen [44], and is a byproduct of cigarette smoke. Epidemiologic data for pancreatic data are sparse, particularly for occupational exposures, which include metal welding, soldering, smelting, electroplating, and manufacturing and/or using batteries, dyes, paints, plastics, fertilizers, and pesticides [43,45]. In the meta-analysis by Ojajärvi et al. cadmium was not associated with increased risk (RR = 0.7, 95%CI: 0.4–1.4) [3]. In the Finnish cohort study of female workers, participants exposed to low levels of cadmium had a significant excess risk (RR = 1.47, 95%CI: 1.01–2.14), but the association was null for those exposed to high levels of cadmium (*P*-trend = 0.21) [42]. In contrast, a hospital-based case–control study in the East Nile Delta region of Egypt, which is an area polluted with heavy metals, pesticides, and hydrocarbons from industrial and agricultural waste, found significantly higher mean serum cadmium levels in cases than controls with a significant positive trend in pancreatic cancer risk with increasing serum cadmium levels (ng/ml) (OR = 1.12, 95%CI: 1.04–1.23, *P*-trend = 0.0089) [46]. It has been suggested that occupational exposure to cadmium may be more prevalent than anticipated; thus, further investigation of this agent seems warranted [43,45].

Nitrosamines

In addition to the metal-related exposures mentioned above, nitrosamines have been reported to be carcinogenic agents in other occupational products, such as rubber and fertilizers/pesticides [4,45,47]. Early studies reported high concentrations of *N*-nitrosamines in the air of rubber factories [48,49]; however, a more recent study found low airborne and urinary levels in exposed workers [50]. A few epidemiologic studies have reported small increased pancreatic cancer risk among rubber and tire manufacturing workers [51–53], but most findings are based on small numbers of cases. With regard to pesticides, two herbicides that metabolize into *N*-nitroso compounds were linked to pancreatic cancer in the Agricultural Health Study [17]. However, the magnitude of effect that occupational exposure to nitrosamines has on pancreatic cancer risk has not been evaluated to date. This may be due to the difficultly in separating nitrosamines from other concomitant agents. Occupational exposure to nitrosamines is a fertile area of future research, particularly since nitrosamines are classified as “probable human carcinogens” by IARC [54], and are the purported pancreatic carcinogens in cigarette smoke [26,45].

Ionizing Radiation

A review of occupational exposure to ionizing radiation in 1990 found no clear evidence of a link with pancreatic cancer [55]. However, a small number of subsequent studies have reported an association. A case–control study in Finland using lifetime occupational

exposure histories reported a 4.3-fold risk (95%CI: 1.6–11.4) [19], and a case–control study in Eastern Spain also found an increased risk, based on three exposed pancreatic cancer cases (OR = 4.73, 95%CI: 0.72–30.88) [7]. A cohort study of nuclear, industrial, medical and dental workers in Canada showed a significant dose–response association (RR per 1 Sv = 9.2, 0.1–36.8) [56].

Airborne Particles

Several airborne particles, such as asbestos, silica, and various dust agents, have been linked to pancreatic cancer in some studies; however, studies are limited and published results are inconsistent [4]. For example, the meta-analysis by Ojajärvi et al. reported null findings for asbestos (MRR = 1.1, 95%CI: 0.9–1.5), wood dust (MRR=1.1, 95%CI: 0.9–2.5), flour dust (MRR = 1.1, 95%CI: 0.8–1.2), and vitreous fibers (MRR = 1.0, 95%CI: 0.6–1.6); whereas silica showed an elevated risk (MRR = 1.4, 95%CI: 0.9–2.0) [3]. Silica was also associated with a significantly increased pancreatic cancer mortality in a cohort of German porcelain and fine ceramic workers (SMR = 1.71, 95%CI: 1.18–2.41) [57]. In contrast, decreasing risks of pancreatic cancer with increasing cumulative exposures to cotton dust (*P*-trend =0.006) and endotoxin (*P*-trend < 0.001) were observed in a cohort of female textile industry workers with a lag time of 20 yr between exposure and diagnosis [58]. The investigators hypothesize that endoxins may be the biologically active agent in cotton dust, and that the reduced risk may be linked to an enhanced immune response [58].

Sedentary Occupations

Physical inactivity, including occupational inactivity or sedentary jobs, has been linked to a higher risk of pancreatic cancer in some studies. However, the association remains inconclusive due to potential confounding by obesity, diabetes, diet, and smoking, as well as the limitations in classifying and accounting for different types of activity (e.g., occupational, leisure, commuting) and the frequency and intensity of the activity [59,60]. A meta-analysis of four prospective studies found that occupational physical activity was associated with a significant protective effect for pancreatic cancer (RR = 0.75, 0.59–0.95) [60]. Although this association persisted after adjustment for smoking (RR = 0.75, 0.59–0.96), it was null after adjustment for body mass index (BMI) (RR = 0.98, 0.71–1.35), suggesting the observed reduced risk associated with physical activity may be due to confounding [58]. Non-occupational physical activity has also been linked to decreased pancreatic cancer risk in a number of other studies [59,60]. Further examination with more detailed measurement of physical activity and control of potential confounders, such as BMI, is warranted, especially given the modifiable nature of this factor.

CONCLUSIONS

Based on a comprehensive meta-analysis of studies published between 1969 and May 1998 and more recent studies published between 1998 and 2010, we conclude that the strongest and most consistent findings linking occupational exposures with pancreatic cancer risk to date are for chlorinated hydrocarbons and PAHs. Some of the specific chlorinated hydrocarbon compounds linked to pancreatic cancer are trichloroethylene, PCB, methylene chloride, vinyl chloride, and tetrachloroethylene; and the most commonly reported industries

associated with chlorinated hydrocarbons are dry cleaning and metal-related work. Organochlorine pesticides have shown relatively strong associations in earlier studies, but appear to be less of a risk factor in the more recent studies where exposure levels may be lower. For PAH exposure, aluminum production and metalworking industries have shown consistent elevated risks for pancreatic cancer. Other agents that have been studied less, but show some provocative findings warranting further research, include non-organo-chlorine pesticides, cadmium, and nitrosamines. Most studies conducted to date have been based on a small number of exposed pancreatic cancer cases, which is not surprising given the rarity and high fatality of this disease, as well as the complexity of obtaining occupational exposure assessment data in epidemiologic studies. In order for future studies to be more robust, they will need to be large enough to have sufficient statistical power to assess occupational exposures while taking into account potential confounding, particularly from smoking. In addition, as more refined exposure assessment techniques become available in occupational epidemiology studies, the individual agents and mixed compounds of exposure will become easier to measure and quantify, which is a limitation of most current occupational studies. Although beyond the scope of this review, studies of biological mechanisms linking these agents to pancreatic cancer will help clarify these epidemiologic findings, as well as provide further insight into the etiology of this cancer.

Abbreviations:

PAHs	polycyclic aromatic hydrocarbons
OR	odds ratio
MRR	meta-risk ratio
PCB	polychlorinated biphenyl
SMR	standardized mortality ratio
RR	risk ratio

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Table 1.

Occupation and Pancreatic Cancer: Selected Publications by Exposure and Publication Year

Occupational exposure category	Refs.	Study design (location)	Study subjects	Occupational exposures	Results
Chlorinated hydrocarbon compounds	Ojajärvi et al. [3]	Meta analysis, 1969–1998 (Asia, Europe, North America)	20 populations	Chlorinated hydrocarbon solvents and related compounds[a]	MRR = 1.4, 1.0–1.8
	Ojajärvi et al. [5]	Meta analysis of chlorinated hydrocarbon solvent exposures, 1969–1998 (Asia, Europe, North America)	5 populations	Trichlorothylene[a]	MRR = 1.24, 0.79–1.97
			5 populations	Polychlorinated biphenyls (PCB)[a]	MRR = 1.37, 0.56–3.31
			4 populations	Methylene chloride[a]	MRR = 1.42, 0.80–2.53
			4 populations	Vinyl and polyvinal chloride[a]	MRR = 1.17, 0.71–1.91
			2 populations	Carbon tetrachloride[a]	MRR = 0.9, 0.2–2.6
			6 populations	Metal degreasing[b]	MRR = 2.0, 1.2–3.6
			8 populations	Laundry and dry cleaning[b]	MRR = 1.4, 1.1–2.4
	Ojajärvi et al. [6]	Meta analysis using hierarchical Bayesian methods, 1969–1998 (Asia, Europe, North America)	20 populations	Chlorinated hydrocarbon solvents and related compounds[a]	MRR = 2.21, 1.31–3.68
			6 populations	Metal-plating workers[b]	MRR = 2.11, 1.33–3.35
			8 populations	Laundry and dry cleaning[b]	MRR = 1.4, 1.12–1.75
	Santibañez et al. [7]	Hospital-based case–control (Eastern Spain)	161 cases, 455 controls	Chlorinated hydrocarbon solvents[a]	All pancreatic cancer: OR = 1.99, 0.62–6.42; Ductal adenocarcinoma: OR = 4.1, 1.11–15.23, *P*-trend = 0.04
Organochlorines	Garabrant et al. [9]	Nested case–control in cohort of chemical manufacturing workers (US)	28 cases, 112 controls	DDT; DDE; ethylan[b]	OR = 4.8, 1.3–17.6; OR = 4.3; OR = 5.0
	Fryzek et al. [11]	Population-based case–control (Southeastern Michigan)	66 cases, 131 controls	Any organochlorine[c]; DDT[c]	OR = 1.5, 0.8–2.9; OR = 1.6, 0.8–3.1
	Porta et al. [13]	Hospital-based case–control (Eastern Spain)	51 cases (34 with *K-ras* mutation, 17 wild-type), 26 controls	Serum concentration of DDT and DDE[d]	DDE cases vs. controls: OR = 5.6, 1.3–24.6, *P*-trend = 0.025; DDE k-ras cases vs. controls: OR = 10.5, 1.9–59.3, *P*-trend = 0.007; DDT K-ras vs. wild-type cases: OR = 8.7, 1.6–48.5, *P*-trend = 0.005; DDE K-ras vs.

Occupational exposure category	Refs.	Study design (location)	Study subjects	Occupational exposures	Results
					wild-type cases: OR = 5.3, 1.1–25.2, *P*-trend = 0.03
	Ojajärvi et al. [3]	Meta analysis, 1969–1998 (Asia, Europe, North America)	3 populations	Organochlorine insecticides[a]	MRR = 1.5, 0.6–3.7
	Hoppin et al. [14]	Population-based case–control (San Francisco)	108 cases, 82 controls	Serum levels of DDE, PCB, HCB, *trans-nonachlor*[d]	Median levels of DDE, PCB, and trans-nonachlor were significantly elevated ($P < 0.5$) in cases compared to controls
	Beard et al. [12]	Cohort of outdoor insecticide applicators compared to non-pesticide workers (Australia)	DDT: 394 exposed, 185 unexposed; 8 cases, 2 controls	DDT[b]	Serum level of DDT five times that of non-exposed; SMR = 1.98, 0.79–4.07
	Cocco et al. [16]	Cohort of antimalarial operation workers (Sardina, Italy)	DDT: 464 exposed, 4088 unexposed; 13 cases, 9 controls	DDT[a]	SMR = 79, 45–139; mortality RR = 0.8, 0.3–1.9
	Andreotti et al. [17]	Nested case–control of pesticide applicators (Iowa, North Carolina)	64 cases, 52 000 controls	DDT[b]	OR = 0.4, 0.2–0.9 based on 6 cases
	Bosch deBasea et al. [15]	Cross-sectional analysis of cases from a hospital-based case–control (Eastern Spain)	135 exocrine pancreatic cancer cases	Serum concentrations of DDT, DDE, PCBs, HCB, HCH[d]	Median levels of PCBs significantly higher in cases whose last occupation included craftsman, manufacturing, construction, mining compared to cases in other occupations ($P \leq 0.005$)
Other pesticides	Forastiere et al. [18]	Population-based case–control (central Italy)	37 cases, 29 controls	Farming[b]	Licensed farmers for >10 yr: OR = 3.78, 1.24–11.0 compared to non-farmers
	Kauppinen et al. [19]	Population-based case–control (Finland)	595 cases, 1622 controls	Pesticides[a]	OR = 1.7, 0.8–3.4
	Cantor and Silberman [20]	Nested case–control in cohort of aerial pesticide applicators and flight instructors (US)	9961 aerial pesticide applicators; 9969 flight instructors; 22 cases, 8 controls	Pesticide application[b]	Mortality RR = 2.71, 1.4–5.3
	Alguacil et al. [21]	Hospital-based case–control (Eastern Spain)	185 cases, 264 controls	Pesticide use[a]	Arsenical pesticides: OR = 3.4, 0.9–12; Other pesticides: OR = 3.17, 1.1–9.2
	Ji et al. [23]	Population-based case–control (US)	484 cases, 2095 controls	Pesticide use[a]	*P*-trend for increasing level of exposure = 0.01

Occupational exposure category	Refs.	Study design (location)	Study subjects	Occupational exposures	Results
	Lo et al. [22]	Hospital-based case–control (East Nile Delta region of Egypt)	129 cases, 194 controls	Pesticide and natural fertilizer exposure[c]	Pesticide: OR = 2.6, 0.97–7.2; natural fertilizer: OR = 0.1, 0.1–0.4
	Andreotti et al. [17]	Nested case–control in cohort of pesticide applicators (Iowa, North Carolina)	64 cases, 52 000 controls	Ever use of 24 pesticides[c]	Pendimethalin: OR = 3.0, 1.3–7.2; EPTC: OR = 2.56, 1.1–5.4
Polycyclic aromatic hydrocarbons (PAHs)	Ojajärvi et al. [3]	Meta analysis, 1969–1998 (Asia, Europe, North America)	4 populations	Polycyclic aromatic hydrocarbons[a]	MRR = 1.5, 0.9–2.5
	Kauppinen et al. [28]	Cohort of road paving workers (Finland)	9643 workers	Bitumen work (6 cases)[a] construction work (9 cases)[b]	SMR = 2.39, 0.88–5.21; SIR 1.52, 0.56–3.31 SMR = 2.35, 1.08–4.47
	Ojajärvi et al. [3]	Meta analysis using hierarchical Bayesian methods, 1969–1998 (Asia, Europe, North America)	20 populations	Polycyclic aromatic hydrocarbons[a]	MRR = 1.14, 0.89–1.45
Aluminum production	Rønneberg et al. [29]	Cohort of aluminum smelter workers (Norway)	2647 short-term workers, 10 cases; 2888 production workers, 12 cases; 373 maintenance workers, 1 case	PAH from aluminum work[b]	*P*-trend for cumulative PAH exposure = 0.13
	Romundstad et al. [30]	Cohort of aluminum plant workers (Norway)	11 103 workers; 46 cases	PAH from aluminum work[b]	SIR = 0.9, 0.7–1.2; *P*-trend for cumulative PAH exposure = 0.08
	Romundstad et al. [31]	Cohort of aluminum reduction workers (Norway)	5627 workers; 13 cases	PAH from aluminum work[b]	SIR = 1.13, 0.6–1.94 for more than 3 yr employment
	Carta et al. [32]	Cohort of prebake aluminum smelter workers (Sardina, Italy)	1152 workers; 6 cases	PAH from aluminum work[b]	SMR = 2.4, 1.1–5.2; SMR for anodes workers = 5.0, 2.1–12.1 (4 deaths)
	Gibbs and Sevigny [33]	Cohort of aluminum smelter workers (Quebec, Canada)	1421 workers; 11 cases	Aluminum reduction[b]	SIR = 259, 129–463
Diesel exhaust	Ojajärvi et al. [3]	Meta analysis, 1969–1998 (Asia, Europe, North America)	7 populations	Diesel engine exhaust[a]	MRR = 1.0, 0.9–1.2
	Boffetta et al. [35]	Cohort of Swedish population using Swedish Cancer Environment Register (Sweden)	1859 male cases, 47 female cases	Diesel exhaust[a]	SIRmen = 1.05, 1.00–1.10; SIR women: 1.09, 0.90–1.45
	Santibañez et al. [7]	Hospital-based case–control (Eastern Spain)	161 cases, 455 controls	Diesel engine exhaust[a]	All pancreatic cancer: OR = 1.88, 0.72–4.90; Ductal adenocarcinoma

Occupational exposure category	Refs.	Study design (location)	Study subjects	Occupational exposures	Results
					of pancreas: OR = 2.08, 0.58–7.38
Metal	Ojajärvi et al. [3]	Meta analysis, 1969–1998 (Asia, Europe, North America)	4 populations	Nickel and related compounds[a]	MRR = 1.9, 1.2–3.2
			9 populations	Chromium and related compounds[a]	MRR = 1.9, 0.9–2.3
	Alguacil et al. [39]	Hospital-based case–control (Eastern Spain)	164 cases, 238 controls	Metal-related jobs[b]	OR = 3.3, 0.5–2.1
	Eisen et al. [38]	Cohort of automobile manufacturing workers (Michigan)	46 399 workers; 66 cases	Metalworking fluids[b]	SMR = 1.44, 1.11–1.83
	Alguacil et al. [40]	Nested case–control in cohort of Swedish workers (Sweden)	4420 male cases, 2143 female cases	Metal processing work[b]	RR = 1.94, 1.12–3.34 based on 13 cases
	Weiderpass et al. [42]	Cohort of female workers based on Population Census of Finland (Finland)	413 877 workers, 1302 cases	Chromium[a]	RR = 1.8, 1.04–3.12; *P* trend = 0.01
	Kriegel et al. [46]	Hospital-based case–control (East Nile Delta region of Egypt)	31 cases, 52 controls	Serum levels of cadmium[d]; Farming[a]	OR = 1.12, 1.04–1.23, *P* trend = 0.0089; OR = 3.25, 1.03–11.64
Nitrosamines	Li and Yu [53]	Nested case–control in rubber industry workers (China)	9 cases, 36 controls	Rubber tire curing[b]	OR = 9.28, 1.00–86.1
Ionizing radiation	Kauppinen et al. [19]	Population-based case–control (Finland)	595 cases, 1622 controls	Ionizing radiation[a]	OR = 4.3, 1.6–11.4
	Zielinski et al. [56]	Cohort of nuclear, industrial, medical and dental workers using National Dose Registry of Canada (Canada)	200 000 workers	Measured ionizing radiation[b]	Excess RR per 1 Sv = 9.2, 0.1–36.8
	Santibañez et al. [7]	Hospital-based case–control (Eastern Spain)	161 cases, 455 controls	Ionizing radiation[a]	OR = 4.73, 0.72–30.88
Airborne particles	Ojajärvi et al. [3]	Meta analysis, 1969–1998 (Asia, Europe, North Americao	3 populations	Silica dust[a]	MRR = 1.4, 0.9–2.0
			4 populations	Wood dust[a]	MRR = 1.1, 0.8–1.5
			1 population	Flour dust[a]	MRR = 1.1, 0.3–3.2
			5 populations	Man-made vitreous fibers[a]	MRR = 1.0, 0.6–1.6
			24 populations	Asbestos[a]	MRR = 1.1, 0.9–1.5
	Li et al. [58]	Nested case–control in cohort of female textile industry workers (Shanghai, China)	267 400 workers; 180 cases, 3183 controls	Cotton dust[a]	HR for 20 yr lag between exposure and diagnosis = 0.6, 0.3–0.9, *P*-trend = 0.006
	Birk et al. [57]	Cohort of porcelain and fine ceramic manufacturing workers (Germany)	17 644 workers, 33 cases	Silica[a]	SMR = 1.71, 1.18–2.41

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Occupational exposure category	Refs.	Study design (location)	Study subjects	Occupational exposures	Results
Sedentary occupations	Bao and Michaud [59]	Meta-analysis	3 studies: Isaksson 2002, Stolzenber-Solomon 2002, Berrington 2006	Occupational physical activity[c]	RR = 0.75, 0.58–0.96
	O'Rorke et al. [60]	Meta-analysis	4 studies: Paffenbarger 1987, Isaksson 2002, Stolzenber-Solomon 2002, Berrington 2006	Occupational physical activity	Crude RR = 0.75, 0.59–0.95; BMI adjusted RR = 0.98, 0.71–1.35; smoking adjusted RR = 0.75, 0.59–0.96

RR, risk ratio; OR, odds ratio; MRR, meta-risk ratio; SMR, standardized mortality ratio; SIR, standardized incidence ratio; HR, Hazard ratio; BMI, body mass index.

[a]Exposure agent based on job exposure matrix (JEM-based).

[b]Based on job or job title.

[c]Self-reported exposure.

[d]Measured in biological sample.