Langenbecks Arch Surg (2008) 393:535–545
DOI 10.1007/s00423-007-0266-2

ORIGINAL ARTICLE

Tobacco and the risk of pancreatic cancer: a review and meta-analysis

Simona Iodice · Sara Gandini · Patrick Maisonneuve · Albert B. Lowenfels

Received: 13 November 2007 / Accepted: 13 November 2007 / Published online: 12 January 2008

Abstract
Background/Aim Smoking is a recognized risk factor for pancreatic cancer. The aim of this study was to perform a meta-analysis to provide a robust estimate of the strength of the association between smoking and pancreatic cancer, to determine the risk of pipe and cigar smoking, and to estimate the duration of an elevated risk after smoking cessation.
Methods We performed a meta-analysis of 82 published studies containing epidemiologic information about smoking and pancreatic cancer. Information on studies published between 1950 and 2007 was abstracted and prepared for analysis using standard meta-analytic procedures.
Results The overall risk of pancreatic cancer estimated from the combined results for current and former smokers was, respectively, 1.74 (95% CI 1.61–1.87) and 1.2 (95% CI 1.11–1.29). The risk of pancreatic cancer for current and former pipe and/or cigar smokers was respectively 1.47 (95% CI 1.17–1.83) and 1.29 (95% CI 0.68–2.45). For former cigarette smokers, the risk remains elevated for a minimum of 10 years after cessation.
Conclusions Based on estimates from four continents, smoking cigarettes causes a 75% increase in the risk of pancreatic cancer compared to non-smokers, and the risk persists for a minimum of 10 years after smoking cessation. This implies that in a population where the prevalence of smoking is 30%, the population's attributable risk (the proportion of pancreatic cancer explained by smoking) is estimated to be 20%.

Keywords Pancreatic cancer · Smoking · Tobacco · Meta-analysis · Epidemiology

Introduction

Pancreatic cancer is one of the most lethal human cancers, estimated to be responsible for more than a quarter of a million deaths worldwide in 2001 [1]. Nearly all patients who contract the disease die, usually within a few months despite surgical or medical intervention.

Several risk factors are known to be related to pancreatic cancer, and of these, smoking has been the most carefully studied. Although there are other stronger risk factors (e.g., certain genetic diseases, pancreatitis), smoking is the suspected cause of 20–30% of all pancreatic cancer, making it the most important preventable cause of pancreatic cancer.

Pancreatic cancer resembles other adenocarcinomas in that it is age related: Only 5–10% of all pancreatic cancers occur before age 50, and 80% of patients who develop pancreatic cancer are ≥60 years. Smoking is believed to be a risk factor for patients in all age groups. Smoking appears to lower the age of developing pancreatic cancer, but this may be an artifact related to competing causes of tobacco-related mortality.

In this report, we have performed a meta-analysis of 82 published articles with information of smoking and pancreatic cancer. In addition to cigarette smoking, we have also

Supported by grants from the Italian Association for Cancer Research (AIRC), Solvay Pharmaceuticals, and the C.D. Smithers Foundation.

S. Iodice · S. Gandini · P. Maisonneuve · A. B. Lowenfels
Division of Epidemiology and Biostatistics,
European Institute of Oncology,
Milan, Italy

S. Iodice · S. Gandini · P. Maisonneuve · A. B. Lowenfels (✉)
Department of Surgery, New York Medical College,
Valhalla, NY 10595, USA
e-mail: Lowenfel@nymc.edu

studied pipe and cigar exposure and have performed an analysis of the impact of smoking cessation on the eventual reduction of risk. The aim was to obtain an overall quantitative estimate of the risk of smoking and to study the impact of smoking cessation on risk reduction. An additional aim was to look for reasons to explain variation between published studies.

Materials and methods

Data sources and search strategy

We reviewed published reports from the following databases using validated search strategies (12–14):

(a) Ovid MEDLINE® database (1950 to March 2007)
(b) ISI Web of Science® Science Citation Index Expanded™ (SCI Expanded)
(c) PUBMED (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi).

Other sources were found in the reference lists of the retrieved articles and preceding reviews on the topic. The following keywords and/or corresponding MESH terms were used for the search: pancreatic cancer, malignancy, tobacco, smoke, cigarette, cigars, and pipe. The search was limited to human studies, but no language or time restrictions were applied.

Data extraction

We extracted and coded the following information from the published papers: authors, year of publication, study period, type of study (cohort, case-control), country of the study, number of cases, number of controls or person-years, histological confirmation, use of proxy respondents for obtaining information about cases, use of matching in study design, features of populations and of the cancer, adjustments used in the analysis.

We used wide inclusion criteria to select and retain a large group of homogeneous studies:

(1) Study reports should contain the minimum information necessary to estimate relative risks (RRs) and corresponding 95% confidence intervals (i.e., odds ratios or RRs and a measure of uncertainty: standard errors, variance, confidence intervals or exact P value of the significance of the estimates) for the tobacco smoking.
(2) The studies should be independent to avoid giving double weight to single studies. In case of multiple reports of the same study, we considered the estimates from the most recent publication.
(3) Homogeneous categories were chosen for the exposure to tobacco smoking. We retrieved data for: ever, current, and former type of exposure for cigarettes and pipes or cigars; dose–response estimates for quantity of cigarettes smoked, duration in years and years since quitting. In case of multiple estimates, we preferred incidence to mortality, population-based estimates to hospital-based ones, estimates separated by gender to overall estimates, estimates separated by type of smoking (pipe vs cigars) to overall estimates, and dose–response estimates for quantity of cigarettes per day to pack-years.
(4) It was necessary that the populations studied be homogeneous, at least for the main risk factor for pancreatic cancer. One study [2], which considered only an unusual familial kindred, was excluded because a distinct etiology, mainly genetic, for this population is suggested, and this could affect smoking-related cancer risk.

Definition of the outcome and exposures

Exocrine pancreatic cancer was the outcome variable for the analysis, and tobacco smoking (either cigarettes, pipes, or cigars) was the exposure variable (risk factor). For smoking, we performed separate analyses for "current" smokers and "former" smokers. We combined other forms of smoking (pipes, cigars) into a single category. For the analysis of cessation of smoking, we examined three time periods: <10, 10–19, and ≥20 years. For estimating dose–response, we examined both daily cigarette exposure and pack-years.

Data analysis strategy

We ignored the distinction among various measures of RR (i.e., odds ratio, rate ratio, risk ratio) on the assumption that these distinctions are unimportant, because pancreas cancer is relatively rare. All measures of association and the corresponding confidence interval were adjusted for the maximum number of confounding variables, and were translated into log RR and corresponding variance, with the formula proposed by Greenland [3]. When several measures of risk were given for a single study, even in absence of heterogeneity, we used random effects models including the two sources of variation (within and between studies), to take into account correlation within study [4].

We used random effects models, with restricted maximum likelihood estimate to evaluate summary RRs. Homogeneity of effects across studies was assessed using the Chi-square statistic and quantified by I^2, which

represents the percentage of total variation across studies that is attributable to heterogeneity rather than chance [5]. *P* values, indicating significance of factors investigated, were obtained with analysis of variance using PROC MIXED in SAS [6]. Sub-group analyses and meta-regressions were carried out to investigate between-study heterogeneity focusing on study type, adjustments used in the analysis, exposure definition, publication year, country and gender, type of controls, cancer among controls, matching, used of proxy, and histological confirmation. As the Chi-square test has limited power, we considered statistically significant heterogeneity at the $P=0.10$ level of association.

For dose–response estimates, we used a linear model within each study to estimate the RR associated with an increase of one cigarette per day. We assigned to each class the number of cigarettes smoked corresponding to the midpoint of the range. We obtained the summarized RR pooling the study-specific estimates by the classical random effects models [7].

Sensitivity analysis was carried out to evaluate whether results were influenced by a single study. Two funnel-plot-based approaches were used for assessing publication bias: Copas and Shi [8] sensitivity analysis and the funnel-plot regression of ln(RR) on the sample size, weighted by the inverse of the pooled variance [9].

Table 1 Characteristics of the included cohort studies on pancreatic cancer and smoking

Cohort name	First author, publication year	Country	Study period	Number of cases	Study size	Gender	% Histological confirmation
Adventist Health Study	Heuch, 1983 [20]	Norway	1960–1978	63	11,959	Men	62
	Mills, 1988 [21]	USA	1974–1982	40	34,198	Both	N.S.
	Hirayama, 1989 [22]	Japan	1965–1982	679	265,118	Both	N.S.
	Akiba and Hirayama, 1990 [23]	Japan	1965–1981	1,250	693,689	Both	N.S.
MRFIT	Kuller, 1991 [24]	USA	1975–1985	349	361,662	Men	N.S.
Lutheran brotherhood	Zheng, 1993 [25]	USA	1966–1986	57	17,633	Men	N.S.
	Tverdal, 1993 [26]	Norway	1972–1988	57	68,825	Men	N.S.
	Shibata, 1994 [27]	USA	1981–1990	65	13,976	Both	N.S.
US veterans	McLaughlin, 1995 [28]	USA	1954–1980	1,264	248,046	Men	N.S.
Migrant study	Engeland, 1996 [29]	Norway	1966–1993	224	26,132	Both	55
NHS+HPFS	Fuchs, 1996 [30]	USA	1980–1992	186	167,767	Both	N.S.
	Yuan, 1996 [31]	China	1986–1993	21	18,244	Men	67
	Liaw and Chen, 1997 [10]	China	1982–1994	15	11,096	Men	N.S.
	Tulinius, 1997 [32]	Iceland	1968–1995	101	22,946	Men	95
	Nordlund, 1997 [33]	Sweden	1963–1989	144	26,032	Women	N.S.
Kaiser Perm. Medical Care program	Iribarren, 1999 [34]	USA	1964–1973	52	17,774	Men	N.S.
CPSII	Coughlin, 2000 [35]	USA	1982–1996	3,751	1,102,308	Both	N.S.
	Nilsen, 2000 [36]	Norway	1984–1996	166	63,374	Both	N.S.
CPSII	Shapiro, 2000 [37]	USA	1982–1994	385	137,555	Men	N.S.
Alpha-Tocoph, Beta-carotene Prevention	Stolzenberg-Solomon, 2001 [38]	Finland	1985–1988	157	27,101	Men	100
	Nilsson, 2001 [39]	Sweden	1960–1996	314	41,544	Both	N.S.
JACC	Lin, 2002 [40]	Japan	1988–1997	225	99,527	Both	N.S.
	Isaksson, 2002 [41]	Sweden	1969–1997	176	21,884	Both	90
	Jee, 2004 [12]	Korea	1993–2001	1,143	1,212,906	Both	N.S.
CPSII	Henley, 2004 [42]	USA	1984–2000	643	138,307	Men	N.S.
SMC+COSM	Larsson, 2005 [43]	Sweden	1987–1997	136	83,053	Both	N.S.
IOWA	Sinner, 2005 [44]	USA	1986–2001	209	37,793	Men	N.S.
	Gallicchio, 2006 [45]	USA	1963–1978	56	45,749	Both	N.S.
	Gallicchio, 2006 [45]	USA	1975–1994	92	48,172	Both	N.S.
Asia Pacific Collaboration	Ansary-Moghaddam, 2006 [46]	Asia, Australia, New-Zealand	1961–1999	324	519,643	Both	N.S.
	Yun, 2006 [47]	Korea	1992–2002	863	44,6407	Men	N.S.
IOWA	Prizment, 2007 [16]	USA	1986–2003	228	37,459	Men	N.S.
Multiethnic study	Nothlings, 2007 [48]	USA	1993–2002	472	167,430	Both	N.S.
CHADP	Gapstur, 2007 [49]	USA	1963–1995	139	35,658	Both	N.S.
HPFS	Michaud, 2007 [50]	USA	1988–2002	190	49,428	Both	N.S.

N.S. Not stated

Results

We retrieved 113 papers published between 1958 and 2007 with data on pancreatic cancer and smoke. Following the inclusion criteria, 82 published papers were included (42 case-control studies, 35 cohort, and five nested case-control studies) and considered for the analysis (Tables 1 and 2). Studies were conducted in many locations (one from

Table 2 Characteristics of the included case-control studies on pancreatic cancer and smoking

First author, publication year	Country	Study period	Number of cases	Number of controls	Gender	% Histological confirmation	Type of controls	Proxy % for cases	Cancers in controls
Wynder, 1973 [51]	USA	1950–1964	142	307	Both	N.S.	Hosp-based	N.S.	Yes
MacMahon, 1981 [52]	USA	1974–1979	367	643	Both	100	Hosp-based	0	Yes
Durbec, 1983 [18]	France	1979–1980	69	199	Both	100	Pop-based	0	N.S.
Whittemore, 1983 [53]	USA	1916–1978	122	481	Both	N.S.	Class mate	N.S.	N.S.
Kinlen and McPherson, 1984 [54]	UK	1952–1954	216	432	Men	N.S.	Hosp-based	N.S.	N.S.
Gold, 1985 [55]	USA	1978–1980	201	201	Both	N.S.	Pop-based	75	N.S.
Hsieh, 1986 [56]	USA	1981–1984	176	273	Both	100	Hosp-based	0	N.S.
Mack, 1986 [57]	USA	1976–1981	490	490	Both	100	Pop-based	75	N.S.
Wynder, 1986 [58]	USA	1981–1984	238	696	Both	N.S.	Hosp-based	0	N.S.
Hiatt, 1988 [59]	USA	1978–1985	49	11,504	Both	78	Pop-based[a]	0	N.S.
Clavel, 1989 [60]	France	1982–1985	161	268	Both	63	Hosp-based	N.S.	Yes
Cuzick and Babiker, 1989 [61]	UK	1983–1986	216	279	Men	30	Hosp-based	0	N.S.
Farrow, 1990 [62]	USA	1982–1986	148	188	Both	46	Pop-based	100	N.S.
Falk, 1990 [63]	USA	1979–1983	198	209	Men	87	Hosp-based	52	N.S.
Baghurst, 1991 [64]	Australia	1984–1987	104	253	Both	N.S.	Pop-based	15	N.S.
Bueno de Mesquita, 1991 [65]	The Neth.	1984–1988	176	487	Both	68	Pop-based	58	N.S.
Howe, 1991 [66]	Canada	1983–1986	249	505	Both	69	Pop-based	78	N.S.
Vioque and Walker, 1991 [67]	Several	1960–1980	108	374	Both	N.S.	Hosp-based	N.S.	N.S.
Ghadirian, 1991 [68]	Canada	1984–1988	179	239	Both	83	Pop-based	75	N.S.
Lyon, 1992 [69]	USA	1984–1987	149	363	Both	N.S.	Pop-based	100	N.S.
Mizuno, 1992 [70]	Japan	1989–1990	124	124	Men	N.S.	Hosp-based	0	N.S.
Zatonski, 1993 [71]	Poland	1985–1988	110	195	Both	N.S.	Pop-based	78	N.S.
Kalapothaki, 1993 [72]	Greece	1991–1992	181	181	Both	100	Hosp-based	0	N.S.
Silverman, 1994 [73]	USA	1986–1989	526	2153	Both	85	Pop-based	0	N.S.
Ji, 1995 [74]	China	1990–1993	451	1552	Both	37	Pop-based	0	N.S.
Gullo, 1995 [75]	Italy	1987–1989	319	319	Both	70	Hosp-based	0	N.S.
Siemiatycki, 1995 [76]	Canada	1979–1986	116	533	Men	100	Pop-based	18	N.S.
Fernandez, 1996 [77]	Italy	1983–1992	362	1408	Both	100	Hosp-based	0	N.S.
Lee, 1996 [78]	China	1989–1994	282	282	Both	46	Hosp-based	N.S.	N.S.
Nishi, 1996 [11]	Japan	1987–1992	141	282	Both	N.S.	Pop-based	N.S.	N.S.
Murata, 1996 [79]	Japan	1984–1993	43	86	Both	N.S.	Pop-based[a]	0	N.S.
Kokic, 1996 [80]	Serbia	1992–1994	100	100	Both	62	Hosp-based	0	N.S.
Muscat, 1997 [81]	USA	1985–1993	484	954	Both	100	Hosp-based	0	Yes
Fryzek, 1997 [82]	USA	1994–1995	66	131	Both	N.S.	Pop-based	0	N.S.
Partanen, 1997 [83]	Finland	1984–1987	662	1770	Both	N.S.	Pop-based	100	Yes
Mori, 1999 [13]	India	1994–1996	79	146	Both	100	Hosp-based	0	N.S.
Alguacil, 2000 [84]	Spain	1992–1995	164	238	Both	N.S.	Hosp-based	6	N.S.
Brian-Chiu, 2000 [85]	USA	1986–1989	362	2336	Both	N.S.	Pop-based	86	N.S.
Villeneuve, 2000 [86]	Canada	1994–1997	583	4813	Both	100	Pop-based	24	N.S.
Inoue, 2003 [14]	Japan	1988–1999	200	2000	Both	N.S.	Hosp-based	6	N.S.
Bonelli, 2003 [87]	Italy	1992–1996	202	406	Both	51	Hosp-based	0	N.S.
Alguacil, 2004 [88]	USA	1986–1989	154	844	Both	85	Pop-based	0	N.S.
Carta, 2004 [89]	Italy	1972–2001	6	72	Men	N.S.	Pop-based[a]	0	N.S.
Duell, 2005 [90]	USA	1995–1999	241	818	Women	100	Pop-based	0	N.S.
Lu, 2006 [91]	China	2002–2004	119	238	Both	35	Pop-based	N.S.	N.S.
Li, 2007 [92]	China	1989–1998	180	3183	Both	25	Pop-based[a]	0	N.S.
Khurana, 2007 [15]	USA	1998–2004	475	483,258	Both	N.S.	Pop-based[a]	0	N.S

N.S. Not stated, *Hosp-based* hospital based, *Pop-based* population based, *The Neth.* The Netherlands
[a] Nested case-control study

Table 3 Pooled risk estimates for pancreas cancer in relation to smoking characteristics from 82 independent studies

		RR[a]	(95% CI)	Number of studies	*P* value for heterogeneity	I^2 %
Cigarettes	Current	1.74	(1.61–1.87)	59	<0.01	50
	Former	1.20	(1.11–1.29)	39	0.08	21
Pipe and/or cigars	Current	1.47	(1.17–1.83)	18	0.03	38
	Former	1.29	(0.68–2.45)	5	<0.01	80
Smoking cessation	<10 years	1.48	(1.25–1.76)	14	<0.01	59
	≥10 years	1.15	(0.95–1.40)	13	<0.01	59
	≥20 years	0.96	(0.85–1.09)	7	0.64	0
Cigarette consumption[b]	×1 cig/day	1.02	(1.02–1.03)	45	<0.01	58
	×20 cig/day	1.62	(1.51–1.75)			
	×1 pack-year	1.01	(1.00–1.01)	6	0.04	51
	×40 packs-year	1.37	(1.09–1.72)			
Smoking duration[b]	×1 year	1.01	(1.01–1.02)	16	<0.01	56
	×10 year	1.16	(1.12–1.19)			

I^2 represents the percentage of total variation across studies that is attributable to heterogeneity rather than to chance.
[a] References category "never smokers"
[b] Dose–response analysis

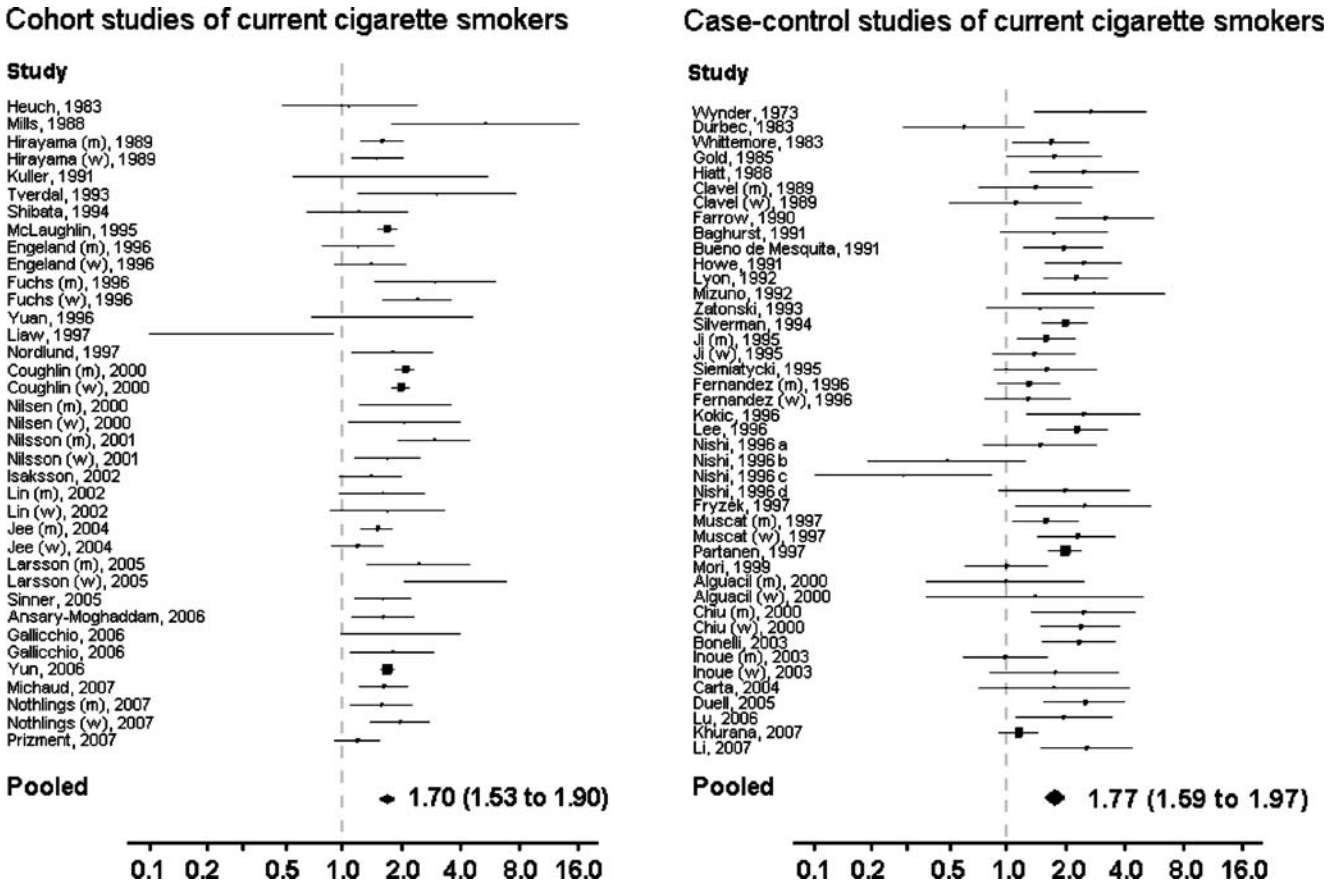

Fig. 1 Forest plot and pooled risk estimates of pancreatic cancer for current smokers from cohort and case control studies. Reference category is never smokers for both cohort and case-control studies; *a* the authors presented RRs for current smokers stratified by coffee consumption; reference category is always never smokers and never drinkers of coffee; *b* RRs for current smokers and occasionally drinkers of coffee, *c* RRs for current smokers and 1–2 cups of coffee/day, *d* RRs for current smokers and 3+ cups of coffee/day

Australia, 15 from Asia, one from India, 39 from USA or Canada, 24 from Europe, and two mixed). Sixty-five studies reported estimates for current and/or former smokers, 51 studies provided estimates for dose–response estimates for cigarettes per day or pack-years, 18 studies gave estimates for pipe and/or cigars, 16 for duration in years, and 14 for cessation.

Overall results are presented in Table 3. For current cigarette exposure, the pooled RR was 1.74 (95% CI 1.61–1.87), and for pipe and/or cigar smokers, the RRs were 1.47 (95% CI 1.17–1.83). For dose–response estimates, we presented the estimates for one cigarette, one pack-year, and for 1-year of duration and for greater doses considering a linear trend. Smoking one cigarette per day raised the RR of pancreatic cancer by an estimated 2%; smoking one pack-year raised the risk of pancreatic cancer by 1%. The risk of pancreatic cancer remains elevated after smoking cessation for a minimum of 10 years.

In Fig. 1, we present a forest plot for current smokers, with data presented separately for case-control studies and cohort studies. With few exceptions, nearly all studies found smoking to increase the risk of pancreatic cancer. In Fig. 2, we present the forest plot for the three categories considered for smoking cessation. Ex-smokers have a significantly elevated risk of smoking for a minimum of 10 years.

In Tables 4 and 5, we reported the estimates by several factors considered in the subgroup analysis that investigates

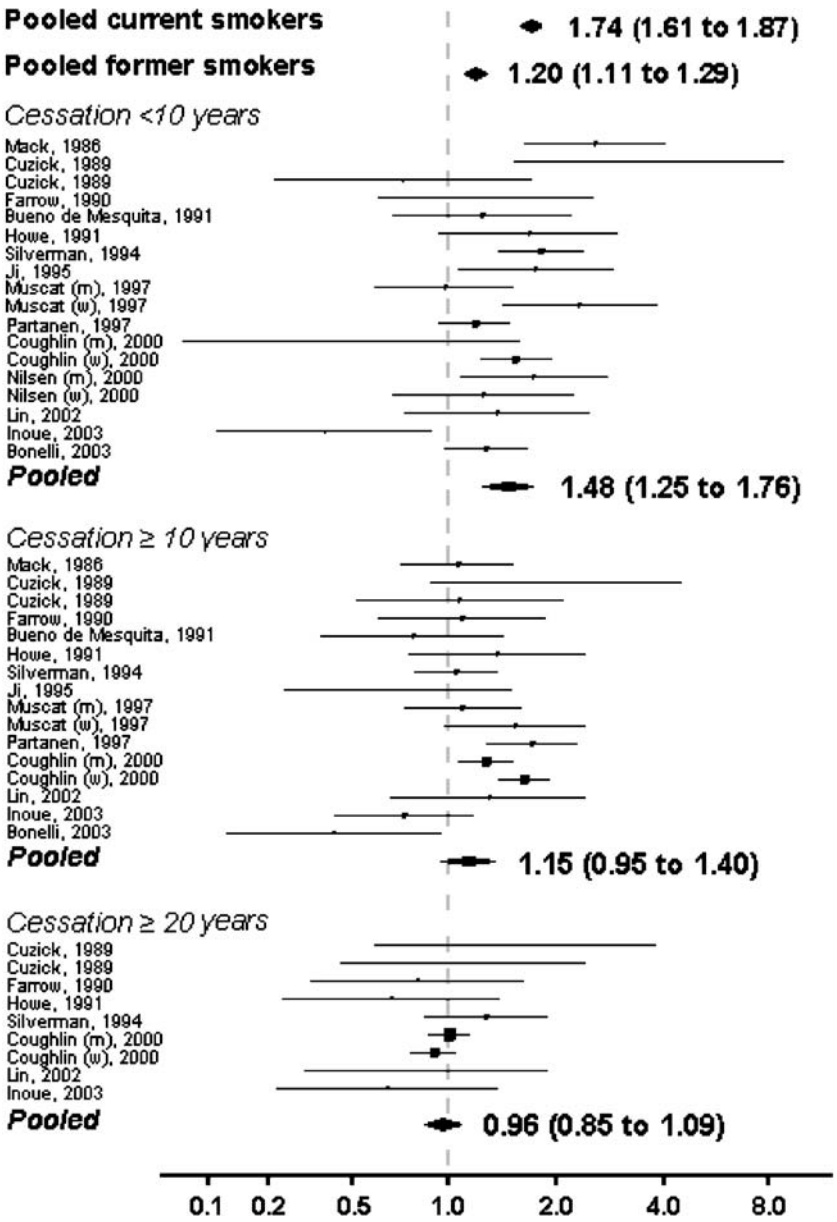

Fig. 2 Forest plot and pooled risk estimates of pancreatic cancer in relation to smoking cessation. Reference category is never smokers

heterogeneity for cigarettes smoking and pipe and/or cigars smokers. The only factor that explained some of the heterogeneity for cigarettes smoking is the adjustment of the estimates for confounders (P=0.08). For pipe/and or cigars, the categorization used (current vs "ever"), the use of proxy, and the inclusion of cancers among controls explained part of the heterogeneity (P=0.05, P=0.07, and P =0.04, respectively). In Table 6, we show the estimates retrieved from the original papers on the effect of cessation of smoking in relation to lifetime or daily cigarette consumption.

Discussion

This meta-analysis reviews cohort studies and case-control studies containing information about smoking and pancreatic cancer from four continents. The overall result suggests

Table 4 Heterogeneity analysis of studies on smoking and pancreatic cancer

Type of factors	Strata	RR[a]	(95% CI)	Number of studies	P value[b]	I^2 %
Current cigarettes smokers						
Study type	Case-controls	1.77	(1.59–1.97)	33	0.62	49
	Cohorts	1.70	(1.53–1.90)	26		48
Estimates type	Adjusted	1.80	(1.65–1.96)	43	0.08	46
	Crude	1.56	(1.36–1.79)	16		45
Area	Asia	1.54	(1.33–1.79)	14	0.11	56
	EU	1.71	(1.48–1.97)	18		39
	USA–Canada	1.87	(1.68–2.09)	26		48
Smokers type	Current	1.80	(1.65–1.96)	41	0.11	51
	Ever	1.57	(1.36–1.81)	18		37
Histological confirmation	<80%	1.77	(1.63–1.92)	50	0.26	49
	≥80%	1.57	(1.28–1.91)	9		56
Gender	Male	1.69	(1.53–1.87)	30	0.76	50
	Female	1.72	(1.53–1.94)	20		33
Case-control studies						
Controls	Population	1.83	(1.58–2.13)	22	0.42	57
	Hospital	1.66	(1.34–2.05)	11		34
Proxy	Any	1.73	(1.42–2.11)	12	0.58	45
	None	1.86	(1.49–2.34)	10		28
Absence of cancers among controls	Stated	1.76	(1.53–2.01)	29	0.69	53
	Not stated	1.87	(1.36–2.59)	4		27
Former cigarettes smokers						
Study type	Case-controls	1.18	(1.05–1.32)	20	0.68	38
	Cohorts	1.21	(1.10–1.35)	19		4
Estimates type	Adjusted	1.19	(1.10–1.30)	31	0.90	19
	Crude	1.21	(1.01–1.44)	8		48
Area	Asia	1.28	(1.16–1.41)	7	0.15	47
	EU	1.07	(0.92–1.25)	11		26
	USA–Canada	1.19	(1.11–1.27)	21		8
Histological confirmation	<80%	1.17	(1.08–1.27)	31	0.21	26
	≥80%	1.31	(1.12–1.53)	8		15
Gender	Male	1.16	(1.06–1.28)	24	0.13	51
	Female	1.29	(1.13–1.46)	20		2
Case-control studies						
Controls	Population	1.31	(1.08–1.60)	10	0.11	47
	Hospital	1.05	(0.86–1.29)	10		40
Proxy	Any	1.21	(1.03–1.42)	13	0.12	27
	None	0.95	(0.72–1.26)	4		37
Absence of cancers among controls	Stated	1.16	(0.99–1.35)	17	0.12	21
	Not stated	1.28	(0.92–1.78)	3		42

P value for publication year, as continuous variable, was never significant.
[a] References category "never smokers"
[b] P value of the difference between strata.

Table 5 Heterogeneity analysis of pipe and/or cigar smoking studies

Type of factors	Strata	RR[a]	(95% CI)	Number of studies	*P* value[a]	I^2%
Current pipe and cigar smokers						
Type of tobacco	Only cigar	1.53	(1.02–2.28)	9	0.65	48
	Only pipe	1.39	(0.94–2.07)	9		16
Study type	Case-controls	1.52	(1.09–2.12)	12	0.65	40
	Cohorts	1.37	(0.90–2.08)	6		42
Estimates type	Adjusted	1.43	(1.06–1.93)	13	0.77	38
	Crude	1.55	(0.90–2.66)	5		45
Area	EU	1.44	(1.01–2.05)	9	0.99	46
	USA–Canada	1.46	(1.04–2.05)	7		37
Smokers type	Current	1.57	(1.29–1.91)	15	0.05	26
	Ever	1.03	(0.71–1.48)	3		36
Histological confirmation	<80%	1.39	(1.05–1.83)	14	0.39	23
	≥80%	1.76	(1.00–3.11)	4		59
Case-control studies						
Control	Population	1.24	(0.82–1.86)	6	0.13	47
	Hospital	1.94	(1.15–3.28)	6		0
Proxy	Any	1.91	(1.22–2.97)	8	0.07	0
	None	1.13	(0.76–1.70)	4		50
Absence of cancers among controls	Stated	1.14	(0.81–1.61)	8	0.04	20
	Not stated	2.14	(1.32–3.49)	4		0

P value for publication year, as continuous variable, was never significant.
[a] References category "never smokers"
[b] *P* value of the difference between strata.

that smoking causes about a 75% increase in the risk of pancreatic cancer, with lower and upper limits ranging from about 60% to 100%. As with other cancers, the risk increases with the number of cigarettes smoked and the duration. The excess risk associated with smoking persists for at least 10 years.

The main source of exposure of the pancreas to tobacco-related carcinogens must be via the blood stream, explaining why the smoking-related risk of pancreatic cancer is remarkably similar to the smoking-related risk of other tumors, such as kidney, stomach, and cervix, where the exposure to tobacco-related carcinogens is indirect. However, it is possible that some carcinogens may reach the pancreas by exposure to bile, which would explain the excess of tumors arising in the head of the gland.

Heterogeneity

A main aim of any meta-analysis is to examine sources of heterogeneity to explain the non-uniformity of reported results. To assess uniformity of results across the various publications, we used both a Chi-square and the I^2 statistics.

Table 6 Effect of cessation of smoking on pancreas cancer risk in relation to lifetime or daily cigarette consumption

First author, publication year	OR (relative to never smokers)	Lifetime cigarette consumption		
		1st tertile	2nd tertile	3rd tertile
Boyle, 1996 [93]	Ex-smokers	1.19	1.28	2.02
	Years since quitting			
	≤4	2.34	2.67	3.80
	5–14	1.23	1.35	2.11
	≥15	1.12	0.81	0.62
Bonelli, 2003 [87]	Years since quitting			
	≤4	1.6 (0.5–6.0)	1.7 (0.4–7.5)	9.4 (0.9–103)
	5–14	2.5 (1.0–6.2)	2.4 (0.8–6.9)	1.1 (0.3–3.7)
	≥15	0.5 (0.2–1.2)	1.6 (0.1–19.1)	0.3 (0.1–1.4)
Ji, 1995 [74]	Years since quitting	<20 cigarette/day	20+ cigarette/day	
	<10	2.2 (1.0–4.9)	1.8 (0.9–3.6)	
	≥10	0.8 (0.2–2.3)	0.7 (0.3–1.7)	

Cigarettes

For cigarette smoking, the results of the meta-analysis found nearly identical risks from combined cohort studies (RR=1.70) compared to case-control studies (RR=1.77). The reported results were consistent over a time period extending from 1973–2007. Two studies found an unexpected protective effect of cigarette smoking: a Chinese cohort study [10], based on 15 deaths with minimal overall impact weight=3.18, and a Japanese case-control study [11] carried out to investigate the effect of coffee and pancreatic cancer. For the Japanese study, we included in the analysis the published estimates which were stratified by four coffee consumption categories with the reference category as never smoker and never coffee drinker: Two strata suggested a protective effect for smokers; one was significant.

The pooled RR for current vs never smokers presented a moderately high heterogeneity because of seven studies. In addition to the Nishi study, these were a large Korean cohort [12] with a low but not significant estimate for women, an Indian hospital-based case-control study [13], a Japanese study [14] with an adjusted estimate for women not significantly lower than 1, a case-control study that presented only crude data stratified by statin use [15], a recent estimate from the Iowa Women's Health Study [16] that differed from estimates in an earlier report based on the same cohort [17], and a 1983 case-control study [18] with no clear definition of categories (cigarettes: yes/no). Excluding these studies, the heterogeneity decreases (P=0.09), but the pooled RR remains the same (RR=1.86, 95% CI 1.76–1.96).

Pipe and cigars

For pipe and cigar smoking, the risk is to some extent lower than for cigarette smokers. However, there were fewer studies to evaluate, and it was not possible to determine whether or not these patients inhaled the tobacco smoke, which would increase blood levels of carcinogens. Furthermore, information was not readily available to determine if pipe/cigar smokers had been former or even were current cigarette smokers.

Some variables, which are indicators of study quality, suggest that the relationship is stronger for weaker studies, suggesting bias or confounding. For example, the risks were not significantly elevated in pooled estimates from the strongest types of studies such as cohort studies, population-based case-control studies, studies with no cancers among controls, and studies with a high percentage of histological confirmed cancers. However, pooled estimates for current smokers were marginally more significant than for ever smokers (P=0.05), and estimates from studies which did not use proxy controls were borderline significantly greater than studies that used proxy controls (P=0.07). For pipe and/or cigars exposures, we found no evidence of publication bias (P=0.48 with Copas and Shi's method, P=0.95 with Macaskill's method).

Impact of smoking cessation

Quantitative information about the impact of smoking cessation on the risk of pancreatic cancer enables health professionals to estimate temporal changes in the incidence of pancreatic cancer in a given population. For example, within Europe, Mulder provides estimates for various reductions in smoking prevalence [19]. If all Europeans had ceased to smoke at about the turn of the century, there would be an estimated 150,000 fewer deaths from pancreatic cancer. Using a more achievable goal (45% reduction in males; 30% reduction in females), there would about 39,000 fewer deaths from pancreatic cancer.

On an individual level, physicians should make all patients aware of the risks of pancreatic cancer if they continue to smoke and the clear risk reduction association with long-term continued smoking cessation. This is especially true for patients with any of the genetic disorders, such as familial pancreatic cancer or hereditary pancreatitis where smoking may augment the already existing genetic risk.

References

1. Danaei G, Vander HS, Lopez AD, Murray CJ, Ezzati M (2005) Causes of cancer in the world: comparative risk assessment of nine behavioural and environmental risk factors. Lancet 366:1784–1793
2. Rulyak SJ, Lowenfels AB, Maisonneuve P, Brentnall TA (2003) Risk factors for the development of pancreatic cancer in familial pancreatic cancer kindreds. Gastroenterology 124:1292–1299
3. Greenland S (1987) Quantitative methods in the review of epidemiologic literature. Epidemiol Rev 9:1–30
4. Van Houwelingen HC, Arends LR, Stijnen T (2002) Advanced methods in meta-analysis: multivariate approach and meta-regression. Stat Med JID-8215016 21:589–624
5. Higgins JP, Thompson SG, Deeks JJ, Altman DG (2003) Measuring inconsistency in meta-analyses. BMJ 327:557–560
6. SAS Institute Inc (1999) SAS Windows version. (8.02). Cary, NC. (GENERIC) Ref Type: Computer Program
7. Greenland S, Longnecker MP (1992) Methods for trend estimation from summarized dose–response data, with applications to meta-analysis. Am J Epidemiol 135:1301–1309
8. Copas JB, Shi JQ (2001) A sensitivity analysis for publication bias in systematic reviews. Stat Methods Med Res 10:251–265
9. Macaskill P, Walter SD, Irwig L (2001) A comparison of methods to detect publication bias in meta-analysis. Stat Med JID-8215016 20:641–654
10. Liaw KM, Chen CJ (1998) Mortality attributable to cigarette smoking in Taiwan: a 12-year follow-up study. Tob Control 7:141–148
11. Nishi M, Ohba S, Hirata K, Miyake H (1996) Dose–response relationship between coffee and the risk of pancreas cancer. Jpn J Clin Oncol 26:42–48

12. Jee SH, Samet JM, Ohrr H, Kim JH, Kim IS (2004) Smoking and cancer risk in Korean men and women. Cancer Causes Control 15:341–348
13. Mori M, Hariharan M, Anandakumar M et al (1999) A case-control study on risk factors for pancreatic diseases in Kerala, India. Hepatogastroenterology 46:25–30
14. Inoue M, Tajima K, Takezaki T et al (2003) Epidemiology of pancreatic cancer in Japan: a nested case-control study from the Hospital-based Epidemiologic Research Program at Aichi Cancer Center (HERPACC). Int J Epidemiol 32:257–262
15. Khurana V, Sheth A, Caldito G, Barkin JS (2007) Statins reduce the risk of pancreatic cancer in humans: a case-control study of half a million veterans. Pancreas 34:260–265
16. Prizment AE, Anderson KE, Hong CP, Folsom AR (2007) Pancreatic cancer incidence in relation to female reproductive factors: Iowa Women's Health Study. JOP 8:16–27
17. Harnack LJ, Anderson KE, Zheng W, Folsom AR, Sellers TA, Kushi LH (1997) Smoking, alcohol, coffee, and tea intake and incidence of cancer of the exocrine pancreas: the Iowa Women's Health Study. Cancer Epidemiol Biomarkers Prev 6:1081–1086
18. Durbec JP, Chevillotte G, Bidart JM, Berthezene P, Sarles H (1983) Diet, alcohol, tobacco and risk of cancer of the pancreas: a case-control study. Br J Cancer 47:463–470
19. Mulder I, Hoogenveen RT, van Genugten ML et al (2002) Smoking cessation would substantially reduce the future incidence of pancreatic cancer in the European Union. Eur J Gastroenterol Hepatol 14:1343–1353
20. Heuch I, Kvale G, Jacobsen BK, Bjelke E (1983) Use of alcohol, tobacco and coffee, and risk of pancreatic cancer. Br J Cancer 48:637–643
21. Mills P, Beeson W, Abbey D, Fraser G, Phillips RL (1988) Dietary habits and past medical history as related to fatal pancreas cancer risk among adventists. Cancer 61:2578–2585
22. Hirayama T (1989) Epidemiology of pancreatic cancer in Japan. Jpn J Clin Oncol 19:208–215
23. Akiba S, Hirayama T (1990) Cigarette smoking and cancer mortality risk in Japanese men and women—results from reanalysis of the six-prefecture cohort study data. Environ Health Perspect 87:19–26
24. Kuller LH, Ockene JK, Meilahn E, Wentworth DN, Svendsen KH, Neaton JD (1991) Cigarette smoking and mortality. MRFIT Research Group. Prev Med 20:638–654
25. Zheng W, McLaughlin JK, Gridley G et al (1993) A cohort study of smoking, alcohol consumption, and dietary factors for pancreatic cancer (United States). Cancer Causes Control 4:477–482
26. Tverdal A, Thelle D, Stensvold I, Leren P, Bjartveit K (1993) Mortality in relation to smoking history: 13 years' follow-up of 68,000 Norwegian men and women 35–49 years. J Clin Epidemiol 46:475–487
27. Shibata A, Mack TM, Paganini-Hill A, Ross RK, Henderson BE (1994) A prospective study of pancreatic cancer in the elderly. Int J Cancer 58:46–49
28. McLaughlin JK, Hrubec Z, Blot WJ, Fraumeni JF (1995) Smoking and cancer mortality among U.S. veterans: a 26-years follow-up. Int J Cancer 60:190–193
29. Engeland A, Andersen A, Haldorsen T, Tretli S (1996) Smoking habits and risk of cancers other than lung cancer: 28 year's follow-up of 26,000 Norwegian men and women. Cancer Causes Control 7:497–506
30. Fuchs CS, Colditz GA, Stampfer MJ et al (1996) A prospective study of cigarette smoking and the risk of pancreatic cancer. Arch Intern Med 156:2255–2260
31. Yuan JM, Ross RK, Wang XL, Gao YT, Henderson BE, Yu MC (1996) Morbidity and mortality in relation to cigarette smoking in Shanghai, China. A prospective male cohort study. JAMA 275:1646–1650
32. Tulinius H, Sigfusson N, Sigvaldason H, Bjarnadottir K, Tryggvadottir L (1997) Risk factors for malignant diseases: a cohort study on a population of 22,946 Icelanders. Cancer Epidemiol Biomarkers Prev 6:863–873
33. Nordlund LA, Carstensen JM, Pershagen G (1997) Cancer incidence in female smokers: a 26-year follow-up. Int J Cancer 73:625–628
34. Iribarren C, Tekawa IS, Sidney S, Friedman GD (1999) Effect of cigar smoking on the risk of cardiovascular disease, chronic obstructive pulmonary disease, and cancer in men. N Engl J Med 340:1773–1780
35. Coughlin SS, Calle EE, Patel AV, Thun MJ (2000) Predictors of pancreatic cancer mortality among a large cohort of United States adults. Cancer Causes Control 11:915–923
36. Nilsen TI, Vatten LJ (2000) A prospective study of lifestyle factors and the risk of pancreatic cancer in Nord-Trondelag, Norway. Cancer Causes Control 11:645–652
37. Shapiro JA, Jacobs EJ, Thun MJ (2000) Cigar smoking in men and risk of death from tobacco-related cancers. J Natl Cancer Inst 92:333–337
38. Stolzenberg-Solomon RZ, Albanes D, Nieto FJ et al (1999) Pancreatic cancer risk and nutrition-related methyl–group availability indicators in male smokers. J Natl Cancer Inst 91:535–541
39. Nilsson S, Carstensen JM, Pershagen G (2001) Mortality among male and female smokers in Sweden: a 33 year follow up. J Epidemiol Community Health 55:825–830
40. Lin Y, Tamakoshi A, Kawamura T et al (2002) A prospective cohort study of cigarette smoking and pancreatic cancer in Japan. Cancer Causes Control 13:249–254
41. Isaksson B, Jonsson F, Pedersen NL, Larsson J, Feychting M, Permert J (2002) Lifestyle factors and pancreatic cancer risk: a cohort study from the Swedish Twin Registry. Int J Cancer 98:480–482
42. Henley SJ, Thun MJ, Chao A, Calle EE (2004) Association between exclusive pipe smoking and mortality from cancer and other diseases. J Natl Cancer Inst 96:853–861
43. Larsson SC, Permert J, Hakansson N, Naslund I, Bergkvist L, Wolk A (2005) Overall obesity, abdominal adiposity, diabetes and cigarette smoking in relation to the risk of pancreatic cancer in two Swedish population-based cohorts. Br J Cancer 93:1310–1315
44. Sinner PJ, Schmitz KH, Anderson KE, Folsom AR (2005) Lack of association of physical activity and obesity with incident pancreatic cancer in elderly women. Cancer Epidemiol Biomarkers Prev 14:1571–1573
45. Gallicchio L, Kouzis A, Genkinger JM et al (2006) Active cigarette smoking, household passive smoke exposure, and the risk of developing pancreatic cancer. Prev Med 42:200–205
46. Ansary-Moghaddam A, Huxley R, Barzi F et al (2006) The effect of modifiable risk factors on pancreatic cancer mortality in populations of the Asia-Pacific region. Cancer Epidemiol Biomarkers Prev 15:2435–2440
47. Yun JE, Jo I, Park J et al (2006) Cigarette smoking, elevated fasting serum glucose, and risk of pancreatic cancer in Korean men. Int J Cancer 119:208–212
48. Nothlings U, Wilkens LR, Murphy SP, Hankin JH, Henderson BE, Kolonel LN (2007) Vegetable intake and pancreatic cancer risk: the multiethnic cohort study. Am J Epidemiol 165:138–147
49. Gapstur SM, Gann PH, Lowe W, Liu K, Colangelo L, Dyer A (2000) Abnormal glucose metabolism and pancreatic cancer mortality. JAMA 283:2552–2558
50. Michaud DS, Joshipura K, Giovannucci E, Fuchs CS (2007) A prospective study of periodontal disease and pancreatic cancer in US male health professionals. J Natl Cancer Inst 99:171–175

51. Wynder EL, Mabuchi K, Maruchi N, Fortner J (1973) A case-control study of cancer of the pancreas. Cancer 31:641–648
52. MacMahon B, Yen S, Trichopoulos D, Warren K, Nardi G (1981) Coffee and Cancer of the Pancreas. N Engl J Med 304:630–633 (Abstract)
53. Whittemore AS, Paffenberger RS, Anderson K, Halpern J (1983) Early precursors of pancreatic cancer in college men. J Chronic Dis 36:251–256
54. Kinlen L, McPherson K (1984) Pancreas cancer and coffee and tea consumption: a case-control study. Br J Cancer 49:93–96
55. Gold EB, Gordis L, Diener MD et al (1985) Diet and other risk factors for cancer of the pancreas. Cancer 55:460–467
56. Hsieh CC, MacMahon B, Yen S, Trichopoulos D, Warren K, Nardi G (1986) Coffee and pancreatic cancer (Chapter 2). N Engl J Med 319:587–589
57. Mack TM, Yu MC, Hanisch R, Henderson BE (1986) Pancreas cancer and smoking, beverage consumption, and past medical history. J Natl Cancer Inst 76:49–60 (Abstract)
58. Wynder EL, Dieck G, Hall NEL (1986) Case-control study of decaffeinated coffee consumption and pancreatic cancer. Cancer Res 46:53600–55363
59. Hiatt RA, Klatsky AL, Armstrong MA (1988) Pancreatic cancer, blood glucose and beverage consumption. Int J Cancer 41:794–797
60. Clavel F, Benhamou E, Auquier A, Tarayre M, Flamant R (1989) Coffee, alcohol, smoking and cancer of the pancreas: a case-control study. Int J Cancer 43:17–21
61. Cuzick J, Babiker AG (1989) Pancreatic cancer, alcohol, diabetes mellitus and gallbladder disease. Int J Cancer 43:415–421
62. Farrow DC, Davis S (1990) Risk of pancreatic cancer in relation to medical history and use of tobacco, alcohol and coffee. Int J Cancer 45:816–820
63. Falk R, Pickle LW, Fontham E (1990) Occupation and pancreatic cancer in Louisiana. Am J Ind Med 18:565–576
64. Baghurst PA, McMichael AJ, Slavotinek A, Baghurst K, Boyle P, Walker AM (1991) A case-control study of diet and cancer of the pancreas. Am J Epidemiol 134:167–179
65. Bueno de Mesquita HB, Maisonneuve P, Moerman CJ, Runia S, Boyle P (1991) Life-time history of smoking and exocrine carcinoma of the pancreas: a population-based case-control study in the Netherlands. Int J Cancer 49:816–822
66. Howe GR, Jain M, Burch JD, Miller AB (1991) Cigarette smoking and cancer of the pancreas: evidence from a population-based case-control study in Toronto, Canada. Int J Cancer 47:323–328
67. Vioque J, Walker AM (1991) [Pancreatic cancer and ABO blood types: a study of cases and controls]. Med Clin (Barc) 96:761–764
68. Ghadirian P, Simard A, Baillargeon J (1991) Tobacco, alcohol, and coffee and cancer of the pancreas: a population-based, case-control study in Quebec, Canada. Cancer 67:2664–2670
69. Lyon JL, Egger MJ, Robison LM, French TK, Gao R (1992) Misclassification of exposure in a case-control study: the effects of different types of exposure and different proxy respondents in a study of pancreatic cancer. Epidemiology 3:223–231
70. Mizuno S, Watanabe S, Nakamura K (1992) A multi-institute case-control study on the risk factors of developing pancreatic cancer. Jpn J Clin Oncol 22:286–291
71. Zatonski W, Boyle P, Przewozniak K, Maisonneuve P, Drosik K, Walker AM (1993) Cigarette smoking, alcohol, tea and coffee consumption and pancreas cancer risk: a case-control study from Opole, Poland. Int J Cancer 53:601–607
72. Kalapothaki V, Tzonou A, Hsieh CC, Toupadaki N, Karakatsani A, Trichopoulos D (1993) Tobacco, ethanol, coffee, pancreatitis, diabetes mellitus, and cholelithiasis as risk factors for pancreatic carcinoma. Cancer Causes Control 4:375–382
73. Silverman DT, Dunn J, Hoover RN et al (1994) Cigarette smoking and pancreas cancer: a case-control study based on direct interviews. J Natl Cancer Inst 86:1510–1516
74. Ji BT, Chow WH, Dai Q et al (1995) Cigarette smoking and alcohol consumption and the risk of pancreatic cancer: a case-control study in Shanghai, China. Cancer Causes Control 6:369–376
75. Gullo L, Pezzilli R, Morselli-Labate AM, The Italian Pancreatic Study Group (1995) Coffee and cancer of the pancreas: an Italian multicenter study. Pancreas 3:223–229
76. Siemiatycki J, Krewski D, Franco E, Kaiserman M (1995) Associations between cigarette smoking and each of 21 types of cancer: a multi-site case-control study. Int J Epidemiol 24:504–514
77. Fernandez E, La Vecchia C, Decarli A (1996) Attributable risks for pancreatic cancer in Northern Italy. Cancer Epidemiol Biomarkers Prev 5:23–27
78. Lee CT, Chang FY, Lee SD (1996) Risk factors for pancreatic cancer in Orientals. J Gastroenterol Hepatol 11:491–495
79. Murata M, Takayama K, Choi BC, Pak AW (1996) A nested case-control study on alcohol drinking, tobacco smoking, and cancer. Cancer Detect Prev 20:557–565
80. Kokic NZ, Adanja JB, Vlajinac DH, Marinkovic PJ, Colovic BR, Jarebinski SM (1996) Case-control study of pancreatic cancer in Serbia, Yugoslavia. Neoplasma 43:353–356
81. Muscat JE, Stellman SD, Hoffmann D, Wynder EL (1997) Smoking and pancreatic cancer in men and women. Cancer Epidemiol Biomarkers Prev 6:15–19
82. Fryzek JP, Garabrant DH, Harlow SD et al (1997) A case-control study of self-reported exposures to pesticides and pancreas cancer in southeastern Michigan. Int J Cancer 72:62–67
83. Partanen TJ, Vainio HU, Ojajarvi IA, Kauppinen TP (1997) Pancreas cancer, tobacco smoking and consumption of alcoholic beverages: a case-control study. Cancer Lett 116:27–32
84. Alguacil J, Porta M, Benavides FG et al (2000) Occupation and pancreatic cancer in Spain: a case-control study based on job titles. PANKRAS II Study Group. Int J Epidemiol 29:1004–1013
85. Maruchi N, Brian D, Ludwig J, Elveback L, Kurland L (1979) Cancer of the pancreas in Olmsted county, Minnesota, 1935–1974. Mayo Clin Proc 54:245–249
86. Villeneuve PJ, Johnson KC, Hanley AJ, Mao Y (2000) Alcohol, tobacco and coffee consumption and the risk of pancreatic cancer: results from the Canadian Enhanced Surveillance System case-control project. Canadian Cancer Registries Epidemiology Research Group.. Eur J Cancer Prev 9:49–58
87. Bonelli L, Aste H, Bovo P et al (2003) Exocrine pancreatic cancer, cigarette smoking, and diabetes mellitus: a case-control study in northern Italy. Pancreas 27:143–149
88. Alguacil J, Silverman DT (2004) Smokeless and other non-cigarette tobacco use and pancreatic cancer: a case-control study based on direct interviews. Cancer Epidemiol Biomarkers Prev 13:55–58
89. Carta P, Aru G, Cadeddu C et al (2004) Mortality for pancreatic cancer among aluminium smelter workers in Sardinia, Italy. G Ital Med Lav Ergon 26:83–89
90. Duell EJ, Holly EA (2005) Reproductive and menstrual risk factors for pancreatic cancer: a population-based study of San Francisco Bay Area women. Am J Epidemiol 161:741–747
91. Lu XH, Wang L, Li H, Qian JM, Deng RX, Zhou L (2006) Establishment of risk model for pancreatic cancer in Chinese Han population. World J Gastroenterol 12:2229–2234
92. Li W, Ray RM, Gao DL et al (2006) Occupational risk factors for pancreatic cancer among female textile workers in Shanghai, China. Occup Environ Med 63:788–793
93. Boyle P, Maisonneuve P, Bueno DM et al (1996) Cigarette smoking and pancreas cancer: a case control study of the search programme of the IARC. Int J Cancer 67:63–71