Pancreatic Cancer

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Introduction

Pancreatic cancer is a fatal malignancy associated with rapid progression. One year relative survival rates are less than 30%, and nearly all patients die from the disease within 7 years of surgery [1, 2]. In 2012, it was estimated that 338,000 men and women were diagnosed with pancreatic cancer and 331,000 died of the disease [2]. Although there have been improvements in the diagnosis and prognosis of pancreatic cancer, these changes are minor [3]. Although smoking is the only established nonheritable risk factor for pancreatic cancer, only approximately 30% of the cases can be attributed to smoking [4]. Despite the inconclusive results, obesity, diabetes, alcohol consumption, chronic pancreatitis, diet, physical inactivity, and genetics have also been suggested as risk factors for pancreatic cancer [5, 6]. Given this poorly understood etiology, prevention of this deadly disease remains a challenge.

Etiological studies of pancreatic cancer have encountered methodological obstacles due to the highly aggressive nature of the disease. Disease and exposure misclassifications were major concerns as most studies had to rely upon death certificates or exposure information from next of kin. In addition, the majority of the cohort studies included very few pancreatic cancer cases (less than 50 exposed cases). Despite these challenges, many potential risk factors in occupational settings have been identified and are suspected to be associated with the pathogenesis of pancreatic cancer; approximately 12% of pancreatic cancer cases have been estimated to be attributable to occupational exposures [7, 8].

Occupational Risk Factors of Pancreatic Cancer

Current available studies which investigated occupational factors and the risk of pancreatic cancer have suggested a connection to working in industries such as chemical production, metal manufacturing, printing and paper manufacturing, transport and communication, and textiles. Other professions associated with an increased risk of pancreatic cancer also include solvent-related occupations such as mechanics, leather tanners, and dry cleaners as well as several silica dusts and asbestos-related occupations such as glass manufacturers, potters, and construction workers.

As shown in Table 6.1 (cohort studies) [9–64] and Table 6.2 (case-control studies) [65–83], a number of studies investigated the association between specific occupations and industries and risk of pancreatic cancer. Although these studies have yielded inconsistent results, they do suggest that several occupations and industries may be associated with higher risk of pancreatic cancer.

Chemical, Petroleum, and Related Processing Industries

Previous studies have shown an increased risk of pancreatic cancer among men and women who worked in chemical industries. In a mortality study involving 3637 deaths from the American Chemical Society between 1948 and 1967, Li et al. [12] reported a significantly higher proportion of deaths from pancreatic cancer among male chemists aged 20–64 years compared to professional men in general. In standardized mortality ratio (SMR) studies, Hanis et al. [11] reported an increased risk of pancreatic cancer (SMR = 152) among refinery and chemical plant workers. Bond et al. [15]

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Table 6.1 Cohort studies of occupational exposure and pancreatic cancer

Reference and study location	Cohort description	Exposure assessment	No. of cases/ deaths	Relative risk (95% CI)*
Li et al. [12]	A mortality study involving 3637 deaths from the American Chemical Society between 1948 and 1967	Occupational history from plant records	56	Significant higher proportion of deaths from pancreatic cancer among male chemists aged 20–64 years compared with professional men in general
Milham [13], Washington State, USA	A PMR study involving male death in Washington state between 1951 and 1970	Death certificates	152	Sheet-metal workers PMR = 132; aluminum mill workers PMR = 204
Williams et al. [23], USA	From the third National Cancer Survey Interview Study of 7518 incident cases, lifetime histories of occupations and industries were studied controlling for age, sex, race, education, use of cigarettes or alcohol, and geographic location	Interview of part of the study subjects	Unknown	Increased risk for farmers, painters, trucking services, and public administration
Decoufle [10], USA	2485 white males employed between 1938 and 1967 and had 5 or more years of employment in jobs exposed to cutting oil mists	Company records	8	Expected death = 7.6 for white male workers exposed to cutting oil mists
Chiazze and Ference [9], USA	A cross-sectional mortality study of 3847 deaths occurring among current and former (white) employees of 17 PVC fabricators during 1964–1973 is presented. Sex-race cause-specific PMRs were computed	Industry records	Male = 37; female = 7	PMR = 113 for male and 116 for female employees of PVC fabricators
Hanis et al. [11], USA	A dynamic retrospective cohort including 8666 employees worked at least 1 month between January 1, 1970, and December 31, 1977, at refinery and chemical plant	Occupational history from plant records	23	SMR = 152(96–228) for workers employed in refinery and chemical plant
Rockette and Arena [22], USA	A cohort of 21,829 workers with 5 or more years of employment in 14 aluminum reduction plants	Plant records	63	SMR = 125 for workers employed in aluminum reduction plants
Howe et al. [18], Canada	A mortality study of a cohort of 43,826 male pensioners of the Canadian National Railway Company. The cause of death of 17,838 pensioners who died between 1965 and 1977 was ascertained by computerized record linkage to the Canadian national mortality database	Occupation at the time of retirement	197	SMR = 93 for workers employed in railway company
Decoufle et al. [16], USA	A historical cohort mortality study of 259 male employees of a chemical plant where benzene has been used in large quantities who were employed by the company any time between January 1, 1947, and December 31, 1960, and were followed through December 31, 1977	Industry records	1	SMR = 164 for workers exposed to benzene
Acheson et al. [14], UK	The mortality experience of 5969 men employed in a factory where insulation board was manufactured using amosite asbestos from 1947 to 1979	An industrial hygienist assigned exposure based on job titles	3	SMR = 96 for workers exposed to asbestos
Elinder et al. [17], Sweden	545 men who had been exposed to cadmium for at least 1 year between 1940 and 1980 in a Swedish cadmium-nickel battery factory and who had not died before 1951 were followed through 1983	Industry records	3	SMR = 130 for workers employed in cadmium and/or nickel battery factory
Lynge [19], Denmark	Registration of the cohort was based on company records, supplemented with data from a public pension scheme from 1964 onward till 1982. Cancer cases were identified by linkage with the National Cancer Register. Totals of 3390 males and 1069 females were included in the study	records	3	RR = 0.59 for workers employed in manufacture of phenoxy herbicides

Table 6.1 (continued)

Reference and study location	Cohort description	Exposure assessment	No. of cases/ deaths	Relative risk (95% CI)*
Bond et al. [15], Texas, USA	A general mortality survey was done on a 5% random-start systematic sample ($N = 1666$) of present and former white male employees of a Texas chemical plant	Occupational history from the plant records	7	SMR = 233 for workers employed in chemical plant
Wen et al. [41], Texas, USA	A retrospective cohort mortality study of 1008 male oil refinery workers who ever worked on the lubricating-dewaxing process of the lube oil department and who have been followed for a period of 43 years (January 15, 1935–January 1, 1978)	Occupational history from the plant records	5	SMR = 1.67(0.54–3.89) for workers on the lubricating-dewaxing process
Vena et al. [40], USA	A PMR study including death certificates for workers from three unions representing an integrated automobile factory composed of forge, foundry, and engine (machine and assembly) plants, who died during the period January 1, 1970–December 31, 1979	Occupational history from the plant records	11	PMR = 297* for worker in the engine plant who were employed for more than 20 years
Ott et al. [21], California, USA	A retrospective cohort mortality study ($n = 1919$) was conducted among men employed for 1 or more years, between 1940 and 1969, at an operating division of a large chemical company, followed through 1979	Occupational history from the plant records	6	SMR = 117(43–254) for workers employed in chemical plant
Milham [20], Washington State, USA	In an occupational mortality analysis of 486,000 adult male death records filed in Washington state in the years 1950–1982	Occupational records	174	PMR = 117* for workers occupationally exposed to electromagnetic fields
Zoloth et al. [43], USA	A PMR study in 1401 commercial pressmen	Occupational records	18	PMR = 162 for those employed as commercial pressmen for more than 20 years
Coggon et al. [28], Finland	A mortality study of 5784 employees at a company which has manufactured, formulated, and sprayed 2 methyl-4 chlorophenoxyacetic acid (MCPA) and other phenoxy acid herbicides who were employed by the company during 1947–1975 was traced to the end of 1983	Records	9	SMR = 68 for workers exposed to MCPA and other phenoxy acid herbicides
Brown [27], USA	A retrospective cohort mortality study of workers exposed to polychlorinated biphenyls (PCBs) in two plants manufacturing electrical capacitors was reported in 1981	Records	2	SMR = 54 for workers exposed to PCBs
Wong [42], USA	A cohort of 7676 chemical workers from seven plants who had been occupationally exposed (continuously or intermittently) to benzene for at least 6 months and a comparison group of male chemical workers from the same plants who had been employed for at least 6 months during the same period but were never occupationally exposed to benzene	Occupational records	14	SMR = 92.1 for workers exposed to benzene; SMR = 133 for workers unexposed to benzene
Enterline et al. [30], USA	A mortality study of 1074 white men who retired from a US asbestos company during the period 1941–1967 and who were exposed to asbestos working as production and maintenance employees for the company is reported to the end of 1980	Industry records	8	SMR = 108 for workers exposed to asbestos
Silverstein et al. [38], Detroit, USA	1766 bearing plant workers died between January 1, 1950, and June 30, 1982	Occupational history from plant records	24	Machining (SMOR = 9.9) and grinding (SMOR = 3.2) jobs in straight oil

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Table 6.1 (continued)

Reference and study location	Cohort description	Exposure assessment	No. of cases/ deaths	Relative risk (95% CI)*
Smulevich et al. [39], Soviet Union	The results of a cancer mortality study among workers employed in the production of vinyl chloride and polyvinyl chloride between 1939 and 1977	Industry records	3	SMR = 172 for males
Boffetta et al. [26], USA	In 1982, the American Cancer Society enrolled over 1.2 million American men and women in a prospective mortality study of cancer and other causes in relation to different risk factors. The 2-year mortality of 461,981 males aged 40–79 years with known smoking habit has been analyzed in relation to exposure to diesel exhaust (DE) and to employment in selected occupations related to DE exposure	Questionnaire	27	RR = 1.39 workers exposed to diesel exhaust
Hansen et al. [33], Denmark	A cohort of auto mechanics has been followed through 10 years with regard to cause-specific mortality	Occupational history from plant records	17	SMR = 219* for workers exposed to auto mechanics
Costantini et al. [29], Italy	The mortality of 2926 male workers at the tanneries in the "leather area" of Tuscany was examined from 1950 to 1983	Occupational history from the tanning industry	4	SMR = 146(39–373) for workers at the tanneries
Hearne et al. [34], New York, USA	Mortality study in a 1964–1970 cohort of 1013 hourly wage men exposed to methylene chloride were followed through 1988	Measurement in plant area	8	SMR = 1.9 for workers exposed to methylene chloride
Langard et al. [36], Norway	A cohort study on the incidence of cancers and crude death rates in ferrochromium and ferrosilicon workers was conducted from January 1, 1953, to December 31, 1985	Measurement in plant area	7	Expected death = 6.2 for ferrochromium and ferrosilicon workers
Gustavsson and Reuterwall [32], Sweden	The mortality and incidence study of cancer of 295 workers at a Swedish gas production company. All men employed for at least 1 year in 1965–1972. The follow-up period for mortality was 1966–1986 and the incidence of cancer from 1966 to 1983	Measurement in plant area	Death = 1; incidence = 1	SMR = 67; SIR = 106 for workers at gas production company
Lanes et al. [35], South Carolina, USA	Mortality study of a cohort of 1271 workers involved in the production of cellulose triacetate fiber at a plant in Rock Hill, South Carolina. Each subject was employed for at least 3 months between 1954 and 1977 in jobs that entailed exposure to the highest concentrations of methylene chloride and were followed through 1990	Industry records	2	SMR = 83 for workers exposed to methylene chloride
Gardner et al. [31], UK	A cohort study of 7660 workers exposed to formaldehyde in the British chemical industries was followed through the end of 1989. Those worker first employed before 1965	Measurement records	27	SMR = 90 for workers exposed to formaldehyde
McDonald et al. [37], Canada	A cohort of some 11,000 men born in 1891–1920 and employed for at least 1 month in the chrysotile mines and mills of Quebec was established in 1966 and has been followed between 1976 and 1988	Industry records	37	SMR = 102 for workers employed in the chrysotile mines and mills
Benson et al. [25], West Virginia, USA	278 men assigned to the chlorohydrin unit, which produced ethylene chlorohydrin (ethylene dichloride and bischloroethyl ether as by-products), were followed up for mortality from 1940 to the end of 1988. Mean duration of assignment was 5.9 years, and mean duration of follow-up was 36.5 years	Occupational records	8	SMR* = 492(158–1140) for workers exposed to ethylene chlorohydrin

Table 6.1 (continued)

Reference and study location	Cohort description	Exposure assessment	No. of cases/ deaths	Relative risk (95% CI)*
Asp et al. [45], USA	An 18-year follow-up for mortality and cancer morbidity in a cohort of 1909 men who had started spraying chlorophenoxy herbicides (mixture of 2,4-dichlorophenoxyacetic acid [2,4-D] and 2,4,5-trichlorophenoxyacetic acid [2,4,5-T]) in 1955 through 1971	Questionnaire to subjects or next of kin	12	SMR = 73–12 for workers exposed to chlorophenoxy herbicides
Yassi et al. [58], Canada	A mortality study to December 1989 of a cohort of 2222 males employed between 1947 and 1975 at a transformer manufacturing plant in Canada where there had been extensive use of transformer fluid, some containing polychlorinated biphenyls (PCBs)	Industry records	11	SMR = 292–764* for workers exposed to PCBs
Wong et al. [57], USA	A mortality study of 15,826 workers employed in the reinforced plastics and composites industry with exposures to styrene monomer and other chemicals for at least 6 months in 1948–1989	Occupational records	19	SMR = 113 for workers exposed to styrene monomer and other chemicals
Brown et al. [49], South Carolina, USA	A retrospective cohort mortality analysis of 3022 workers from a South Carolina textile plant where chrysotile asbestos was the primary exposure	Records	15	SMR = 146 for workers exposed to chrysotile asbestos
Anttila et al. [44], Finland	A cohort of 2050 male and 1924 female workers monitored for occupational exposure to trichloroethylene, tetrachloroethylene, or 1,1,1-trichloroethane was followed up for cancer incidence in 1967–1992	Personal measurement, monitoring	12	SIR = 204* for after 10 years of exposure to trichloroethylene, tetrachloroethylene, or 1,1,1-trichloroethane
Enterline et al. [54], England	A mortality study of 2802 men who worked at a copper smelter for a year or more during the period 1940–1964 and who were followed up for deaths during the period 1941–1986. Estimates of exposure for the period 1977–1984 were added	Measurement from air and urine	14	SMR = 86 for workers worked at a copper smelter
Hansen and Olsen [56], Denmark	The risk for cancer morbidity in Denmark during 1970–1984 was estimated among men whose longest employment had been held since 1964, at least 10 years before diagnosis, in 265 companies in which exposure to formaldehyde was identified	Registry data	69	Standardized proportionate incidence ratio (SPIR) = 1.0 for workers exposed to formaldehyde
Baris et al. [47], Canada	A historical cohort mortality study was carried out on 21,744 workers who were employed in an electrical company in the province of Quebec between 1970 and 1988	The last job held by each study subject was coded. A job-exposure matrix (JEM) was used to estimate the exposure to 60 Hz electromagnetic fields (EMFs) and pulsed EMFs in this job	23	SMR = 76 exposed to EMFs
Gibbs et al. [55],	A mortality study of 3211 cellulose fiber production workers who were on the payroll on or after January 1, 1970, and who had worked at a plant for 3 or more months were followed through December 31, 1989	Measurement records	3	SMR = 35–89 for cellulose fiber production workers

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Table 6.1 (continued)

Reference and study location	Cohort description	Exposure assessment	No. of cases/ deaths	Relative risk (95% CI)*
Boffetta et al. [48], Europe	A follow-up of cancer mortality for a cohort study of 22,002 workers employed in man-made vitreous fiber production industries from Denmark, Finland, Norway, Sweden, the United Kingdom, Germany, and Italy, from 1982 to 1990	Factory records	60	SMR = 120 for workers employed in man-made vitreous fiber production industries
Cocco et al. [53], Italy	A mortality study of 1388 workers and laborers in production and maintenance departments was conducted in an Italian lead-smelting plant. The vital status of cohort members was determined from 1950 to 1992	Measurement from industrial hygiene survey	7	SMR = 99 for workers employed in lead-smelting plant
Cocco et al. [52], Italy	A PMR of 1043 deaths among men who took part in an antimalarial campaign in Sardinia, Italy, from 1946 to 1950	Records	3	PMR = 55 for workers exposed to DDT
Kogevinas et al. [61], International	Cancer mortality in a historical cohort study of 21,863 male and female workers in 36 cohorts exposed to phenoxy herbicides, chlorophenols, and dioxins in 12 countries. Subjects were followed from 1939 to 1992	Job records, company exposure questionnaire	47	SMR = 94 for workers exposed to phenoxy herbicides, chlorophenols, and dioxins
Anttila et al. [51], Finland	Cancer incidence among 3922 male and 1379 female workers monitored for exposure to styrene, toluene, or xylene was followed after the first personal measurement comprised 66,500 person-years at risk over the period 1973–1992	Personal measurement, monitoring	5	SIR = 277 for those exposed to aromatic hydrocarbons for more than 10 years
Hooiveld et al. [59], Netherlands	A mortality study of 1167 workers exposed to phenoxy herbicides, chlorophenols, and contaminants (2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) and other polychlorinated dioxins and furans) between 1955 and 1985 were followed through 1991 in a chemical industry in the Netherlands	Industry records and questionnaire	4	SMR = 250 for workers exposed to phenoxy herbicides, chlorophenols, and contaminants
Sathiakumar et al. [63], USA	A retrospective follow-up study (1943–1991) was conducted of 15,649 men employed for at least 1 year at any of eight north American styrene-butadiene rubber plant	Occupational records	43	SMR = 82 for workers employed in styrene-butadiene rubber plant
Jarup et al. [60], Sweden	869 battery workers exposed to nickel hydroxide and cadmium oxide, employed at least 1 year between the years 1940 and 1980, were followed up until 1992. Incidence obtained from the Swedish Cancer registry, vital status and cause of death obtained from the Swedish cause of death registry	Employment records, workplace measurement reports, and interviews with key informants in the factory	Death (male = 6; female = 1); incidence (male = 7)	SMR = 148 for males; SMR = 220 for females; SIR = 194 for male workers exposed to nickel hydroxide and cadmium oxide
Wiebelt et al. [64], Germany	A historical cohort included 6830 German men from 11 plants who were exposed to toluene from 1960 to 1992 in three work areas with different exposure levels	Industry records	5	SMR = 94.3 for workers exposed to toluene
Rafnsson et al. [62], Iceland	A cohort comprised 1332 men and 426 women employed in the printing industry in Iceland according to a published union registry, then linked to the Cancer registry	Industry records	Death (male = 3, female = 1)	SIR = 83 for male workers; SIR = 124 for female workers employed in printing industry

Table 6.1 (continued)

Reference and study location	Cohort description	Exposure assessment	No. of cases/ deaths	Relative risk (95% CI)*
Alguacil et al. [50], Sweden	Historical cohort of 1,779,646 men and 1,101,669 women gainfully employed at the time on January 1, 1970, census and were still alive and over age 24 on January 1, 1971, followed up for 19 years until 1989	Occupational records from Swedish cancer environment register and census	4420 men and 2143 women	Women: Educational methods advisors (RR = 2.6*); librarian, archivist, and curator (RR = 1.7*); motor vehicle or train driver (RR = 2.5*); typographer and lithographer (RR = 2.3*); purser, steward, and stewardess (RR = 5.2*); other housekeeping and related workers (RR = 2.9*); electrical, electronic, and related workers (RR = 1.7*); and glass, pottery, and tile workers (RR = 2.4*). Men: Technical assistants (RR = 2.8*), traveling agents (RR = 1.6*), other metal processing workers (RR = 1.9*), baker and pastry cook (RR = 1.4*), docker and freight handler (RR = 1.6*), and waiters (RR = 2.1)

Cohort studies reported results on pancreatic cancer somewhere in the tables but not in the abstract or the title were not included in this table
*$P < 0.05$

vreported an increased risk of pancreatic cancer (SMR = 233) among chemical workers. Wen et al. [41] reported an elevated risk among oil refinery workers (SMR = 167). Ott et al. [21] found an increased risk of pancreatic cancer associated with chemical manufacturing job. However, none of the results from the above studies were statistically significant. In a mortality study of chlorohydrin production workers, Benson and Teta [25] observed a statistically significantly elevated death due to pancreatic cancer (SMR = 492) in these workers who produced dichloromethane. An occupational mortality study in Washington State also indicated that chemists, chemical engineers, and chemical company workers experienced elevated proportional mortality rate (PMR) for pancreatic cancer [84].

A case-control study using the death certificates of 343 pancreatic cancer cases and 1315 other-cause-of-death cases as controls observed an odds ratio (OR) of 1.4 for people working in the chemical and allied industries [73]. A hospital-based case-control study of 198 pancreatic cancer cases and 209 controls reported a slightly elevated risk (OR = 1.2) among long-term workers in a chemical processing industry [68]. One case-control study of 625 pancreatic cancer cases and 1700 other cancer controls by Partanen et al. [80] reported a slightly reduced risk of pancreatic cancer associated with employment in the chemical and allied industries. In a high pancreatic cancer mortality region of Louisiana, 876 pancreatic cancer death records were matched to controls by age, race, sex, year of death, and parish of residence. The study found a twofold OR for workers in the oil refining industries [75]. A population-based case-control study in Iowa by Zhang et al. [83] observed a statistically significantly increased risk of pancreatic cancer associated with industries of chemical and allied products (OR = 3.5).

It is biologically plausible that an increased risk of pancreatic cancer can be associated with working in chemical industries, since many chemical agents have been suggested as carcinogens and some have been shown to increase the risk of pancreatic cancer. For example, a cohort study in Finland including 2050 male and 1924 female workers exposed to trichloroethylene, tetrachloroethylene, or 1,1,1-trichloroethane between 1967 and 1992 reported an increased risk of pancreatic cancer [44]. In a nested case-control study involving 28 pancreatic cancer deaths and 140 randomly selected controls, Selenskas et al. [82] observed an increased risk of pancreatic cancer associated with processing vinyl and polyethylene. Another nested case-control study by Garabrant et al. [69] involving 28 pancreatic cancer deaths and 112 matched controls reported that exposure to DDT was associated with an increased risk of pancreatic cancer. A population-based case-control study from Finland

Table 6.2 Case-control studies of occupational exposure and pancreatic cancer

Reference, study location and period	Characteristics of cases	Characteristics of controls	Exposure assessment	Results	Comments
Pickle et al. [75], Louisiana, USA, 1960–1975	876 death of pancreatic cancer	Death controls matched by age, race, sex, year of death, and parish of residence	Death certificate	Oil refining (OR = 2.1); paper processing (OR = 1.8)	
Lin and Kessler [71], USA	109 incident cases	109 cancer-free hospital controls	Personal interview	OR = 5.1* for men exposed to dry cleaning and gasoline for more than 10 years	Adjusted for smoking
Mack et al. [72], Los Angeles, USA, 1975–1981	490 cases representing working-age population	Equal number of neighborhood controls	Questionnaire directly from 124 pairs	No association	
Magnani et al. [73], UK	343 aged 18–54 male pancreatic cancer identified from 1959–1963 to 1965–1979 death certificates	Each case was assigned two controls who had died in the same year from other causes	Death certificate, JEM	Paper, printing, and publishing (OR = 2.2*); chemicals and allied industries (OR = 1.4); coal and petroleum products (OR = 1.8); food, drink, and tobacco (OR = 1.5);public administration and defense (OR = 1.6)	No confounding information available
Mallin et al. [74], Illinois, USA	2444 pancreatic cancer deaths	3198 noncancer death	Death certificates	OR = 3.7* for metal workers; OR = 4.2* for photoengravers and lithographers; OR = 5.3* for sales occupation; and OR = 3.8* for brickmasons and stonemasons	No confounding information available
Pietri et al. [76], France, 1982–1985	171 (105 men and 66 women) from 7 hospitals in Paris	317 controls matched for age at interview, sex, hospital, and interviewer	In-person interview	Workers in the textile industry (OR = 1.87), food industry (OR = 1.86)	Adjusted for smoking
Falk et al. [68], Louisiana, USA, 1979–1983	198 cases	209 hospital-based controls	Questionnaire	White-collar occupations showed consistent elevations in risk; risks for truck drivers (OR = 1.7) and those with long-term employment in machine repair or as mechanics were suggestive (OR = 2.5); risks were slightly elevated for long-term workers in the chemical processing industry (OR = 1.2)	Adjusted for smoking
Garabrant et al. [69], Philadelphia, USA, 1953–1988	28 cases from a mortality cohort in chemical plant	112 matched controls	Questionnaire from next of kin	Exposure to DDT associated with increased risk RR = 4.8*	Adjusted for smoking
Partanen et al. [80], Finland, 1984–1987	625 incident cases aged 40–74	1700 cancer referents (stomach, colon, and rectum) matched on age	Job history obtained from next of kin	Elevated risk for stone mining (OR = 3.7), cement and building materials (OR = 11.1), pharmacists and sales associates in pharmacies (OR = 12.9), male wood machinists (OR = 4.1), male gardeners (OR6.7), female textile workers (OR = 5.4), and male transport inspectors and supervisors (OR = 9.4)	No confounding information available

Table 6.2 (continued)

Reference, study location and period	Characteristics of cases	Characteristics of controls	Exposure assessment	Results	Comments
Selenskas et al. [82], New Jersey, 1946–1988	28 male cases from a mortality cohort with potential exposure at plastics manufacturing and research and development facility	140 randomly selected controls	Job history obtained from work plant records	OR = 7.15* for male worker assigned to a work area that processed vinyl resins and polyethylene more than 16 years	Nested case-control study, no confounding information available
Kauppinen et al. [77], Finland, 1984–1987	595 incident cases with a response rate of 47%	1622 community controls with a response rate of 50%	Mailed questionnaire to next of kin, job-exposure matrix	Ionizing radiation (OR = 4.3*), nonchlorinated solvents (OR = 1.6–1.8), pesticides (OR = 1.7), inorganic dust containing crystalline silica (OR = 2.0*), heat stress (OR = 2.2), rubber chemicals including acrylonitrile (OR = 2.1)	Adjusted for smoking, all proxies
Mikoczy et al. [79], Sweden, 1900–1989	Nested case-control study, cases = 68 with 10 pancreatic cancer cases	178 matched controls from the cohort of 2487 workers employed for at least 6 months during the period 1900–1989 in three Swedish leather tanneries	Industry records	OR = 7.2* for leather dust exposure	Adjusted for tobacco smoking
Bardin et al. [67], Michigan, USA	97 deceased cases from a cohort of 46,384 hourly employees who had worked at least 3 years prior to January 1, 1985, at three auto part manufacturing facilities	1825 controls selected from the same cohort matched on race, sex, plant, and date of birth (±5 years)	Exposures were estimated for each unique plant, department, job, and calendar period in an exposure matrix	OR = 3.0* for those exposure to synthetic fluids in grinding operations with more than 1.4 mg/m^3 years of exposure	No confounding information available
Ji et al. [70], Shanghai, China, 1990–1993	451 incident cases with a response rate of 78.2%, 37% histologically confirmed	1552 population controls with a response rate of 84.5%	In-person interview, JEM	Men: Electrician (OR = 7.5*); metal workers (OR = 2.1); toolmakers (OR = 3.4*); plumbers and welders (OR = 3.0*); glass manufacturers, potters, painters, and construction workers (OR = 2.6*); exposure to electromagnetic fields (EMFs). Women: Textile workers (OR = 1.4)	Adjusted for confounding factors
Kernan, et al. [78], 24 US states, 1984–1993	63,097 persons who died from pancreatic cancer in 24 US states	252,386 persons who died from causes other than cancer in the same period	Death certificate, JEM	Industries (i.e., printing and paper manufacturing; chemical, petroleum, and related processing; transport, communication and public service; medical and other health-related services) and occupations (i.e., managerial, administrative, and other professional occupations; technical occupations; and sales, clerical, and other administrative support occupations) associated with increased risk with OR = 1.1–1.2. Based on JEM, formaldehyde OR = 1.4 for high probabilities of exposure	No confounding information available

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Table 6.2 (continued)

Reference, study location and period	Characteristics of cases	Characteristics of controls	Exposure assessment	Results	Comments
Alguacil et al. [65, 66], Spain, 1992–1995	185 incident cases with 164 included	264 hospital-based controls with 238 included	In-person interview	Men: Significant increased risks for physical, chemistry, and engineering science technicians; nonsignificant risks for metal molders, sheet-metal workers, structural metal workers, welders, and related workers; painters and varnishers; machinery mechanics and fitters. Women: Elevated risks for agricultural workers; textile and garment workers. Mutations in K-ras gene modified association with hydrocarbon solvents	Adjusted for smoking
Zhang et al. [83], Iowa, USA, 1985–1987	376 incident cases (202 males and 174 females) with a response rate of 88%	2434 population-based controls (1601 males and 833 females) with response rates of 82% (<65 years) and 79% (≥65 years)	Self-administered questionnaire, 90.2% of cases and 10% of controls from proxies	Men: Industries of chemicals and allied products (OR = 3.5*) and railroad transportation (OR = 4.1*); insurance sales occupations (OR = 5.5*) and railroad brake, signal, and switch operators (OR = 5.9*). Women: Industries of furniture and home furnishing stores (OR = 5.5*); textile sewing machine operators and tenders(OR = 3.9*)	Adjusted for smoking, but too many proxies in cases
Santibanez et al. [81], Spain, 1995–1999	161 incident cases (95 cases histologically confirmed) with a response rate of 80.9%	455 hospital-based controls with a response rate of 99.6%	In-person interviews; 12% of cases and 4% of controls are proxies, JEM	Men: Worked as miners, shot-firers, stone cutters, and carvers; machinery mechanics and fitters; building trades workers; motor vehicle drivers; and waiters. Women: Office clerks and waiters. Occupational exposure to chlorinated hydrocarbon solvents (OR = 4.1*), synthetic polymer dust, ionizing radiation, suggestion risk for pesticides, diesel and gasoline engine exhaust, and hydrocarbon solvents	Adjusted for smoking

*$P < 0.05$

including 595 cases and 1622 controls reported an elevated risk associated with occupational exposure to solvents (including aliphatic and aromatic hydrocarbons) [77]. Two meta-analyses reported an elevated risk of pancreatic cancer associated with occupational exposure to chlorinated hydrocarbons [7, 85]. One examined 32 specific agents and found that chlorinated hydrocarbon solvents and related compounds had a meta-risk ratio (MRR) of 1.4 (95%CI: 1.0–1.8) [7]. Another one applied hierarchical Bayesian methods using both job title and exposure data; they observed a more than twofold increased risk of pancreatic cancer associated with occupational exposure to chlorinated hydrocarbon compounds (MRR = 2.21, 95%CI: 1.31–3.68) [85]. A recent hospital-based case-control study in Spain further supports a positive association between exposure to chlorinated hydrocarbon solvents and pancreatic cancer, but the association seemed stronger for 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 for trend = 0.04) [81].

Metal Manufacturing Industries

Elevated risks of pancreatic cancer have been reported to be associated with metal manufacturing industries by a number of studies. Milham [13] reported an increased mortality of pancreatic cancer in aluminum mill workers and in sheet-metal workers. Maruchi et al. [86] reviewed all cases diagnosed in bona fide residents of Olmsted County, Minnesota, from 1935 to 1974 and found an overrepresentation of metal workers among patients with pancreatic cancer. A PMR study in workers from an automobile factory composed of forge, foundry, and engine (machine and assembly) plants reported a statistically significant PMR of pancreatic cancer in the engine plant (PMR = 1.9) [40]. Another PMR study in a bearing plant also reported an increased risk of pancreatic cancer [38]. A death certificate mortality study in Illinois reported an elevated risk of pancreatic cancer among metal workers [74]. Acquavella et al. [24] examined a metal work cohort ($n = 3630$) and found an excess in the mortality rate of pancreatic cancer. Ji et al. [70] reported an increased risk of pancreatic cancer among Chinese metal workers.

Studies have also investigated specific metals and metallic compounds in relation to pancreatic cancer. A study followed a group of Swedish battery workers exposed to nickel hydroxide and cadmium oxide and found an increased SIR and SMR for pancreatic cancer [60]. Rockette and Arena [22] followed a cohort of 21,829 workers with 5 or more years of employment in 14 aluminum reduction plants and found an elevated mortality for pancreatic cancer. A meta-analysis reported an excess in pancreatic cancer risk for nickel and nickel compounds and chromium and chromium compounds, but not for cadmium and cadmium compounds [7]. Individuals who work in metal manufacturing industries are exposed not only to different metals and metallic compounds but also to silica, lubricants, and chemical fumes [13]. For example, exposure to polycyclic aromatic hydrocarbons (PAHs), a class of chemicals including hundreds of compounds, was found in metal manufacturing industries such as aluminum production industry and iron and steel foundry [87]. While earlier meta-analyses showed a nonsignificant increased risk of pancreatic cancer associated with occupational exposure to PAHs [7, 85], subsequent studies supported a positive association between PAHs and pancreatic risk [88]. It is possible that the elevated risk of pancreatic cancer associated with metal manufacturing industries could be the joint effect of multiple exposures.

Printing and Paper Manufacturing Industries

A PMR study of 1401 commercial pressmen showed a significant PMR of pancreatic cancer among those employed 20 years or longer [43]. Similar results were found in another study of printing pressmen [89]. The Third National Cancer Survey of 7518 incident cancer cases found an elevated risk of pancreatic cancer associated with printing workers [23]. Wingren et al. [90] investigated mortality patterns among Swedish pulp and paper mill workers and reported excess risk of pancreatic cancer. The Louisiana study found twofold odds ratios for workers in the paper manufacturing industries [75]. Kernan et al. [78] reported a statistically significant increase in risk of pancreatic cancer associated with printing and paper manufacturing. In the Swedish population, Alguacil et al. [50] reported an elevated risk of pancreatic cancer among printing workers in women. While most studies reported an elevated risk, some studies did not observe an association with pancreatic cancer among those workers [62, 64]. It was suggested that exposures to solvents might be the most likely explanation for the association even though specific solvents were not identified [78].

Transport and Communication Industries

A prospective mortality study of cancer by the American Cancer Society involving 461,981 males aged 40–79 years with known smoking habits reported an elevated risk of pancreatic cancer among truck drivers [26]. The Finland study, using other cancer patients as controls, reported an elevated risk of pancreatic cancer for male transport inspectors and supervisors [80]. A hospital-based case-control study of 198 cases and 209 controls indicated an increased risk of pancreatic cancer for truck drivers [68]. A population-based study in Iowa reported that men who worked as heavy truck drivers, or as railroad brake, signal, and switch operators, had an increased risk of pancreatic cancer [83]. A recent hospital-based case-control study in Spain found an approximately twofold increased risk associated with diesel engine exhaust and two to threefold increased risk among truck drivers [81]. Workers in these occupations may be heavily exposed to motor exhaust, which contains PAHs that have been classified as human carcinogens [91] and have been linked to an increased risk of pancreatic cancer [7, 85, 88]. In addition to PAHs, individuals who worked in such industries may also be exposed to a variety of hazardous materials such as cutting oils, solvents, and metal dust, which have been suggested as risk factors [38, 85, 92].

Textile Industries

An occupational mortality study in Washington State reported a threefold increase in pancreatic cancer mortality in both men and women fabric workers under 65 years old [93]. A case-control study involving 625 pancreatic cancer cases and 1700 other cancer controls in Finland found an

increased risk among female textile workers [80]. A hospital-based case-control study in Spain observed an elevated risk among female textile and garment workers [65]. A hospital-based case-control study in France reported an increased risk of pancreatic cancer associated with textile industry [76]. A population-based case-control study in Iowa observed an increased risk of pancreatic cancer for female textile sewing machine operators and tenders, and the risk was greater with longer duration of employment in this occupation [83]. A population-based case-control study in Shanghai China also found an elevated risk among female textile workers [70]. It has been speculated that the excessive risk associated with textiles workers may be related to exposure to spinning oils or textile dusts [68]. In contrast, a cohort study in Shanghai China reported that occupational exposure to cotton dust and endotoxin in the textile industry was associated with a reduced risk of pancreatic cancer [94].

Other Occupations and Industries

In addition to the abovementioned industries and occupations that have been relatively well studied, an increased risk of pancreatic cancer has been linked to several other occupational settings. Results from these epidemiological studies, however, have been inconsistent. For example, an elevated risk in glass manufacturers, potters, and construction workers was suggested by some studies [70, 76]. It was unclear whether the association was due to exposures to silica dusts, asbestos, or other industrial dusts [68, 93]. Several solvent-related occupations or industries such as mechanics [33, 65, 68, 80], leather tanners or other leather industries [29, 43, 73, 76], and dry cleaners [71] have been associated with an increased risk of pancreatic cancer. Although farmers are typically exposed to pesticides which have been linked to an increased risk of pancreatic cancer [69, 95, 96], studies have not observed an increased risk of pancreatic cancer among farmers [78, 82]. Employment in furniture and home furnishing stores, medical and other health-related services, educational services, purchasing agents and buyers, supervisors of sales occupations, and insurance sales people have also been suggested to be associated with pancreatic cancer risk [78, 83]. In the absence of exposure to environmental hazards, lifestyle risk factors, such as lack of physical activity [97, 98], may play a role in the development of pancreatic cancer among these workers. While occupational physical activity was associated with a reduced risk of pancreatic cancer based on a meta-analysis of four prospective cohort studies [99], another study found that a reduced risk of pancreatic cancer associated with occupational exposure to physical activity became null after adjusting for body mass index (BMI), suggesting that the observed reduced risk associated with occupational physical activity may be due to confounding factors [94]. It is also possible that exposure to infectious agents may play a role in the development of pancreatic cancer in these professions, since they require extensive personal contacts [83].

General Considerations

When interpreting results from occupational studies, it is important to take the "healthy worker effect" into consideration. Individuals able to sustain employment require a minimum level of health. Employed individuals tend to be healthier than the general population that includes both healthy and sick people. In studies comparing the incidence or mortality of occupational settings to those of the general population, true associations are likely to be underestimated.

Several other issues needed to be considered as well, when interpreting the occupational risk factors.

First, studies using occupation/industry titles to evaluate occupational exposures are likely to introduce exposure misclassification. Occupation/industry titles lack information on specific environmental hazardous agents. Workers classified under a specific occupational title or employed in a specific industry can be exposed to more than one agent. On the other hand, exposure to one agent can occur at multiple occupations or industries. The same occupational title may vary between different industries and may have different exposure levels with regard to agents. A job-exposure matrix, linking information from both occupation and industry titles with specific exposure, would therefore minimize exposure misclassification.

Second, many occupational studies were based on deceased cases due to the clinically aggressive nature of the disease. This limits the quality and quantity of information available. As a result, many previous studies have failed to control for potentially confounding factors such as smoking.

Third, given the rarity of pancreatic cancer, most available studies had limited power to detect small to moderate associations between certain occupational exposures and risk of pancreatic cancer. Thus, many studies were likely unpublished because they were unable to detect meaningful associations. For this reason, pooling of data from projects and replication of studies is very important.

Fourth, nonoccupational risk factors may play a synergistic role with occupational factors in the risk of pancreatic cancer. Integration of occupational and nonoccupational risk factors would provide a more precise profile for predicting individuals' risks. Finally, genetic susceptibility should also be considered when investigating occupational risk factors.

Non-occupational Risk Factors of Pancreatic Cancer

Smoking

A positive association between cigarette smoking and pancreatic cancer has been demonstrated by nearly all studies published since the 1960s. In a large meta-analysis, current smokers experienced a 70% increased risk of pancreatic cancer compared to nonsmokers, and the risk showed clear dose–responses [100]. After cessation of cigarette smoking, the risk remains elevated for a minimum of 10 years [100]. A recent pooled analysis from the International Pancreatic Cancer Cohort Consortium further demonstrated that current smokers had significantly elevated risk of pancreatic cancer (OR = 1.77) compared to nonsmokers and the risk increased significantly with greater intensity, duration, and cumulative smoking dose [101]. This pooled analysis also indicated that risks after more than 15 years after smoking cessation were similar to that for never smokers [101], which highlights the importance of smoking cessation in disease prevention. Environmental tobacco smoke or passive smoke contains many of the same carcinogenetic chemicals as active smoke [102]. However, very few studies have investigated the association between passive smoke and pancreatic cancer risk. Results from the limited studies have provided mixed results [103–106].

Alcohol Consumption

Based on the results from most case-control and cohort studies, an International Agency for Research on Cancer (IARC) Monograph working group in 2007 concluded that there was an inadequate evidence of the role of alcohol in pancreatic cancer in humans [107]. However, a positive association between heavy alcohol consumption and pancreatic cancer has been suggested by studies that collected detailed information on alcohol consumption [108–119]. A recent pooled analysis using data from the International Pancreatic Cancer Case-Control Consortium further demonstrated that heavy drinkers experienced an increased risk of pancreatic cancer, whereas light to moderate alcohol consumption was not associated with an increased risk of pancreatic cancer [120].

Coffee Consumption

Since McMahon et al. [121] in 1981 reported a strong positive association between coffee consumption and risk of pancreatic cancer, numerous studies have subsequently investigated the relationship and have provided inconsistent results. A meta-analysis of 14 cohort studies conducted in 2011 showed a significant inverse association between coffee consumption and risk of pancreatic cancer [122]. A subsequent meta-analysis including 37 case-control studies and 17 cohort studies suggested a nonsignificant increase of such risk associated with coffee consumption [123]. A recent updated meta-analysis including 20 cohort studies reported a protective effect of high coffee consumption for pancreatic cancer risk (OR = 0.75; 95%CI: 0.63–0.86) [124].

Obesity

World Cancer Research Fund (WCRF) and American Institute of Cancer Research (AICR) panel concluded that there was a dose–response relationship between BMI and pancreatic cancer risk based on 23 cohort studies (RR = 1.14; 95% CI, 1.07, 1.22 per 5 kg/m^2 increase in BMI) and 15 case-control studies (OR = 1.00; 95% CI, 0.87, 1.15 per 5 kg/m^2 increase in BMI) [125]. A pooled analysis including 14 cohort studies reported that the risk of pancreatic cancer was 47% greater among obese (BMI ≥30 kg/m^2) individuals compared to individuals with BMIs between 21 and 22.9 kg/m^2 [126]. It was estimated that approximately 12.8% of pancreatic cancers in men and 11.5% in women could be attributed to overweight/obesity [4]. A meta-analysis confirmed that both general and abdominal obesity were associated with increased pancreatic cancer risk [127].

Nutrition

Although studies linking dietary intake and risk of pancreatic cancer have provided inconclusive results, a majority of studies have suggested a reduced risk of pancreatic cancer associated with high fruit and vegetable intake [98, 128–132]. Studies also suggested that certain nutrients found in fruits and vegetables (i.e., vitamin C, vitamin E, carotenoids, and other antioxidants) were associated with a reduced risk of pancreatic cancer [133–138]. High fat and red meat intake was associated with an increased risk of pancreatic cancer in some studies [98, 139–141] but not in others [132, 136, 142, 143]. A meta-analysis of 11 prospective studies found a positive association between pancreatic cancer incidence and processed meat consumption [144]. However, subsequent cohort studies did not support such findings [145–147]. A large cohort study detected no association between intakes of red and processed meat and risk of pancreatic cancer, but the study found that poultry consumption was associated with an increased risk of pancreatic cancer [145]. Another cohort study suggested that processed meat sources of dietary nitrate and nitrite might be associated with pancreatic cancer among men only [147]. A recent large cohort study reported that low meat eaters and vegetarians and vegans had lower

mortality for pancreatic cancer compared with regular meat eaters [148]. Frequent nut consumption had been inversely associated with risk of pancreatic cancer in women [149, 150]. Findings from the latest meta-analysis supported that fruit and vegetable intake was inversely associated with the risk of pancreatic cancer [151]. Furthermore, another study suggested that 0–12% of pancreatic cancer cases could be prevented by increasing fruit or folate intake [152].

Diabetes

Diabetes has been considered to be associated with the risk of pancreatic cancer, but the causal relationship between diabetes and pancreatic cancer remains controversial. A recent meta-analysis including 35 cohort studies reported that diabetes was associated with 90% increased risk of pancreatic cancer. The risk was inversely correlated with the duration of diabetes with the highest risk found among patients diagnosed within less than a year [153]. Several studies reported that type I and type II diabetes doubled the risk of pancreatic cancer [154–156]. The United States National Cancer Institute estimates that diabetes is associated with a 1.8-fold increased risk of pancreatic cancer in Hispanic men and Asians compared to whites and blacks [67]. Pancreatic cancer risk decreased with the duration of diabetes, but a 30% excess risk persists for those with more than two decades of diabetes diagnosis [70]. Oral antidiabetics or insulin use were associated with a reduced risk of pancreatic cancer [67, 70].

Pancreatitis

Chronic pancreatitis is another established risk factor for pancreatic cancer. A six-country historical cohort study consisting of 2015 subjects with chronic pancreatitis reported 1.8% 10-year and 4.0% 20-year cumulative risks of pancreatic cancer [157]. About 4% of chronic pancreatitis patients developed pancreatic cancer [158]. The risk of pancreatic cancer associated with pancreatitis was two times higher among people who were younger than 65 years old compared to those who were 65 years or older [159]. Patients with hereditary pancreatitis a rare, autosomal-dominant disease that usually occurs at a young age had a risk that was 50–60 times greater than expected [160].

Helicobacter pylori

Studies have shown that *Helicobacter pylori* infection, a major risk factor associated with pancreatic cancer, has an estimated population attributable fraction of 4–25% [152]. According to a recent follow-up study, these results were not supported [161].

Clinical and Pathological Features of Pancreatic Cancer

Clinical Features

Pancreatic cancer is rare before the age of 40, and the median age at diagnosis is approximately age 70. Pancreatic cancer is difficult to detect and diagnose because of the insidious nature of early stage signs and symptoms as well as the relatively inaccessible anatomic location of the pancreas. The presenting symptoms of pancreatic cancer depend on the location of the tumor within the gland. For tumors located in the head and body of the pancreas, symptoms are generally precipitated by compression of surrounding structures such as the bile duct, the mesenteric and celiac nerves, the pancreatic duct, and the duodenum [162]. As a result, classic symptoms include unexplained weight loss, jaundice, and pain in the upper or middle abdomen and back. Other symptoms may include dyspepsia, nausea, vomiting, and fatigue. Pain is the most common presenting symptom in patients with pancreatic cancer. As a result of tumor invasion of the celiac and mesenteric plexus, the pain may take on a gnawing nature. Besides abdominal pain, patients with pancreatic head cancer usually suffer from jaundice caused by biliary tract obstruction that can increase levels of conjugated bilirubin and alkaline phosphatase. As a result, the patient's urine darkens. In addition, the stool may be pale from decreased stercobilinogen in the bowel. On rare occasions, a pancreatic tumor may cause duodenal obstruction or gastrointestinal bleeding. Obstruction of the pancreatic duct may lead to pancreatitis. Patients with pancreatic cancer often have dysglycemia. As such, pancreatic cancer should be considered in the differential diagnoses of acute pancreatitis and newly diagnosed diabetes.

Pathological Features

Pancreatic cancer tumors can arise anywhere in the pancreas with the most frequent focus being in the head, followed by the body and tail. Pancreatic cancer grossly produces a firm, poorly demarcated, multinodular mass with an intense desmoplastic reaction [163]. In addition to ductal adenocarcinomas, a number of histological types of pancreatic cancer have been recognized, including adenosquamous carcinoma, colloid carcinoma, hepatoid carcinoma, medullary carcinoma, signet-ring cell carcinoma, undifferentiated carcinoma, and undifferentiated carcinoma with osteoclast-like giant cells. Pancreatic cancers are extremely infiltrative

neoplasms. Vascular and perineural invasion are present in the majority of surgically resected cancers. Pancreatic cancer metastasizes most commonly to regional lymph nodes and the liver. Other frequent metastatic sites include the peritoneum, lungs, adrenals, and bones [163].

Molecular Markers

The most widely utilized tumor marker for pancreatic cancer in the clinic is cancer antigen (CA) 19–9. The serum marker CA 19–9 is useful in confirming the diagnosis in symptomatic patients and in predicting prognosis and recurrence after resection [164, 165]. Due to its lack of sensitivity and specificity, this antigen is not useful in screening asymptomatic patients [162].

Global gene expression studies of pancreatic cancers have suggested several potential new serum markers for pancreatic cancer. One such marker is the macrophage inhibitory cytokine 1 (MIC1) [166]. Elevated serum MIC1 antigen levels significantly outperformed CA 19–9 and other tumor markers in distinguishing patients with resectable pancreatic cancers from healthy controls [167]. In addition to MIC1, gene products of *osteopontin* [168], *tissue inhibitor of metalloproteinase-1* [169], and *mesothelin* genes [170] have also been suggested as potential novel tumor markers of pancreatic cancer.

Using pancreatic juice as a potential source of biomarkers of early stage pancreatic cancer has attracted significant interest [171, 172]. Because of its direct relationship to the ductal system of the pancreas, it would undoubtedly contain enriched fractions of tumor markers unadulterated by serum components [173]. However, pancreatic juice can only be obtained during an invasive endoscopic procedure. Thus, pancreatic juice-based biomarkers are not feasible for screening.

Carcinogenic Mechanisms

During the past two decades, the rapid accumulation of knowledge of the molecular biology of this disease has significantly advanced our understanding of pancreatic carcinogenesis. Like many other malignancies, pancreatic carcinogenesis involves multiple subsets of genes undergoing genetic changes [174]. Pancreatic cancer develops from normal ductular epithelium through a sequential worsening of precursor lesions that can be identified through histology and genetic testing [175, 176]. Overexpression of *HER2/neu* and point mutations in the *K-ras* gene present in more than 90% of pancreatic cancer cases at early stages of the disease [175, 177, 178]. The p16 tumor suppressor gene is inactivated in more than 80–90% of pancreatic cancer cases at an intermediate stage [179]. The *P53* and *DPC4* genes are inactivated in about 50% of pancreatic cancer cases and *BRCA2* in about 7–10% at a relatively later stage [174, 180, 181].

Several genetic syndromes (i.e., hereditary pancreatitis, hereditary nonpolyposis colorectal cancer, ataxia-telangiectasia, Peutz–Jehers syndrome, familial breast cancer, and familial atypical multiple-mole melanoma) have been associated with pancreatic cancer risk [182]. However, the carriers of these genetic disorders in the general population are rare. It has been recognized that single-nucleotide polymorphisms (SNPs) in common and low-penetrance genes influence both the response and susceptibility to carcinogens and may play important roles in pancreatic carcinogenesis. Exogenous and endogenous carcinogens can alter gene expression, proliferation, or differentiation through mechanisms such as aberrant DNA methylation, oxidative effects, impaired DNA repair pathways, and abnormal activation of receptors, transcription factors, and cell cycle proteins [183]. While major advances have been made to better understand the interaction between environmental factors and genetic susceptibility to human cancers, the gene–environment interaction for pancreatic cancer has not yet been fully evaluated. There are currently several studies investigating the association between genetic polymorphisms and risk of pancreatic cancer.

Genetic Susceptibility

Studies using candidate gene approaches have mainly focused on genes in the following pathways: carcinogen metabolism [184–193], DNA repair [186, 194–199], inflammatory response [200, 201], alcohol-metabolizing enzymes [202, 203], methylation [117, 202–206], and protease inhibitors [191, 207–209]. Associations between polymorphisms in metabolic genes (i.e., *GSTM1*, *GSTT1*, *CYP1A1*, *CYP1A2*, *NAT1 NAT2*, and *UGT1A7*) and risk of pancreatic cancer were generally null from a meta-analysis [175]. However, studies suggested that the combination of *GSTT1-null* and *GSTP1*-codon 105 Val variants significantly increased the risk for pancreatic cancer [193]. Individuals who were heavy smokers and carried *GSTT1*-null genotype significantly increased their risk of pancreatic cancer compared to non-smokers with *GSTT1*-present genotype [185]. Heavy smokers with the *CYP1A2*∗1F(A-163C) C allele or *NAT1* rapid alleles experienced a significantly elevated risk of pancreatic cancer as compared to never smokers carrying non-at-risk alleles [188].

A case-control study conducted at the MD Anderson Cancer Center investigated genetic variants in glucose metabolism genes and risk of pancreatic cancer in 1654 cases and 1182 controls [210]. The study genotyped 26 SNPs of five glucose metabolism genes, *GCK*, *GFPT1*, *GPI*, *HK2*,

and *OGT*, and found a significant association of *HK2* R844K GA/AA genotype with reduced pancreatic cancer risk (OR = 0.78). A significant interaction with diabetes was observed. The *HK2* R844K GA/AA genotype was associated with a reduced risk of pancreatic cancer among nondiabetic individuals (OR = 0.68) but with increased risk among diabetic patients (OR = 3.69). These risk associations remained statistically significant when the analysis was restricted to whites or after exclusion of recent-onset diabetes. No significant effect of other genes or significant interaction of genotype with other risk factors was observed.

Two studies from Japan examined polymorphisms in alcohol-metabolizing enzyme genes and risk of pancreatic cancer [202, 203]. Miyasaka et al. [203] reported that the risk of pancreatic cancer associated with smoking was enhanced in subjects with an inactive form of *ALDH2* in a male population. Kanda et al. [202] found that drinkers carrying both *ADH1B* His/His and *ALDH2* Lys+ had significantly increased risk of pancreatic cancer as compared to nondrinkers with both *ADH1B* His/His and *ALDH2* Glu/Glu.

Li et al. [197] investigated nine SNPs of seven DNA repair genes (*LIG3*, *LIG4*, *OGG1*, *ATM*, *POLB*, *RAD54L*, and *RECQL*) and found SNPs in *ATM* and *LIG3* genes significantly associated with the risk of pancreatic cancer and suggested significant interactions between SNPs in *ATM* or *LIG4* genes and diabetes to pancreatic cancer. Several studies suggested that polymorphisms of *XRCC2* and *XPD* genes modified smoking-related pancreatic cancer [186, 196, 198]. Some studies also suggested potential gene–gene interactions within the same pathway (i.e., XRCC1 with APE1, XRCC1 with MGMT, OGG1 with XPC, XPA with ERCC2) [195] or cross different pathways (i.e., XRCC1 with GSTT1/GSTM1) [194] in relation to pancreatic cancer risk.

A case-control study from Mayo Clinic of 1354 Caucasian pancreatic cancer patients and 1189 healthy Caucasian controls investigated 1538 SNPs in 102 inflammatory pathway genes [201]. After adjusting for known risk factors for pancreatic cancer, single SNP analysis revealed an association between four SNPs in *NOS1* and one in the *CD101* gene with pancreatic cancer risk. These results, however, were not replicated in other pancreatic cancer case-control and cohort populations. A population-based case-control study with 308 cases and 964 controls from the San Francisco Bay Area suggested that proinflammatory gene polymorphisms in combination with proinflammatory conditions might influence pancreatic cancer development [200].

Suzuki et al. [117] investigated polymorphisms in *MTHFR*, *MTR*, *MTRR*, and *TS* genes and found that heavy drinkers carrying *MTHFR* 667 CC, *MTR* 2756 AA, or *MTRR* 66G allele had significantly increased risk of pancreatic cancer compared to nondrinkers, suggesting that folate-related enzyme polymorphisms modify the association between alcohol consumption and pancreatic cancer risk. Wang et al. [206] reported an increased risk of pancreatic cancer associated with *MTHFR* 677CT or TT genotypes compared to *MTHFR* CC genotype and with *TS* 3Rc/3RC genotype compared to *TS* 3Rg/3Rg genotype. This study also suggested an interaction between *MTHFR* C677T polymorphism and smoking and drinking. Similar interactions were also reported in another study [204].

Recently, genome-wide association studies (GWAS) among the population of European ancestry identified common SNPs in several genomic regions (i.e., 1q32.1, 2p14, 3q28, 5p15.33, 7p14.1, 7q32.3, 8q24.21, 9q34.2, 12q24.31, 13q22.1, 16q23.1, 17q24.3, 22112.1) that are associated with pancreatic cancer risk [211–214]. A GWAS from China identified five significant genomic regions (5p13.1, 10q26.11, 21q21.3, 21q22.3, and 22q13.32) that are associated with risk of pancreatic cancer [215]. A Japanese GWAS reported three significant loci (6p25.3, 7q36.2, and 12p11.21) associated with pancreatic cancer risk [216]. Future studies are needed to investigate gene–environmental interactions with a broad spectrum of occupational and environmental factors in addition to smoking and alcohol consumption.

Conclusion

Although the overall incidence of pancreatic cancer is low in comparison to other cancers, this devastating disease is associated with a low survival rate, often claiming the life of its victims within the first year. From previous studies, a wide array of contributing occupational and nonoccupational risk factors has been suggested. Some of these include smoking, excessive alcohol consumption, obesity, physical inactivity, diabetes, chronic pancreatitis, nutritional considerations, and complex genetic predispositions and interactions. Further studies and data pooling may help gain a better understanding of such risk factors, ultimately leading to effective awareness and prevention programs.

Since delays in early diagnosis may contribute to poor prognosis, misclassification of initial symptoms may be prevented and earlier diagnosis accomplished through the use of specific molecular markers. Thus, the identification and implementation of pancreatic tumors markers has potential to be an important diagnostic tool.

References

1. Garcea G, Dennison AR, Pattenden CJ, Neal CP, Sutton CD, Berry DP. Survival following curative resection for pancreatic ductal adenocarcinoma. A systematic review of the literature. JOP. 2008;9(2):99–132.
2. Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, et al. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. Lyon:

International Agency for Research on Cancer; 2013. http://globocan.iarc.fr, accessed on day/month/year.
3. David M, Lepage C, Jouve JL, Jooste V, Chauvenet M, Faivre J, et al. Management and prognosis of pancreatic cancer over a 30-year period. Br J Cancer. 2009;101(2):215–8.
4. Parkin DM. The fraction of cancer attributable to lifestyle and environmental factors in the UK in 2010. Br J Cancer. 2011;105(Suppl 2):S2–5.
5. Bosetti C, Bertuccio P, Negri E, La Vecchia C, Zeegers MP, Boffetta P. Pancreatic cancer: overview of descriptive epidemiology. Mol Carcinog. 2012;51(1):3–13.
6. Dunphy EP. Pancreatic cancer: a review and update. Clin J Oncol Nurs. 2008;12(5):735–41.
7. Ojajarvi IA, Partanen TJ, Ahlbom A, Boffetta P, Hakulinen T, Jourenkova N, et al. Occupational exposures and pancreatic cancer: a meta-analysis. Occup Environ Med. 2000;57(5):316–24.
8. Seilkop SK. Occupational exposures and pancreatic cancer: a meta-analysis. Occup Environ Med. 2001;58(1):63–4.
9. Chiazze L Jr, Ference LD. Mortality among PVC-fabricating employees. Environ Health Perspect. 1981;41:137–43.
10. Decoufle P. Further analysis of cancer mortality patterns among workers exposed to cutting oil mists. J Natl Cancer Inst. 1978;61(4):1025–30.
11. Hanis NM, Holmes TM, Shallenberger G, Jones KE. Epidemiologic study of refinery and chemical plant workers. J Occup Med. 1982;24(3):203–12.
12. Li FP, Fraumeni JF Jr, Mantel N, Miller RW. Cancer mortality among chemists. J Natl Cancer Inst. 1969;43(5):1159–64.
13. Milham S Jr. Cancer mortality pattern associated with exposure to metals. Ann N Y Acad Sci. 1976;271:243–9.
14. Acheson ED, Gardner MJ, Winter PD, Bennett C. Cancer in a factory using amosite asbestos. Int J Epidemiol. 1984;13(1):3–10.
15. Bond GG, Reeve GR, Ott MG, Waxweiler RJ. Mortality among a sample of chemical company employees. Am J Ind Med. 1985;7(2):109–21.
16. Decoufle P, Blattner WA, Blair A. Mortality among chemical workers exposed to benzene and other agents. Environ Res. 1983;30(1):16–25.
17. Elinder CG, Kjellstrom T, Hogstedt C, Andersson K, Spang G. Cancer mortality of cadmium workers. Br J Ind Med. 1985;42(10):651–5.
18. Howe GR, Fraser D, Lindsay J, Presnal B, Yu SZ. Cancer mortality (1965-77) in relation to diesel fume and coal exposure in a cohort of retired railway workers. J Natl Cancer Inst. 1983;70(6):1015–9.
19. Lynge E. A follow-up study of cancer incidence among workers in manufacture of phenoxy herbicides in Denmark. Br J Cancer. 1985;52(2):259–70.
20. Milham S Jr. Mortality in workers exposed to electromagnetic fields. Environ Health Perspect. 1985;62:297–300.
21. Ott MG, Carlo GL, Steinberg S, Bond GG. Mortality among employees engaged in chemical manufacturing and related activities. Am J Epidemiol. 1985;122(2):311–22.
22. Rockette HE, Arena VC. Mortality studies of aluminum reduction plant workers: potroom and carbon department. J Occup Med. 1983;25(7):549–57.
23. Williams RR, Stegens NL, Goldsmith JR. Associations of cancer site and type with occupation and industry from the Third National Cancer Survey Interview. J Natl Cancer Inst. 1977;59(4):1147–85.
24. Acquavella J, Leet T, Johnson G. Occupational experience and mortality among a cohort of metal components manufacturing workers. Epidemiology. 1993;4(5):428–34.
25. Benson LO, Teta MJ. Mortality due to pancreatic and lymphopoietic cancers in chlorohydrin production workers. Br J Ind Med. 1993;50(8):710–6.
26. Boffetta P, Stellman SD, Garfinkel L. Diesel exhaust exposure and mortality among males in the American Cancer Society prospective study. Am J Ind Med. 1988;14(4):403–15.
27. Brown DP. Mortality of workers exposed to polychlorinated biphenyls—an update. Arch Environ Health. 1987;42(6):333–9.
28. Coggon D, Pannett B, Winter PD, Acheson ED, Bonsall J. Mortality of workers exposed to 2 methyl-4 chlorophenoxyacetic acid. Scand J Work Environ Health. 1986;12(5):448–54.
29. Costantini AS, Paci E, Miligi L, Buiatti E, Martelli C, Lenzi S. Cancer mortality among workers in the Tuscan tanning industry. Br J Ind Med. 1989;46(6):384–8.
30. Enterline PE, Hartley J, Henderson V. Asbestos and cancer: a cohort followed up to death. Br J Ind Med. 1987;44(6):396–401.
31. Gardner MJ, Pannett B, Winter PD, Cruddas AM. A cohort study of workers exposed to formaldehyde in the British chemical industry: an update. Br J Ind Med. 1993;50(9):827–34.
32. Gustavsson P, Reuterwall C. Mortality and incidence of cancer among Swedish gas workers. Br J Ind Med. 1990;47(3):169–74.
33. Hansen ES. Mortality of auto mechanics. A ten-year follow-up. Scand J Work Environ Health. 1989;15(1):43–6.
34. Hearne FT, Pifer JW, Grose F. Absence of adverse mortality effects in workers exposed to methylene chloride: an update. J Occup Med. 1990;32(3):234–40.
35. Lanes SF, Rothman KJ, Dreyer NA, Soden KJ. Mortality update of cellulose fiber production workers. Scand J Work Environ Health. 1993;19(6):426–8.
36. Langard S, Andersen A, Ravnestad J. Incidence of cancer among ferrochromium and ferrosilicon workers: an extended observation period. Br J Ind Med. 1990;47(1):14–9.
37. McDonald JC, Liddell FD, Dufresne A, McDonald AD. The 1891-1920 birth cohort of Quebec chrysotile miners and millers: mortality 1976-88. Br J Ind Med. 1993;50(12):1073–81.
38. Silverstein M, Park R, Marmor M, Maizlish N, Mirer F. Mortality among bearing plant workers exposed to metalworking fluids and abrasives. J Occup Med. 1988;30(9):706–14.
39. Smulevich VB, Fedotova IV, Filatova VS. Increasing evidence of the rise of cancer in workers exposed to vinylchloride. Br J Ind Med. 1988;45(2):93–7.
40. Vena JE, Sultz HA, Fiedler RC, Barnes RE. Mortality of workers in an automobile engine and parts manufacturing complex. Br J Ind Med. 1985;42(2):85–93.
41. Wen CP, Tsai SP, Weiss NS, Gibson RL, Wong O, McClellan WA. Long-term mortality study of oil refinery workers. IV. Exposure to the lubricating-dewaxing process. J Natl Cancer Inst. 1985;74(1):11–8.
42. Wong O. An industry wide mortality study of chemical workers occupationally exposed to benzene. I. General results. Br J Ind Med. 1987;44(6):365–81.
43. Zoloth SR, Michaels DM, Villalbi JR, Lacher M. Patterns of mortality among commercial pressmen. J Natl Cancer Inst. 1986;76(6):1047–51.
44. Anttila A, Pukkala E, Sallmen M, Hernberg S, Hemminki K. Cancer incidence among Finnish workers exposed to halogenated hydrocarbons. J Occup Environ Med. 1995;37(7):797–806.
45. Asp S, Riihimaki V, Hernberg S, Pukkala E. Mortality and cancer morbidity of Finnish chlorophenoxy herbicide applicators: an 18-year prospective follow-up. Am J Ind Med. 1994;26(2):243–53.
46. Axelson O, Selden A, Andersson K, Hogstedt C. Updated and expanded Swedish cohort study on trichloroethylene and cancer risk. J Occup Med. 1994;36(5):556–62.
47. Baris D, Armstrong BG, Deadman J, Theriault G. A mortality study of electrical utility workers in Quebec. Occup Environ Med. 1996;53(1):25–31.
48. Boffetta P, Saracci R, Andersen A, Bertazzi PA, Chang-Claude J, Cherrie J, et al. Cancer mortality among man-made vitreous fiber production workers. Epidemiology. 1997;8(3):259–68.

49. Brown DP, Dement JM, Okun A. Mortality patterns among female and male chrysotile asbestos textile workers. J Occup Med. 1994;36(8):882–8.
50. Alguacil J, Pollan M, Gustavsson P. Occupations with increased risk of pancreatic cancer in the Swedish population. Occup Environ Med. 2003;60(8):570–6.
51. Anttila A, Pukkala E, Riala R, Sallmen M, Hemminki K. Cancer incidence among Finnish workers exposed to aromatic hydrocarbons. Int Arch Occup Environ Health. 1998;71(3):187–93.
52. Cocco P, Blair A, Congia P, Saba G, Ecca AR, Palmas C. Long-term health effects of the occupational exposure to DDT. A preliminary report. Ann N Y Acad Sci. 1997;837:246–56.
53. Cocco P, Hua F, Boffetta P, Carta P, Flore C, Flore V, et al. Mortality of Italian lead smelter workers. Scand J Work Environ Health. 1997;23(1):15–23.
54. Enterline PE, Day R, Marsh GM. Cancers related to exposure to arsenic at a copper smelter. Occup Environ Med. 1995;52(1):28–32.
55. Gibbs GW, Amsel J, Soden K. A cohort mortality study of cellulose triacetate-fiber workers exposed to methylene chloride. J Occup Environ Med. 1996;38(7):693–7.
56. Hansen J, Olsen JH. Formaldehyde and cancer morbidity among male employees in Denmark. Cancer Causes Control. 1995;6(4):354–60.
57. Wong O, Trent LS, Whorton MD. An updated cohort mortality study of workers exposed to styrene in the reinforced plastics and composites industry. Occup Environ Med. 1994;51(6):386–96.
58. Yassi A, Tate R, Fish D. Cancer mortality in workers employed at a transformer manufacturing plant. Am J Ind Med. 1994;25(3):425–37.
59. Hooiveld M, Heederik DJ, Kogevinas M, Boffetta P, Needham LL, Patterson DG Jr, et al. Second follow-up of a Dutch cohort occupationally exposed to phenoxy herbicides, chlorophenols, and contaminants. Am J Epidemiol. 1998;147(9):891–901.
60. Jarup L, Bellander T, Hogstedt C, Spang G. Mortality and cancer incidence in Swedish battery workers exposed to cadmium and nickel. Occup Environ Med. 1998;55(11):755–9.
61. Kogevinas M, Becher H, Benn T, Bertazzi PA, Boffetta P, Bueno-de-Mesquita HB, et al. Cancer mortality in workers exposed to phenoxy herbicides, chlorophenols, and dioxins. An expanded and updated international cohort study. Am J Epidemiol. 1997;145(12):1061–75.
62. Rafnsson V. Incidence of cancer among bookbinders, printers, photoengravers, and typesetters. Occup Environ Med. 2001;58(8):523–7.
63. Sathiakumar N, Delzell E, Hovinga M, Macaluso M, Julian JA, Larson R, et al. Mortality from cancer and other causes of death among synthetic rubber workers. Occup Environ Med. 1998;55(4):230–5.
64. Wiebelt H, Becker N. Mortality in a cohort of toluene exposed employees (rotogravure printing plant workers). J Occup Environ Med. 1999;41(12):1134–9.
65. Alguacil J, Porta M, Benavides FG, Malats N, Kogevinas M, Fernandez E, et al. Occupation and pancreatic cancer in Spain: a case-control study based on job titles. PANKRAS II Study Group. Int J Epidemiol. 2000;29(6):1004–13.
66. Alguacil J, Porta M, Malats N, Kauppinen T, Kogevinas M, Benavides FG, et al. Occupational exposure to organic solvents and K-ras mutations in exocrine pancreatic cancer. Carcinogenesis. 2002;23(1):101–6.
67. Bardin JA, Eisen EA, Tolbert PE, Hallock MF, Hammond SK, Woskie SR, et al. Mortality studies of machining fluid exposure in the automobile industry. V: a case-control study of pancreatic cancer. Am J Ind Med. 1997;32(3):240–7.
68. Falk RT, Pickle LW, Fontham ET, Correa P, Morse A, Chen V, et al. Occupation and pancreatic cancer risk in Louisiana. Am J Ind Med. 1990;18(5):565–76.
69. Garabrant DH, Held J, Langholz B, Peters JM, Mack TM. DDT and related compounds and risk of pancreatic cancer. J Natl Cancer Inst. 1992;84(10):764–71.
70. Ji BT, Silverman DT, Dosemeci M, Dai Q, Gao YT, Blair A. Occupation and pancreatic cancer risk in Shanghai, China. Am J Ind Med. 1999;35(1):76–81.
71. Lin RS, Kessler II. A multifactorial model for pancreatic cancer in man. Epidemiologic evidence. JAMA. 1981;245(2):147–52.
72. Mack TM, Peters JM, Yu MC, Hanisch R, Wright WE, Henderson BE. Pancreas cancer is unrelated to the workplace in Los Angeles. Am J Ind Med. 1985;7(3):253–66.
73. Magnani C, Coggon D, Osmond C, Acheson ED. Occupation and five cancers: a case-control study using death certificates. Br J Ind Med. 1987;44(11):769–76.
74. Mallin K, Rubin M, Joo E. Occupational cancer mortality in Illinois white and black males, 1979-1984, for seven cancer sites. Am J Ind Med. 1989;15(6):699–717.
75. Pickle LW, Gottlieb MS. Pancreatic cancer mortality in Louisiana. Am J Public Health. 1980;70(3):256–9.
76. Pietri F, Clavel F, Auquier A, Flamant R. Occupational risk factors for cancer of the pancreas: a case-control study. Br J Ind Med. 1990;47(6):425–8.
77. Kauppinen T, Partanen T, Degerth R, Ojajarvi A. Pancreatic cancer and occupational exposures. Epidemiology. 1995;6(5):498–502.
78. Kernan GJ, Ji BT, Dosemeci M, Silverman DT, Balbus J, Zahm SH. Occupational risk factors for pancreatic cancer: a case-control study based on death certificates from 24 U.S. states. Am J Ind Med. 1999;36(2):260–70.
79. Mikoczy Z, Schutz A, Stromberg U, Hagmar L. Cancer incidence and specific occupational exposures in the Swedish leather tanning industry: a cohort based case-control study. Occup Environ Med. 1996;53(7):463–7.
80. Partanen T, Kauppinen T, Degerth R, Moneta G, Mearelli I, Ojajarvi A, et al. Pancreatic cancer in industrial branches and occupations in Finland. Am J Ind Med. 1994;25(6):851–66.
81. Santibanez M, Vioque J, Alguacil J, de la Hera MG, Moreno-Osset E, Carrato A, et al. Occupational exposures and risk of pancreatic cancer. Eur J Epidemiol. 2010;25(10):721–30.
82. Selenskas S, Teta MJ, Vitale JN. Pancreatic cancer among workers processing synthetic resins. Am J Ind Med. 1995;28(3):385–98.
83. Zhang Y, Cantor KP, Lynch CF, Zhu Y, Zheng T. Occupation and risk of pancreatic cancer: a population-based case-control study in Iowa. J Occup Environ Med. 2005;47(4):392–8.
84. Milham S. Occupational mortality in Washington state, 1950–1989. Cincinnati: DHHS (NIOSH); 1997.
85. Ojajarvi A, Partanen T, Ahlbom A, Hakulinen T, Kauppinen T, Weiderpass E, et al. Estimating the relative risk of pancreatic cancer associated with exposure agents in job title data in a hierarchical Bayesian meta-analysis. Scand J Work Environ Health. 2007;33(5):325–35.
86. Maruchi N, Brian D, Ludwig J, Elveback LR, Kurland LT. Cancer of the pancreas in Olmsted County, Minnesota, 1935-1974. Mayo Clin Proc. 1979;54(4):245–9.
87. Boffetta P, Jourenkova N, Gustavsson P. Cancer risk from occupational and environmental exposure to polycyclic aromatic hydrocarbons. Cancer Causes Control. 1997;8(3):444–72.
88. Andreotti G, Silverman DT. Occupational risk factors and pancreatic cancer: a review of recent findings. Mol Carcinog. 2012;51(1):98–108.
89. Lloyd JW, Decoufle P, Salvin LG. Unusual mortality experience of printing pressmen. J Occup Med. 1977;19(8):543–50.

90. Wingren G, Persson B, Thoren K, Axelson O. Mortality pattern among pulp and paper mill workers in Sweden: a case-referent study. Am J Ind Med. 1991;20(6):769–74.
91. Mastrangelo G, Fadda E, Marzia V. Polycyclic aromatic hydrocarbons and cancer in man. Environ Health Perspect. 1996;104(11):1166–70.
92. Calvert GM, Ward E, Schnorr TM, Fine LJ. Cancer risks among workers exposed to metalworking fluids: a systematic review. Am J Ind Med. 1998;33(3):282–92.
93. Milham S. Occupational mortality in Washington state, 1950–1979. Washington, DC: US NIOSH; 1983.
94. Li W, Ray RM, Gao DL, Fitzgibbons ED, Seixas NS, Camp JE, et al. Occupational risk factors for pancreatic cancer among female textile workers in Shanghai, China. Occup Environ Med. 2006;63(12):788–93.
95. Cantor KP, Silberman W. Mortality among aerial pesticide applicators and flight instructors: follow-up from 1965-1988. Am J Ind Med. 1999;36(2):239–47.
96. Porta M, Malats N, Jariod M, Grimalt JO, Rifa J, Carrato A, et al. Serum concentrations of organochlorine compounds and K-ras mutations in exocrine pancreatic cancer. PANKRAS II Study Group. Lancet. 1999;354(9196):2125–9.
97. Hanley AJ, Johnson KC, Villeneuve PJ, Mao Y, Canadian Cancer Registries Epidemiology Research Group. Physical activity, anthropometric factors and risk of pancreatic cancer: results from the Canadian enhanced cancer surveillance system. Int J Cancer. 2001;94(1):140–7.
98. Stolzenberg-Solomon RZ, Pietinen P, Taylor PR, Virtamo J, Albanes D. A prospective study of medical conditions, anthropometry, physical activity, and pancreatic cancer in male smokers (Finland). Cancer Causes Control. 2002;13(5):417–26.
99. O'Rorke MA, Cantwell MM, Cardwell CR, Mulholland HG, Murray LJ. Can physical activity modulate pancreatic cancer risk? A systematic review and meta-analysis. Int J Cancer. 2010;126(12):2957–68.
100. Iodice S, Gandini S, Maisonneuve P, Lowenfels AB. Tobacco and the risk of pancreatic cancer: a review and meta-analysis. Langenbeck's Arch Surg. 2008;393(4):535–45.
101. Lynch SM, Vrieling A, Lubin JH, Kraft P, Mendelsohn JB, Hartge P, et al. Cigarette smoking and pancreatic cancer: a pooled analysis from the pancreatic cancer cohort consortium. Am J Epidemiol. 2009;170(4):403–13.
102. Brownson RC, Figgs LW, Caisley LE. Epidemiology of environmental tobacco smoke exposure. Oncogene. 2002;21(48):7341–8.
103. Gallicchio L, Kouzis A, Genkinger JM, Burke AE, Hoffman SC, Diener-West M, et al. Active cigarette smoking, household passive smoke exposure, and the risk of developing pancreatic cancer. Prev Med. 2006;42(3):200–5.
104. Tranah GJ, Holly EA, Wang F, Bracci PM. Cigarette, cigar and pipe smoking, passive smoke exposure, and risk of pancreatic cancer: a population-based study in the San Francisco Bay Area. BMC Cancer. 2011;11:138.
105. Villeneuve PJ, Johnson KC, Mao Y, Hanley AJ, Canadian Cancer registries research Group. Environmental tobacco smoke and the risk of pancreatic cancer: findings from a Canadian population-based case-control study. Can J Public Health. 2004;95(1):32–7.
106. Vrieling A, Bueno-de-Mesquita HB, Boshuizen HC, Michaud DS, Severinsen MT, Overvad K, et al. Cigarette smoking, environmental tobacco smoke exposure and pancreatic cancer risk in the European Prospective Investigation into Cancer and Nutrition. Int J Cancer. 2010;126(10):2394–403.
107. International Agency for Research on Cancer. IARC monographs on the evaluation of carcinogenic risks to humans, vol. 96. Alcohol consumption and ethyl carbamate. Lyon: International Agency for Research on Cancer; 2010.
108. Cuzick J, Babiker AG. Pancreatic cancer, alcohol, diabetes mellitus and gall-bladder disease. Int J Cancer. 1989;43(3):415–21.
109. Falk RT, Pickle LW, Fontham ET, Correa P, Fraumeni JF Jr. Lifestyle risk factors for pancreatic cancer in Louisiana: a case-control study. Am J Epidemiol. 1988;128(2):324–36.
110. Harnack LJ, Anderson KE, Zheng W, Folsom AR, Sellers TA, Kushi LH. Smoking, alcohol, coffee, and tea intake and incidence of cancer of the exocrine pancreas: the Iowa Women's Health Study. Cancer Epidemiol Biomark Prev. 1997;6(12):1081–6.
111. Hassan MM, Bondy ML, Wolff RA, Abbruzzese JL, Vauthey JN, Pisters PW, et al. Risk factors for pancreatic cancer: case-control study. Am J Gastroenterol. 2007;102(12):2696–707.
112. Heinen MM, Verhage BA, Ambergen TA, Goldbohm RA, van den Brandt PA. Alcohol consumption and risk of pancreatic cancer in the Netherlands cohort study. Am J Epidemiol. 2009;169(10):1233–42.
113. Heuch I, Kvale G, Jacobsen BK, Bjelke E. Use of alcohol, tobacco and coffee, and risk of pancreatic cancer. Br J Cancer. 1983;48(5):637–43.
114. Jiao L, Silverman DT, Schairer C, Thiebaut AC, Hollenbeck AR, Leitzmann MF, et al. Alcohol use and risk of pancreatic cancer: the NIH-AARP Diet and Health Study. Am J Epidemiol. 2009;169(9):1043–51.
115. Olsen GW, Mandel JS, Gibson RW, Wattenberg LW, Schuman LM. A case-control study of pancreatic cancer and cigarettes, alcohol, coffee and diet. Am J Public Health. 1989;79(8):1016–9.
116. Silverman DT, Brown LM, Hoover RN, Schiffman M, Lillemoe KD, Schoenberg JB, et al. Alcohol and pancreatic cancer in blacks and whites in the United States. Cancer Res. 1995;55(21):4899–905.
117. Suzuki T, Matsuo K, Sawaki A, Mizuno N, Hiraki A, Kawase T, et al. Alcohol drinking and one-carbon metabolism-related gene polymorphisms on pancreatic cancer risk. Cancer Epidemiol Biomark Prev. 2008;17(10):2742–7.
118. Talamini R, Polesel J, Gallus S, Dal Maso L, Zucchetto A, Negri E, et al. Tobacco smoking, alcohol consumption and pancreatic cancer risk: a case-control study in Italy. Eur J Cancer. 2010;46(2):370–6.
119. Zheng W, McLaughlin JK, Gridley G, Bjelke E, Schuman LM, Silverman DT, et al. A cohort study of smoking, alcohol consumption, and dietary factors for pancreatic cancer (United States). Cancer Causes Control. 1993;4(5):477–82.
120. Lucenteforte E, La Vecchia C, Silverman D, Petersen GM, Bracci PM, Ji BT, et al. Alcohol consumption and pancreatic cancer: a pooled analysis in the International Pancreatic Cancer Case-Control Consortium (PanC4). Ann Oncol. 2012;23(2):374–82.
121. MacMahon B, Yen S, Trichopoulos D, Warren K, Nardi G. Coffee and cancer of the pancreas. N Engl J Med. 1981;304(11):630–3.
122. Dong J, Zou J, Yu XF. Coffee drinking and pancreatic cancer risk: a meta-analysis of cohort studies. World J Gastroenterol. 2011;17(9):1204–10.
123. Turati F, Galeone C, Edefonti V, Ferraroni M, Lagiou P, La Vecchia C, et al. A meta-analysis of coffee consumption and pancreatic cancer. Ann Oncol. 2012;23(2):311–8.
124. Ran HQ, Wang JZ, Sun CQ. Coffee consumption and pancreatic cancer risk: an update meta-analysis of cohort studies. Pak J Med Sci. 2016;32(1):253–9.
125. World Cancer Research Fund/American Institute for Cancer Research. Food, nutrition, physical activity, and the prevention of cancer: a global perspective. Washington, DC: AICR; 2007. p. 211–42.
126. Genkinger JM, Spiegelman D, Anderson KE, Bernstein L, van den Brandt PA, Calle EE, et al. A pooled analysis of 14 cohort studies of anthropometric factors and pancreatic cancer risk. Int J Cancer. 2011;129(7):1708–17.

127. Aune D, Greenwood DC, Chan DS, Vieira R, Vieira AR, Navarro Rosenblatt DA, et al. Body mass index, abdominal fatness and pancreatic cancer risk: a systematic review and non-linear dose-response meta-analysis of prospective studies. Ann Oncol. 2012;23(4):843–52.
128. Chan JM, Wang F, Holly EA. Vegetable and fruit intake and pancreatic cancer in a population-based case-control study in the San Francisco bay area. Cancer Epidemiol Biomark Prev. 2005;14(9):2093–7.
129. Mills PK, Beeson WL, Abbey DE, Fraser GE, Phillips RL. Dietary habits and past medical history as related to fatal pancreas cancer risk among adventists. Cancer. 1988;61(12):2578–85.
130. Nkondjock A, Krewski D, Johnson KC, Ghadirian P, Canadian Cancer Registries Epidemiology Research Group. Dietary patterns and risk of pancreatic cancer. Int J Cancer. 2005;114(5):817–23.
131. Shibata A, Mack TM, Paganini-Hill A, Ross RK, Henderson BE. A prospective study of pancreatic cancer in the elderly. Int J Cancer. 1994;58(1):46–9.
132. Silverman DT, Swanson CA, Gridley G, Wacholder S, Greenberg RS, Brown LM, et al. Dietary and nutritional factors and pancreatic cancer: a case-control study based on direct interviews. J Natl Cancer Inst. 1998;90(22):1710–9.
133. Gong Z, Holly EA, Wang F, Chan JM, Bracci PM. Intake of fatty acids and antioxidants and pancreatic cancer in a large population-based case-control study in the San Francisco Bay Area. Int J Cancer. 2010;127(8):1893–904.
134. Howe GR, Ghadirian P, Bueno de Mesquita HB, Zatonski WA, Baghurst PA, Miller AB, et al. A collaborative case-control study of nutrient intake and pancreatic cancer within the search programme. Int J Cancer. 1992;51(3):365–72.
135. Nkondjock A, Ghadirian P, Johnson KC, Krewski D, Canadian Cancer Registries Epidemiology Research Group. Dietary intake of lycopene is associated with reduced pancreatic cancer risk. J Nutr. 2005;135(3):592–7.
136. Olsen GW, Mandel JS, Gibson RW, Wattenberg LW, Schuman LM. Nutrients and pancreatic cancer: a population-based case-control study. Cancer Causes Control. 1991;2(5):291–7.
137. Stolzenberg-Solomon RZ, Albanes D, Nieto FJ, Hartman TJ, Tangrea JA, Rautalahti M, et al. Pancreatic cancer risk and nutrition-related methyl-group availability indicators in male smokers. J Natl Cancer Inst. 1999;91(6):535–41.
138. Zatonski W, Przewozniak K, Howe GR, Maisonneuve P, Walker AM, Boyle P. Nutritional factors and pancreatic cancer: a case-control study from south-west Poland. Int J Cancer. 1991;48(3):390–4.
139. Chan JM, Wang F, Holly EA. Pancreatic cancer, animal protein and dietary fat in a population-based study, San Francisco Bay Area, California. Cancer Causes Control. 2007;18(10):1153–67.
140. Larsson SC, Hakanson N, Permert J, Wolk A. Meat, fish, poultry and egg consumption in relation to risk of pancreatic cancer: a prospective study. Int J Cancer. 2006;118(11):2866–70.
141. Nothlings U, Wilkens LR, Murphy SP, Hankin JH, Henderson BE, Kolonel LN. Meat and fat intake as risk factors for pancreatic cancer: the multiethnic cohort study. J Natl Cancer Inst. 2005;97(19):1458–65.
142. Coughlin SS, Calle EE, Patel AV, Thun MJ. Predictors of pancreatic cancer mortality among a large cohort of United States adults. Cancer Causes Control. 2000;11(10):915–23.
143. Michaud DS, Giovannucci E, Willett WC, Colditz GA, Fuchs CS. Dietary meat, dairy products, fat, and cholesterol and pancreatic cancer risk in a prospective study. Am J Epidemiol. 2003;157(12):1115–25.
144. Larsson SC, Wolk A. Red and processed meat consumption and risk of pancreatic cancer: meta-analysis of prospective studies. Br J Cancer. 2012;106(3):603–7.
145. Rohrmann S, Linseisen J, Nothlings U, Overvad K, Egeberg R, Tjonneland A, et al. Meat and fish consumption and risk of pancreatic cancer: results from the European Prospective Investigation into Cancer and Nutrition. Int J Cancer. 2013;132(3):617–24.
146. Arem H, Mayne ST, Sampson J, Risch H, Stolzenberg-Solomon RZ. Dietary fat intake and risk of pancreatic cancer in the prostate, lung, colorectal and ovarian cancer screening trial. Ann Epidemiol. 2013;23(9):571–5.
147. Aschebrook-Kilfoy B, Cross AJ, Stolzenberg-Solomon RZ, Schatzkin A, Hollenbeck AR, Sinha R, et al. Pancreatic cancer and exposure to dietary nitrate and nitrite in the NIH-AARP Diet and Health Study. Am J Epidemiol. 2011;174(3):305–15.
148. Appleby PN, Crowe FL, Bradbury KE, Travis RC, Key TJ. Mortality in vegetarians and comparable nonvegetarians in the United Kingdom. Am J Clin Nutr. 2016;103(1):218–30.
149. Bao Y, Hu FB, Giovannucci EL, Wolpin BM, Stampfer MJ, Willett WC, et al. Nut consumption and risk of pancreatic cancer in women. Br J Cancer. 2013;109(11):2911–6.
150. Wu L, Wang Z, Zhu J, Murad AL, Prokop LJ, Murad MH. Nut consumption and risk of cancer and type 2 diabetes: a systematic review and meta-analysis. Nutr Rev. 2015;73(7):409–25.
151. Wu QJ, Wu L, Zheng LQ, Xu X, Ji C, Gong TT. Consumption of fruit and vegetables reduces risk of pancreatic cancer: evidence from epidemiological studies. Eur J Cancer Prev. 2016;25(3):196–205.
152. Maisonneuve P, Lowenfels AB. Risk factors for pancreatic cancer: a summary review of meta-analytical studies. Int J Epidemiol. 2015;44(1):186–98.
153. Ben Q, Xu M, Ning X, Liu J, Hong S, Huang W, et al. Diabetes mellitus and risk of pancreatic cancer: a meta-analysis of cohort studies. Eur J Cancer. 2011;47(13):1928–37.
154. Batabyal P, Vander Hoorn S, Christophi C, Nikfarjam M. Association of diabetes mellitus and pancreatic adenocarcinoma: a meta-analysis of 88 studies. Ann Surg Oncol. 2014;21(7):2453–62.
155. Haugvik SP, Hedenstrom P, Korsaeth E, Valente R, Hayes A, Siuka D, et al. Diabetes, smoking, alcohol use, and family history of cancer as risk factors for pancreatic neuroendocrine tumors: a systematic review and meta-analysis. Neuroendocrinology. 2015;101(2):133–42.
156. Stevens RJ, Roddam AW, Beral V. Pancreatic cancer in type 1 and young-onset diabetes: systematic review and meta-analysis. Br J Cancer. 2007;96(3):507–9.
157. Lowenfels AB, Maisonneuve P, Cavallini G, Ammann RW, Lankisch PG, Andersen JR, et al. Pancreatitis and the risk of pancreatic cancer. International Pancreatitis Study Group. N Engl J Med. 1993;328(20):1433–7.
158. Kudo Y, Kamisawa T, Anjiki H, Takuma K, Egawa N. Incidence of and risk factors for developing pancreatic cancer in patients with chronic pancreatitis. Hepato-Gastroenterology. 2011;58(106):609–11.
159. Duell EJ, Lucenteforte E, Olson SH, Bracci PM, Li D, Risch HA, et al. Pancreatitis and pancreatic cancer risk: a pooled analysis in the international pancreatic Cancer case-control consortium (PanC4). Ann Oncol. 2012;23(11):2964–70.
160. Lowenfels AB, Maisonneuve P, Whitcomb DC. Risk factors for cancer in hereditary pancreatitis. International Hereditary Pancreatitis Study Group. Med Clin North Am. 2000;84(3):565–73.
161. Chen XZ, Schottker B, Castro FA, Chen H, Zhang Y, Holleczek B, et al. Association of helicobacter pylori infection and chronic atrophic gastritis with risk of colonic, pancreatic and gastric cancer: a ten-year follow-up of the ESTHER cohort study. Oncotarget. 2016;7(13):17182–93.
162. Freelove R, Walling AD. Pancreatic cancer: diagnosis and management. Am Fam Physician. 2006;73(3):485–92.

163. Lauwers GY, Mino-Kenudson M, Rubin R. In: Rubin R, Strayer D, editors. Rubin's pathology: clinicopathologic foundations of medicine. Wolters Kluwer Lippincott Williams & Wilkins: Baltimore; 2008.
164. Malesci A, Montorsi M, Mariani A, Santambrogio R, Bonato C, Bissi O, et al. Clinical utility of the serum CA 19-9 test for diagnosing pancreatic carcinoma in symptomatic patients: a prospective study. Pancreas. 1992;7(4):497–502.
165. Montgomery RC, Hoffman JP, Riley LB, Rogatko A, Ridge JA, Eisenberg BL. Prediction of recurrence and survival by postresection CA 19-9 values in patients with adenocarcinoma of the pancreas. Ann Surg Oncol. 1997;4(7):551–6.
166. Koopmann J, Buckhaults P, Brown DA, Zahurak ML, Sato N, Fukushima N, et al. Serum macrophage inhibitory cytokine 1 as a marker of pancreatic and other periampullary cancers. Clin Cancer Res. 2004;10(7):2386–92.
167. Koopmann J, Rosenzweig CN, Zhang Z, Canto MI, Brown DA, Hunter M, et al. Serum markers in patients with resectable pancreatic adenocarcinoma: macrophage inhibitory cytokine 1 versus CA19-9. Clin Cancer Res. 2006;12(2):442–6.
168. Koopmann J, Fedarko NS, Jain A, Maitra A, Iacobuzio-Donahue C, Rahman A, et al. Evaluation of osteopontin as biomarker for pancreatic adenocarcinoma. Cancer Epidemiol Biomark Prev. 2004;13(3):487–91.
169. Zhou W, Sokoll LJ, Bruzek DJ, Zhang L, Velculescu VE, Goldin SB, et al. Identifying markers for pancreatic cancer by gene expression analysis. Cancer Epidemiol Biomark Prev. 1998;7(2):109–12.
170. Argani P, Iacobuzio-Donahue C, Ryu B, Rosty C, Goggins M, Wilentz RE, et al. Mesothelin is overexpressed in the vast majority of ductal adenocarcinomas of the pancreas: identification of a new pancreatic cancer marker by serial analysis of gene expression (SAGE). Clin Cancer Res. 2001;7(12):3862–8.
171. Chen R, Pan S, Cooke K, Moyes KW, Bronner MP, Goodlett DR, et al. Comparison of pancreas juice proteins from cancer versus pancreatitis using quantitative proteomic analysis. Pancreas. 2007;34(1):70–9.
172. Gronborg M, Bunkenborg J, Kristiansen TZ, Jensen ON, Yeo CJ, Hruban RH, et al. Comprehensive proteomic analysis of human pancreatic juice. J Proteome Res. 2004;3(5):1042–55.
173. Rosty C, Goggins M. Early detection of pancreatic carcinoma. Hematol Oncol Clin North Am. 2002;16(1):37–52.
174. Hruban RH, Goggins M, Parsons J, Kern SE. Progression model for pancreatic cancer. Clin Cancer Res. 2000;6(8):2969–72.
175. Mazaki T, Masuda H, Takayama T. Polymorphisms and pancreatic cancer risk: a meta-analysis. Eur J Cancer Prev. 2011;20(3):169–83.
176. Wilentz RE, Iacobuzio-Donahue CA, Argani P, McCarthy DM, Parsons JL, Yeo CJ, et al. Loss of expression of Dpc4 in pancreatic intraepithelial neoplasia: evidence that DPC4 inactivation occurs late in neoplastic progression. Cancer Res. 2000;60(7):2002–6.
177. Almoguera C, Shibata D, Forrester K, Martin J, Arnheim N, Perucho M. Most human carcinomas of the exocrine pancreas contain mutant c-K-ras genes. Cell. 1988;53(4):549–54.
178. Aspinall RJ, Lemoine NR. Gene therapy for pancreatic and biliary malignancies. Ann Oncol. 1999;10(Suppl 4):188–92.
179. Schutte M, Hruban RH, Geradts J, Maynard R, Hilgers W, Rabindran SK, et al. Abrogation of the Rb/p16 tumor-suppressive pathway in virtually all pancreatic carcinomas. Cancer Res. 1997;57(15):3126–30.
180. Cowgill SM, Muscarella P. The genetics of pancreatic cancer. Am J Surg. 2003;186(3):279–86.
181. Sohn TA, Yeo CJ. The molecular genetics of pancreatic ductal carcinoma: a review. Surg Oncol. 2000;9(3):95–101.
182. Lowenfels AB, Maisonneuve P. Epidemiology and risk factors for pancreatic cancer. Best Pract Res Clin Gastroenterol. 2006;20(2):197–209.
183. Li D, Xie K, Wolff R, Abbruzzese JL. Pancreatic cancer. Lancet. 2004;363(9414):1049–57.
184. Bartsch H, Malaveille C, Lowenfels AB, Maisonneuve P, Hautefeuille A, Boyle P. Genetic polymorphism of N-acetyltransferases, glutathione S-transferase M1 and NAD(P)H:quinone oxidoreductase in relation to malignant and benign pancreatic disease risk. The International Pancreatic Disease Study Group. Eur J Cancer Prev. 1998;7(3):215–23.
185. Duell EJ, Holly EA, Bracci PM, Liu M, Wiencke JK, Kelsey KT. A population-based, case-control study of polymorphisms in carcinogen-metabolizing genes, smoking, and pancreatic adenocarcinoma risk. J Natl Cancer Inst. 2002;94(4):297–306.
186. Jiao L, Hassan MM, Bondy ML, Abbruzzese JL, Evans DB, Li D. The XPD Asp312Asn and Lys751Gln polymorphisms, corresponding haplotype, and pancreatic cancer risk. Cancer Lett. 2007;245(1–2):61–8.
187. Lee HC, Yoon YB, Kim CY. Association between genetic polymorphisms of the cytochromes P-450 (1A1, 2D6, and 2E1) and the susceptibility to pancreatic cancer. Korean J Intern Med. 1997;12(2):128–36.
188. Li D, Jiao L, Li Y, Doll MA, Hein DW, Bondy ML, et al. Polymorphisms of cytochrome P4501A2 and N-acetyltransferase genes, smoking, and risk of pancreatic cancer. Carcinogenesis. 2006;27(1):103–11.
189. Liu G, Ghadirian P, Vesprini D, Hamel N, Paradis AJ, Lal G, et al. Polymorphisms in GSTM1, GSTT1 and CYP1A1 and risk of pancreatic adenocarcinoma. Br J Cancer. 2000;82(10):1646–9.
190. Ockenga J, Vogel A, Teich N, Keim V, Manns MP, Strassburg CP. UDP glucuronosyltransferase (UGT1A7) gene polymorphisms increase the risk of chronic pancreatitis and pancreatic cancer. Gastroenterology. 2003;124(7):1802–8.
191. Piepoli A, Gentile A, Valvano MR, Barana D, Oliani C, Cotugno R, et al. Lack of association between UGT1A7, UGT1A9, ARP, SPINK1 and CFTR gene polymorphisms and pancreatic cancer in Italian patients. World J Gastroenterol. 2006;12(39):6343–8.
192. Verlaan M, Drenth JP, Truninger K, Koudova M, Schulz HU, Bargetzi M, et al. Polymorphisms of UDP-glucuronosyltransferase 1A7 are not involved in pancreatic diseases. J Med Genet. 2005;42(10):e62.
193. Vrana D, Pikhart H, Mohelnikova-Duchonova B, Holcatova I, Strnad R, Slamova A, et al. The association between glutathione S-transferase gene polymorphisms and pancreatic cancer in a central European Slavonic population. Mutat Res. 2009;680(1–2):78–81.
194. Duell EJ, Holly EA, Bracci PM, Wiencke JK, Kelsey KT. A population-based study of the Arg399Gln polymorphism in X-ray repair cross- complementing group 1 (XRCC1) and risk of pancreatic adenocarcinoma. Cancer Res. 2002;62(16):4630–6.
195. Jiao L, Bondy ML, Hassan MM, Wolff RA, Evans DB, Abbruzzese JL, et al. Selected polymorphisms of DNA repair genes and risk of pancreatic cancer. Cancer Detect Prev. 2006;30(3):284–91.
196. Jiao L, Hassan MM, Bondy ML, Wolff RA, Evans DB, Abbruzzese JL, et al. XRCC2 and XRCC3 gene polymorphism and risk of pancreatic cancer. Am J Gastroenterol. 2008;103(2):360–7.
197. Li D, Suzuki H, Liu B, Morris J, Liu J, Okazaki T, et al. DNA repair gene polymorphisms and risk of pancreatic cancer. Clin Cancer Res. 2009;15(2):740–6.
198. McWilliams RR, Bamlet WR, Cunningham JM, Goode EL, de Andrade M, Boardman LA, et al. Polymorphisms in DNA repair genes, smoking, and pancreatic adenocarcinoma risk. Cancer Res. 2008;68(12):4928–35.
199. Wang L, Lin DX, Lu XH, Miao XP, Li H. Polymorphisms of the DNA repair genes XRCC1 and XPC: relationship to pancreatic cancer risk. Wei Sheng Yan Jiu. 2006;35(5):534–6.

200. Duell EJ, Casella DP, Burk RD, Kelsey KT, Holly EA. Inflammation, genetic polymorphisms in proinflammatory genes TNF-A, RANTES, and CCR5, and risk of pancreatic adenocarcinoma. Cancer Epidemiol Biomark Prev. 2006;15(4):726–31.
201. Reid-Lombardo KM, Fridley BL, Bamlet WR, Cunningham JM, Sarr MG, Petersen GM. Inflammation-related gene variants as risk factors for pancreatic cancer. Cancer Epidemiol Biomark Prev. 2011;20(6):1251–4.
202. Kanda J, Matsuo K, Suzuki T, Kawase T, Hiraki A, Watanabe M, et al. Impact of alcohol consumption with polymorphisms in alcohol-metabolizing enzymes on pancreatic cancer risk in Japanese. Cancer Sci. 2009;100(2):296–302.
203. Miyasaka K, Kawanami T, Shimokata H, Ohta S, Funakoshi A. Inactive aldehyde dehydrogenase-2 increased the risk of pancreatic cancer among smokers in a Japanese male population. Pancreas. 2005;30(2):95–8.
204. Li D, Ahmed M, Li Y, Jiao L, Chou TH, Wolff RA, et al. 5,10-Methylenetetrahydrofolate reductase polymorphisms and the risk of pancreatic cancer. Cancer Epidemiol Biomark Prev. 2005;14(6):1470–6.
205. Matsubayashi H, Skinner HG, Iacobuzio-Donahue C, Abe T, Sato N, Riall TS, et al. Pancreaticobiliary cancers with deficient methylenetetrahydrofolate reductase genotypes. Clin Gastroenterol Hepatol. 2005;3(8):752–60.
206. Wang L, Miao X, Tan W, Lu X, Zhao P, Zhao X, et al. Genetic polymorphisms in methylenetetrahydrofolate reductase and thymidylate synthase and risk of pancreatic cancer. Clin Gastroenterol Hepatol. 2005;3(8):743–51.
207. Lempinen M, Paju A, Kemppainen E, Smura T, Kylanpaa ML, Nevanlinna H, et al. Mutations N34S and P55S of the SPINK1 gene in patients with chronic pancreatitis or pancreatic cancer and in healthy subjects: a report from Finland. Scand J Gastroenterol. 2005;40(2):225–30.
208. Matsubayashi H, Fukushima N, Sato N, Brune K, Canto M, Yeo CJ, et al. Polymorphisms of SPINK1 N34S and CFTR in patients with sporadic and familial pancreatic cancer. Cancer Biol Ther. 2003;2(6):652–5.
209. Teich N, Schulz HU, Witt H, Bohmig M, Keim V. N34S, a pancreatitis associated SPINK1 mutation, is not associated with sporadic pancreatic cancer. Pancreatology. 2003;3(1):67–8.
210. Dong X, Li Y, Chang P, Tang H, Hess KR, Abbruzzese JL, et al. Glucose metabolism gene variants modulate the risk of pancreatic cancer. Cancer Prev Res (Phila). 2011;4(5):758–66.
211. Amundadottir L, Kraft P, Stolzenberg-Solomon RZ, Fuchs CS, Petersen GM, Arslan AA, et al. Genome-wide association study identifies variants in the ABO locus associated with susceptibility to pancreatic cancer. Nat Genet. 2009;41(9):986–90.
212. Petersen GM, Amundadottir L, Fuchs CS, Kraft P, Stolzenberg-Solomon RZ, Jacobs KB, et al. A genome-wide association study identifies pancreatic cancer susceptibility loci on chromosomes 13q22.1, 1q32.1 and 5p15.33. Nat Genet. 2010;42(3):224–8.
213. Wolpin BM, Rizzato C, Kraft P, Kooperberg C, Petersen GM, Wang Z, et al. Genome-wide association study identifies multiple susceptibility loci for pancreatic cancer. Nat Genet. 2014;46(9):994–1000.
214. Childs EJ, Mocci E, Campa D, Bracci PM, Gallinger S, Goggins M, et al. Common variation at 2p13.3, 3q29, 7p13 and 17q25.1 associated with susceptibility to pancreatic cancer. Nat Genet. 2015;47(8):911–6.
215. Wu C, Miao X, Huang L, Che X, Jiang G, Yu D, et al. Genome-wide association study identifies five loci associated with susceptibility to pancreatic cancer in Chinese populations. Nat Genet. 2011;44(1):62–6.
216. Low SK, Kuchiba A, Zembutsu H, Saito A, Takahashi A, Kubo M, et al. Genome-wide association study of pancreatic cancer in Japanese population. PLoS One. 2010;5(7):e11824.