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Epidemiology of Pancreas Cancer (1988)

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Summary

This article reviews the epidemiology of cancer of the pancreas, both descriptive and analytical, at all times cognizant of the problems of misdiagnosis, particularly underdiagnosis, of this lethal disease that continue to hinder epidemiological studies. Pancreas cancer is consistently reported to occur more frequently in men than in women, in blacks than in whites, and in urban rather than rural population groups. In some countries, the mortality rates continue to rise, whereas in others, declining levels of disease can be seen among members of younger birth cohorts. Although some of these patterns can be explained by variation in pancreas cancer risk factors, many cannot. Analytical studies consistently demonstrate that cigaret smoking increases the risk of cancer of the pancreas, and this appears, at the present time, to be the only clearly demonstrated risk factor for pancreatic cancer. Although the association with disease risk and coffee consumption, alcohol consumption, occupational exposures, diabetes, pancreatitis, and other factors requires clarification, it appears likely that the most fruitful research area in the coming years may involve exploration of pancreatic cancer risk and nutritional practices.

Key Words: Pancreas cancer, epidemiology of; risk factors; mortality rates; incidence rates; time trends.

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INTRODUCTION

In Europe, cancer of the pancreas is the seventh commonest form of cancer in men behind stomach, colon, rectum, lung, prostate, and bladder. In contrast with the US, pancreas cancer is generally found to be less common than stomach cancer. In females in Europe, cancer of the pancreas is generally the eleventh commonest form of cancer behind stomach, colon, rectum, lung, breast, cervix, corpus, ovary, and bladder. A similar situation pertains in the US, apart from pancreas cancer, which is generally more common than stomach cancer (*1,2*). The reasons why pancreas cancer should be less common than stomach cancer in Europe, but not in North America, are not well understood.

The purpose of this article is to summarize the current status of the epidemiology of pancreas cancer, including both descriptive epidemiology and results from analytical epidemiology. It is particularly important to improve our knowledge of pancreas cancer in view of the fact that it is a relatively common form of cancer and one that, almost uniformly, carries a dire prognosis. In view of the absence of effective treatment and the meager prospects for improvements in therapy, the only way to reduce the mortality from cancer of the pancreas would lie in preventing the occurrence of this disease in the first instance.

DESCRIPTIVE EPIDEMIOLOGY

Pancreas Cancer Incidence

The lowest incidence rates of pancreas cancer in each sex are to be found in those regions of India with population-based cancer registration data: Madras, Bangalore, Poona, Nagpur, and Bombay. The lowest rates of the disease are fairly similar in each sex (Table 1). In contrast, the highest rates in males (Table 2) are approximately 50–100% higher than the highest rates recorded in females (Table 3). The finding of higher rates in males than females within areas is a general feature of cancer of the pancreas.

The highest incidence of pancreas cancer recorded around the early 1980's (*2*) in males (Table 2) is among Koreans in Los Angeles (16.4/100,000/year) followed by, in turn, the black population groups in Alameda County (16.3), the Bay Area (15.5), Detroit (12.8), New Orleans (12.0), and Atlanta (11.9), the Polynesian Islander population of New Zealand (11.4), and the black population of Los Angeles (11.0). The highest rates recorded in females (Table 3) come from the black population groups of Alameda County (9.4), Atlanta (8.7), Detroit (8.6), the Bay Area (8.3), and Connecticut (8.2), the white population of Hawaii (8.0), the Hawaiian population of Hawaii (7.8), the Hispanic population of New Mexico (7.4), and a number of population groupings with a rate of 7.0 (New Orleans blacks, Denmark, eastern Scotland, Australian Capital Territory, and Chinese in Hawaii).

The high rates in black populations of the US are evident. Table 4 compares the rates in blacks and whites of the seven areas of the SEER (Surveillance Epidemiology and End Results) program where data are available for

Table 1
Lowest Incidence Rates of Pancreas Cancer[a]

	Males	Females
Bangalore, India	0.7	0.5
Madras, India	0.9	0.4
Nagpur, India	0.9	0.8
Poona, India	1.5	1.3
Bombay, India	2.1	1.3
Kuwait, Kuwaitis	1.2	1.3
Singapore, Malay	1.9	2.2

[a]Source: Muir et al. (1988).

Table 2
Highest Recorded Age-Standardized Incidence Rates of Pancreas Cancer in Males[a]

Population	Rate per 100,000
Los Angeles-Korean	16.4
Alameda County-Blacks	16.3
Bay Area-Blacks	15.5
Detroit-Blacks	12.8
New Orleans-Blacks	12.0
Atlanta-Blacks	11.9
New Zealand-Polynesian	11.4
Los Angeles-Blacks	11.0
Neuchatel (Switzerland)	10.4
Finland	10.0

[a]Source: Muir et al. (1988).

Table 3
Highest Recorded Age-Standardized Incidence Rates of Pancreas Cancer in Females[a]

Population	Rate per 100,000
Alameda County-Blacks	9.4
Atlanta-Blacks	8.7
Detroit-Blacks	8.6
Bay Area-Blacks	8.3
Connecticut-Blacks	8.2
Hawaii-Whites	8.0
Hawaii-Hawaiian	7.8
New Mexico-Hispanic	7.4
New Orleans-Blacks	7.0
Denmark	7.0
Scotland (East)	7.0
Capital Territory (Australia)	7.0
Hawaii-Chinese	7.0

[a]Source: Muir et al. (1988).

Table 4
Average, Annual, All-Ages, Age-Standardized Incidence Rates of Pancreas Cancer in Black and White Population Groups of the US[a]

	Male			Female		
	Black	White	(R.R.)	Black	White	(R.R.)
Alameda County	16.3	8.4	(1.9)	9.4	6.2	(1.5)
Bay Area	15.5	9.2	(1.7)	8.3	6.9	(1.2)
Los Angeles	11.0	8.1	(1.4)	6.7	5.7	(1.2)
Connecticut	8.7	8.1	(1.1)	8.2	5.5	(1.5)
Atlanta	11.9	8.5	(1.4)	8.7	5.1	(1.7)
New Orleans	12.0	9.8	(1.2)	7.0	5.3	(1.3)
Detroit	12.8	9.2	(1.4)	8.6	6.2	(1.4)

[a]Source: cancer rates abstracted from Muir et al. (1988).

Table 5
Average, Annual, All-Ages, Age-Standardized Incidence Rates per 100,000 from Pancreas Cancer in Urban and Rural Areas in Males and Females[a]

	Male			Female		
	Urban	Rural	(R.R.)	Urban	Rural	(R.R.)
Miyagi	9.6	8.5	(1.1)	5.4	4.7	(1.1)
Slovakia	9.1	8.2	(1.1)	5.5	4.3	(1.3)
Saarland	7.0	5.9	(1.2)	3.9	3.4	(1.1)
Calvados	6.2	4.1	(1.5)	2.8	2.2	(1.3)
Doubs	4.7	3.8	(1.2)	2.2	1.2	(1.8)
Szabolcs	5.5	5.5	(1.0)	3.1	3.5	(0.9)
Norway	9.2	7.9	(1.2)	6.0	4.6	(1.3)
Cluj	7.1	5.6	(1.3)	3.4	3.0	(1.1)
England and Wales	8.0	6.7	(1.2)	4.9	4.7	(1.1)
New South Wales	7.5	7.5	(1.0)	4.4	4.3	(1.0)

[a]Data abstracted from Muir et al. (1988).

blacks and whites. In both sexes (Table 4), the incidence is uniformly higher in blacks than whites, sometimes by a ratio approaching 2.

Of 10 regions with cancer registration data classified by urban or rural residence, the rates for males among residents of rural areas were never higher than the rates among residents of urban areas (Table 5). A similar picture was found in females with the sole exception being the finding of a higher rate in the rural population of Szabolcs in Hungary.

It is sometimes argued that pancreas cancer rates are partially determined by the availability of advanced technology in medical services. These findings of higher rates in urban, as opposed to rural residents, could be interpreted as being supportive of this position, whereas the uniformly higher rates in blacks as opposed to whites in population groups of the US would be in conflict with this proposition.

Table 6
Pancreas Cancer Mortality in Males, 1955 and 1985, in Selected Countries[a]

	1955			1985		
	No. Deaths	SRW	% Cancer	No. Deaths	SRW	% Cancer
Austria	277	6.30	3.3	473	9.07	5.1
Belgium	201	3.27	2.2	531[b]	7.36	3.4
Czechoslovakia	296	4.30	2.6	908	9.74	4.4
Denmark	181	6.28	4.3	367	9.00	4.9
France	967	3.64	2.4	2849	7.11	3.6
FRG	1134	3.79	2.5	3612	8.18	4.5
Ireland	121	6.44	4.6	213[c]	9.89	5.9
Italy	698	2.69	2.2	2671	6.79	3.5
Greece[d]	109	2.31	1.8	470	6.15	4.2
UK E & W	1830	6.46	3.8	3063	7.74	4.2
Scotland	197	6.42	3.6	272	7.26	3.7
N. Ireland	41	5.25	3.8	75	7.82	4.4
Netherlands	256	4.37	2.9	813	8.51	4.2
Poland	280	2.28	2.0	1559	7.93	4.1
Yugoslavia[e]	172	2.23	2.2	714[b]	5.96	4.0
Canada	587	7.24	5.3	1304	8.55	5.1
Australia	279	5.72	4.4	647	6.96	4.1
New Zealand	80	6.67	4.8	138	7.36	4.2
Japan	625	1.83	1.5	5953	8.11	5.4

[a]Columns refer to two time periods, each year closest to 1955 or 1985. The following information is recorded: No. deaths = Number of deaths; SRW = Age adjusted rate (World Standard Population) per 100,000; and % Cancer = Percentage of all cancer deaths.
[b]1983 data.
[c]1984 data.
[d]1961 data.
[e]1966 data.

Pancreas Cancer Mortality

There are two prominent features of pancreas cancer mortality data among males (Table 6) and females (Table 7). First, the relative lack of variation in mortality rates within each year chosen and, second, the uniform increase that has taken place in every country over the past three decades.

Among males, the highest rates (ca. 1985) are currently found in Ireland (9.89 per 100,000), Czechoslovakia (9.74), and Austria (9.07). Interestingly, the highest rate in females is also found in Ireland.

The largest increase has taken place in males in Japan: the standardized rate rising from 1.83 to 8.11, the latter figure based on 5953 deaths that represents 5.4% of all cancer deaths among male Japanese. It is important to observe, however, that there appears to be a downward turn in the cohort effects among younger ages (Fig. 1), which should lead ultimately to an overall reduction in the rate of this disease in future years if it continues.

Table 7
Pancreas Cancer Mortality in Females, 1955 and 1985, in Selected Countries[a]

	1955			1985		
	No. Deaths	SRW	% Cancer	No. Deaths	SRW	% Cancer
Austria	246	3.86	3.1	552	5.60	5.8
Scotland	193	4.72	3.8	312	5.62	4.4
England and Wales	1628	4.07	3.8	3014	5.16	4.5
Netherlands	206	3.24	2.6	834	6.00	5.9
Italy	550	1.77	1.8	2199[b]	3.83	4.1
N. Ireland	41	4.10	3.6	70	4.89	4.5
Ireland	84	4.08	4.0	162[c]	6.34	5.3
FRG	968	2.47	2.0	4235	5.24	5.2
France	940	2.32	2.4	2258	3.45	4.4
Denmark	133	4.29	3.1	362	6.27	5.2
Czechoslovakia	208	2.43	2.0	748	5.38	4.9
Yugoslavia[d]	148	1.49	1.8	528[b]	3.38	4.0
Poland[e]	276	1.68	1.8	1406	4.74	4.8
Greece[f]	102	1.74	2.4	303	3.05	4.3
New Zealand	63	4.68	4.2	137	5.19	4.8
Australia	214	3.73	3.8	566	4.47	4.7
Japan	477	1.25	1.3	4488	4.48	5.8
Canada	370	4.57	4.0	1116	5.47	5.4
Belgium	193	2.48	2.1	480[c]	4.21	4.2

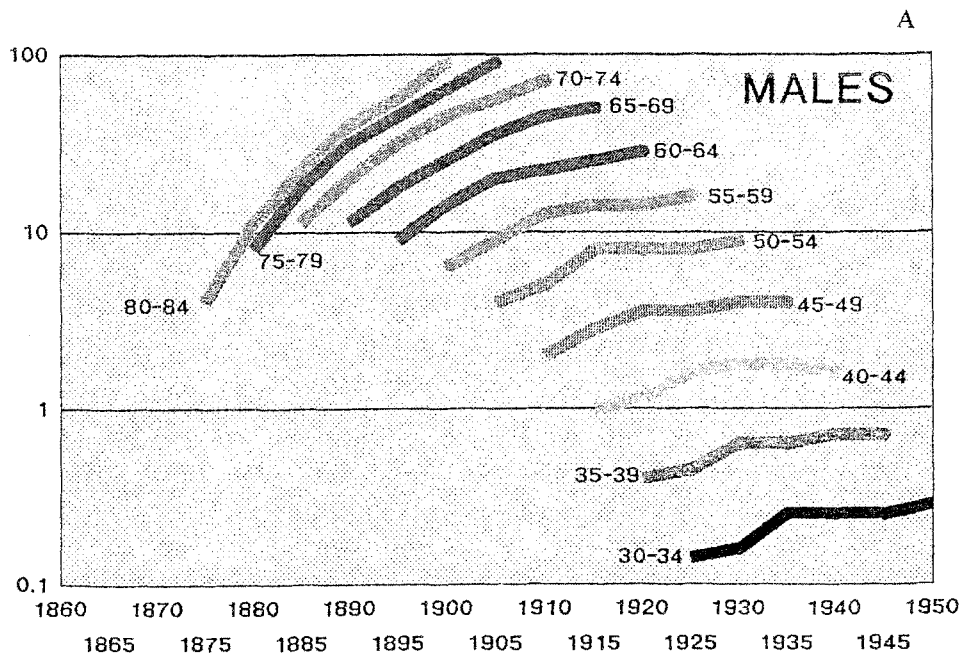
[a]Columns refer to two time periods, each year closest to 1955 or 1985. The following information is recorded: No. deaths = Number of deaths; SRW = Age adjusted rate (World Standard Population) per 100,000; and % Cancer = Percentage of all cancer deaths.
[b]1983 data.
[c]1984 data.
[d]1960 data.
[e]1961 data.
[f]1966 data.

There are also indications of downward cohort trends in a number of other countries such as Canada (Fig. 2), whereas in others, such as Italy (Fig. 3), there is no such indication (in either sex).

ANALYTICAL EPIDEMIOLOGY

Tobacco Smoking

Correlation studies of pancreas cancer mortality rates and estimates of per capita consumption of tobacco all report nonsignificant, although positive, correlations (*3–6*). Other correlation studies, comparing pancreas cancer rates with lung cancer rates, all found positive correlations (*7–9*). Overall, these findings provide, at best, very weak evidence associating cigaret smoking and pancreatic cancer risk.



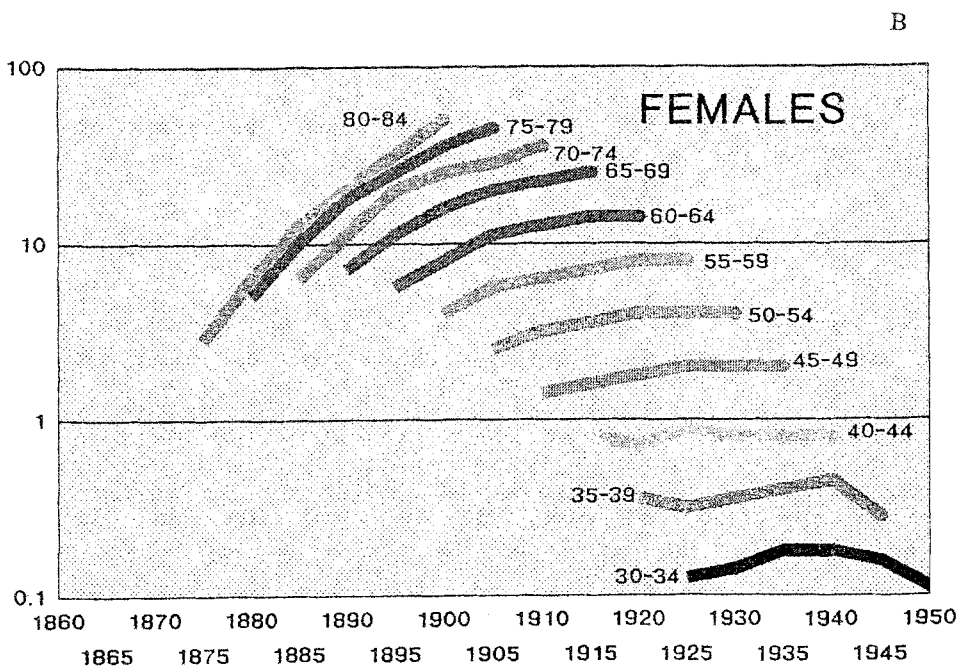


Fig. 1. Age-specific mortality rates for pancreas cancer in Japan (1955–1985) by age and median year of birth: (a) males; (b) females.

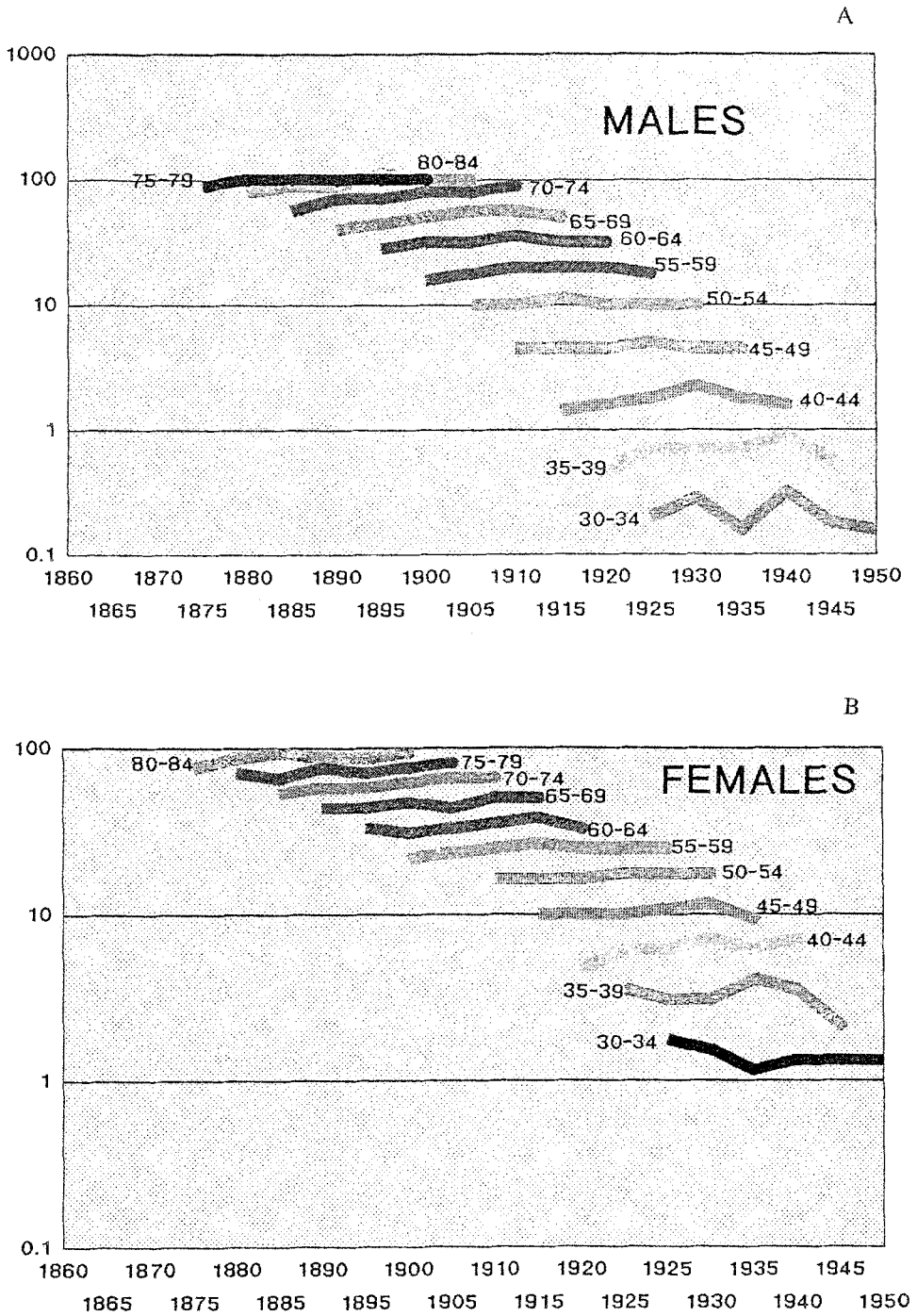


Fig. 2. Age-specific mortality rates for pancreas cancer in Canada (1955–1985) by age and median year of birth: (a) males; (b) females.

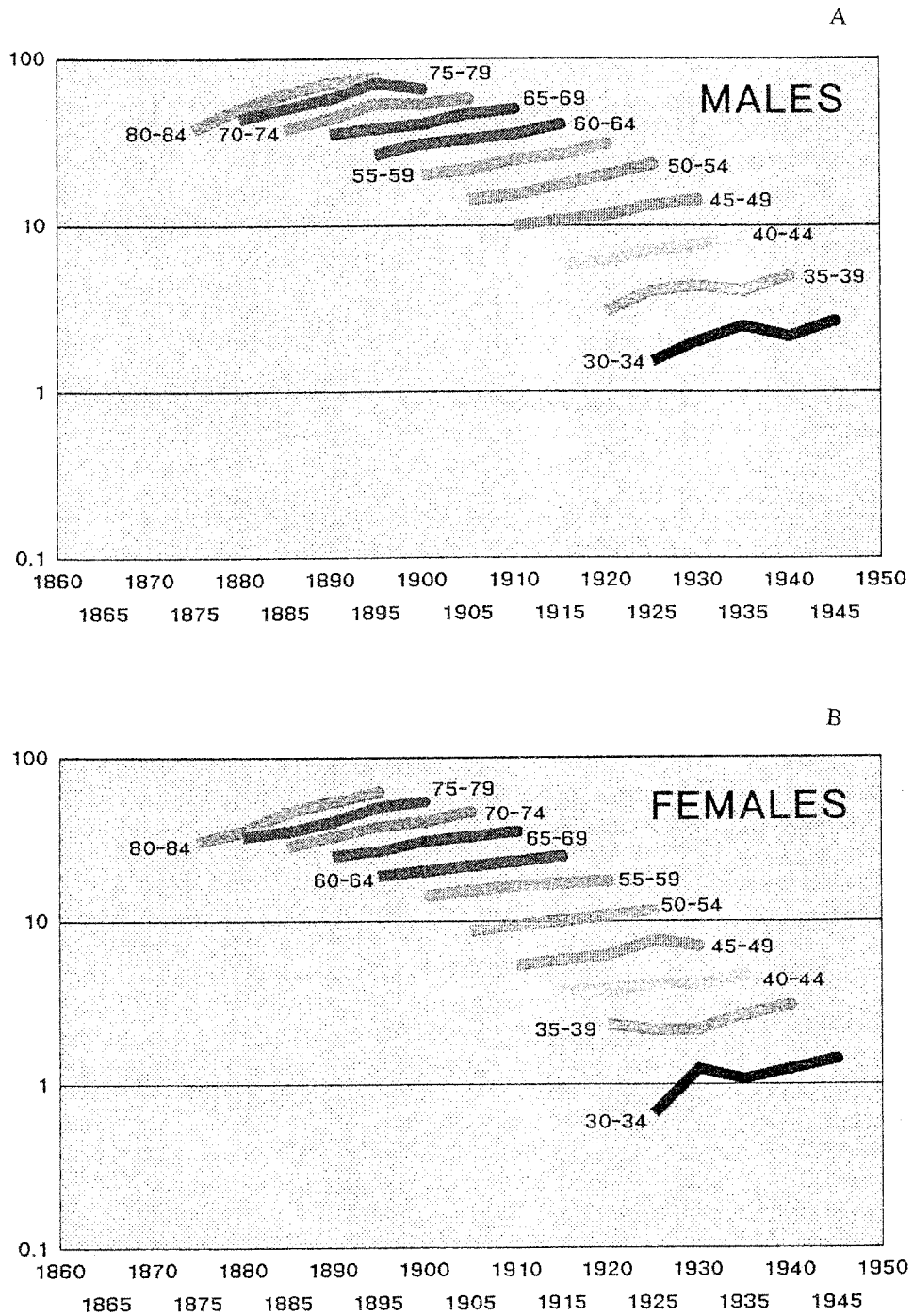


Fig. 3. Age-specific mortality rates for pancreas cancer in Italy (1955–1985) by age and median year of birth: (a) males; (b) females.

By contrast, studies making direct assessments on persons with pancreas cancer have provided consistent evidence linking cigaret smoking with an increased risk of pancreatic cancer. The strength of the available evidence was such that an IARC (International Agency for Research on Cancer) Working Group concluded that the occurrence of malignant tumors of the pancreas is causally related to the smoking of cigarets (*10*). This decision was based on the results of seven cohort studies, based in different populations, each of which found an increased risk in smokers (*11–13*) that appeared to increase with number of cigarets smoked (*14–17*).

Of eight case control studies available for the Working Group to consider, seven found an association with cigaret smoking, which appeared to increase with the amount smoked (*18–24*). The only study that failed to find an association included smoking-related diseases in the comparison group, which could have biased the results toward unity (*25*). A further study reported a risk among regular smokers of 2.7 (95% CI, 1.2–6.0) (*26*).

Subsequent to the IARC evaluation in 1986, there have been three additional cohort studies and six further case control studies.

Hirayama (*27*) reported a further follow-up of a Japanese cohort of 265,118 adults and compared the risk in daily smokers with nonsmokers. In males, he found a ratio of 1.56 (95% confidence interval, 1.22 to 1.99) and in females 1.45 (CI, 1.09 = 1.92). Hirayama (*27*) also reported a monotonically increasing risk with increasing levels of cigaret smoking in men (nonsmokers, OR = 1.0), 1–14 daily (OR = 1.47), 15–29 daily (OR = 1.59), 30–39 daily (OR = 1.70), 40–49 daily (OR = 1.82), and 50 or more (OR = 2.63) (trend test $p < .002$)). A prospective study of Seventh Day Adventists in California reported a relative risk of 5.42 (95% CI, 1.78–16.48) among current smokers and 1.59 (95% CI, 0.69–3.38) among exsmokers (*28*).

Hiatt et al. (*29*) report a follow-up of members of the Kaiser Permanente Medical Care Programme and found relative risks of 1.0 (among nonsmokers), 1.8 (less than half a pack per day), 1.9 (half to one pack), 2.1 (1–2 packs), and 6.6 (greater than 2 packs per day). These risk estimates (adjusted for age, sex, blood glucose levels, and consumption of alcohol, tea, and coffee) demonstrate a graded and continuous increased risk of pancreatic cancer with increasing dose of cigarets (*29*).

All six case control studies support the association between cigaret smoking and pancreas cancer risk. Mack et al. (*30*) found an increased risk among both directly-interviewed cases and the total case group of direct and proxy interviews. Norell et al. (*31*) found similar risk increases with both hospital and neighborhood controls. Hsieh et al. (*32*) found a positive association, as did Wynder et al. (*33*), in the latter in both sexes. La Vecchia et al. (*34*) also reported higher risks in cigaret users as did Falk et al. (*35*).

In summary, the conclusion reached by the IARC Working Party (*10*), based on the evidence available in 1985, has been uniformly supported by the results of studies published subsequently. There is clear and consistent evidence linking an increased risk of pancreas cancer with the habit of cigaret smoking.

Alcohol Consumption

In a series of 280 cases of pancreatic cancer, Dorken (*36*) observed that 30 (11%) had a history of regular to heavy alcohol consumption. These findings, confirmed by Ansari and Burch (*37*) from New Orleans, led to a series of prospective and retrospective studies on this issue. The possibility of alcohol consumption being influential in the risk of cancer of the pancreas is plausible. Pancreatitis is often observed in conjunction with pancreas cancer, and clinical experience, as well as epidemiological studies, support a strong association between heavy alcohol consumption and development of pancreatitis. For example, Lowenfels (*38*) followed 245 patients with chronic pancreatitis and found a significant excess of cancers of the pancreas among this group; he did not, however, find a risk difference between outcome of cancer in alcohol-induced and nonalcohol-induced pancreatitis.

Breslow and Enstrom (*4*) reported significant positive correlations (males 0.42, females 0.61) between per capita consumption of alcohol and pancreas cancer mortality in regions of the US. Blot et al. (*8*), in a similar exercise, found results that were quite inconsistent over different areas. Although Kono and Ikeda (*5*) reported a positive correlation between consumption of saki and whisky with pancreatic cancer mortality, the results must be dealt with cautiously since the same study found no association with alcohol consumption and esophageal cancer where the risk has been clearly demonstrated to be strong. Yani et al. (*39*) and Hinds et al. (*40*) both demonstrated no association in ecological studies.

There have been nine prospective studies of persons with a high alcoholic intake reported in the literature (*41–49*). None reported a significant number of observed cases over that expected if local pancreas cancer rates were applied. However, when all studies were combined, it was revealed that the total number of the observed cases was 90 against 76.6 expected, which produced an approximate O/E ratio of 1.17 and a 95% confidence interval that included unity (0.94, 1.43) (*50*).

Hirayama, following over one quarter of a million members of the general population of Japan, reported a relative risk for those who consumed alcoholic beverages daily compared with those who did not drink of 1.06 (after eight years of follow-up) (*51*) and 0.94 (after nine years of follow-up) (*52*). Hirayama (*27*) found no excess after 12 years of follow-up. Klatsky et al. (*53*) found a significantly elevated risk in a follow-up study of members of a health plan. He observed six pancreatic cancer deaths in 'heavy' drinkers (defined as taking 6 or more drinks daily) compared to two cases in nondrinkers; this produced a relative risk of 3 although there was no evidence of dose-response at intermediate levels of intake. In a cohort study of 16,713 Norwegians, Heuch et al. (*54*) found a relative risk of 2.7 (95% CI, 1.2–6.4) among those who drank at least 14 times per month compared to those who did not drink or who drank infrequently.

Case control studies of pancreas cancer and alcohol consumption have generally reported no significant increase in risk (*19,20,25,26,30,31,55–57*).

Durbec et al. (*23*) reported the relative risk of 2.7 (95% CI, 1.17–4.3) in those who averaged more than 40 g of alcohol per day.

In summary, the results from ecological studies provide no consistent support for an association between alcohol consumption and risk of pancreatic cancer. In general, there is minimal evidence provided from case control studies, and population-based cohort studies provide conflicting results. Cohort studies of people with high alcoholic beverage intake provide no significant evidence of an association with alcohol consumption and pancreatic cancer risk, and even those studies that report elevated risks generally report risks of the same order as general population case control studies. The available evidence, then, for the risk of pancreatic cancer associated with high level, long-term consumption of alcohol provides insufficient evidence for a causal relationship. It is also likely to be the case that even if a causal association exists between alcohol consumption and pancreas cancer, the risk is likely to be small.

Coffee Consumption

MacMahon et al. (*19*) reported that the risk of pancreas cancer increased with increasing daily consumption of coffee. However, this finding has not been one that has been consistently reported by other studies of the topic (*20,21,28–30,32–35,58,59*).

When the results from individual studies were analyzed to obtain a pooled relative risk associated with coffee consumption (*34*), there appeared to be evidence of a small effect of moderate and heavy coffee consumption. When the study of MacMahon et al. (*19*) was included, the risk increased from 1.0 among nondrinkers to 1.34 (1.13, 1.60) in moderate drinkers, and 1.58 (1.27, 1.98) in heavy drinkers: these pooled relative risks were adjusted for study, sex, and cigaret smoking. Even when the data from MacMahon et al. (*19*), which first proposed the association, are excluded, the risk rose from 1.0 in nondrinkers to 1.22 in moderate drinkers (1.01, 1.46) to 1.41 (1.10, 1.80) in heavy drinkers (*34*).

La Vecchia et al. (*34*) concluded that the published evidence is compatible with a moderate effect for coffee on pancreatic cancer risk. It must be stressed, however, that the possibility remains that there is residual, confounding (at least with cigaret smoking), and other potential sources of error and bias in these analyses.

Dietary Factors

Animal experiments have suggested an association with fat intake (*60*), and Hirayama (*12*) suggested a specific association with meat consumption. Durbec et al. (*23*) reported that the risk of pancreatic cancer increased 2.21 (1.64, 2.97)/10 g of fat intake/d. Mack et al. (*30*) reported increases, not all statistically significant, in pancreatic cancer risk with increasing consumption of beef and bacon and that risk seemed slightly reduced by frequent consumption of fresh fruit and vegetables. Norell et al. (*31*) reported the association between increased pancreatic cancer risk and increasing frequency of

consumption of fried and grilled meat and also noted that pancreatic cancer risk seemed to decrease with increasing consumption of carrots and citrus fruits. Falk et al. (*35*) report an increased risk with consumption of pork products and rice, each showing a positive dose-response, whereas fruit consumption exerted a protective influence (OR = 0.63, 95% CI, 0.49–0.82). Risks for beef and vegetables were not significantly different from unity (*35*).

Raymond et al. (*61*) could find no association with meat intake although he did find increasing pancreatic cancer risk associated with increasing consumption of pasta. Pancreatic cancer risk in the same study decreased with increasing consumption of fresh vegetables and (nonsignificantly) with increasing consumption of fresh fruit, particularly citrus fruit. Mills et al. (*28*), in a study based on 40 cases from a cohort of 34,000 Californian Seventh Day Adventists, found nonsignificant protection with frequent intake of vegetarian protein products, beans, lentils, peas, and dried fruit.

The association between pancreas cancer and nutritional practices remains an important unresolved research question. Present knowledge in this field is hampered by the small number of studies that have been designed to address this issue: this has led to confusion in the results obtained. As an example, Norell et al. (*31*) reported that the risk of pancreas cancer decreased (OR = 0.6, 95% CI, 0.4–1.0) if butter was used on bread. Raymond et al. (*61*) reported that the risk of pancreas cancer increased with increasing consumption of butter; the risk was 1.0 in those who consumed less than 108 g/wk and it rose to 1.4 (0.77, 2.56) in those who consumed between 108 g and 195 g/wk and rose to 2.09 (1.14, 3.84) in those who used more than 195 g of butter/wk. Similarly, for margarine, Raymond et al. (*61*) reported a risk of 0.35 (0.2, 0.6) in those who consumed some margarine. Norell et al. (*31*), on the other hand, reported a risk of 1.3 (0.8, 2.2) associated with the use of margarine on bread. In a further analysis based on the proportion of a 15 g packet of margarine used on a sandwich, Norell et al. (*31*) reported a risk of 1.0 in those who used less than half a packet, rising to 2.3 (0.9, 5.9) in those who reported using half to 3.2 (1.0, 10.3) among those who used the whole 15 g on a sandwich.

Occupational Factors

A large number of occupations have been, at one point or another, implicated in the genesis of pancreas cancer; workers in the petrochemical industry (*31,62–64*), chemists (*64–66*), and a group comprising managers, administrators, proprietors, and public administrators (*25,65,67–71*), are groups that have been found to be at an increased risk by more than one study. However, Mack et al. (*72*) observed that each workplace implicated as carrying a high risk of pancreas cancer has also been found to be unrelated to pancreas cancer by at least one other population-based investigation.

There may be some biologic credibility underlying the "high risk" of pancreas cancer from reports among radiologists (*73*) and atomic energy workers (*74*). However, the lack of specificity of occupation implicated as carrying a high risk of pancreas cancer, and more importantly, the lack of confirmation

in many studies, in the absence of any well-defined and plausible pancreas cancer mechanism, argues against occupational factors being an important cause of pancreas cancer on the basis of present evidence.

Aspects of Medical History

Ross et al. (*75*) reported 11 cases of pancreas cancer against 3.9 expected in a follow-up study of a cohort of 700 male gastrectomies. Mack et al. (*30*) reported an increased risk of pancreas cancer for gastrectomy both among direct interviewees only (OR = 7.0, 95% CI, 1.0–9.99) and among direct plus proxy interviewees (OR = 5.3, 95% CI, 1.6–21.5). Confirmatory results were found in the cohort study of Seventh Day Adventists (RR = 2.6, 95% CI, 1.0–6.9) (*28*) and in the large ongoing case control study in Milan (La Vecchia, personal communication).

Mack et al. (*30*) reported, among directly interviewed cases only, significant protective effects in pancreas cancer for asthma, allergic skin reactions, allergy to natural antigens, and any allergic disease. These results subsequently have received some support (*28*), but still require confirmation.

A considerable number of case series have called attention to the development of diabetes near the time of onset of tumors of the exocrine pancreas (*see 76* and *77* for reviews of these sources that accept the association as real; *see* 78 for a more jaundiced view). A simplistic explanation of the diabetes–pancreatic cancer association might invoke islet cell destruction by direct extension of the tumor (*79*), but this does not account for the bulk of cases or for more subtle effects. Schwarts and colleagues (*80*) have shown that those pancreatic cancer patients who are not overtly diabetic frequently have abnormal carbohydrate metabolism even in very early symptomatic stages of the cancer. Faith and Bierman (*81*) have shown diminished insulin responses to glucose challenge in 14 of 16 patients with pancreatic cancer, and Korolyuk and Gorbunov (*82*) have shown that there is no relation between the severity of functional disorders and the degree of cancer-mediated damage to the pancreas.

A number of epidemiologic investigations have commented on increased risk for pancreatic cancer in persons previously diagnosed as diabetics. The earliest long-term follow-up study was that of Lancaster and Maddox (*83*), who identified 894 patients of a Sydney diabetic clinic between 1932 and 1947. There were 15 pancreatic cancer deaths, as opposed to only 1.62 expected, for a mortality increase of more than eightfold. Kessler (*84*) examined the mortality from all causes in a cohort of patients who attended a Boston clinic for diabetics from 1930 through 1956. There were over 21,000 patients who survived at least one year beyond diagnosis. After exclusion of those who developed cancer within a year of onset of diabetes, the relative mortality for pancreatic cancer based on the remaining 67 cases was 1.3 for males and 1.8 for females. Of 55 subjects, for whom there was a clear date of diagnosis that preceded cancer onset by more than a year, the interval from diabetes to death was 11.4 years.

A much smaller cohort study (*85*) of diabetics yielded results somewhat stronger than those reported by Kessler (*84*). Among 1135 residents of Rochester, Minnesota, diagnosed with diabetes in the period 1945–1969, there were nine cancers of the pancreas as opposed to 2.1 expected. Excluding five cases with diagnosis in the first year following onset of diabetes, the SMR (Standard Mortality Ratio) was 2.6 (95% CI, 0.9–6.1).

Morris and Nabarro (*86*) found significant increases in pancreatic cancer in both males and females among 6500 diabetics, with no preponderance among long-standing diabetics. They estimated that there might be a period of as long as four years separating a tumor-associated diabetes from the clinical onset of the tumor.

Whittemore and her colleagues (*22*) reported on mail surveys of some 30,000 graduates of Harvard and the University of Pennsylvania who were part of a larger follow-up study. Fifty-seven persons with pancreatic cancer before 1978 were compared to 221 classmates. Three of the cases and two of the controls had reported diabetes (RR = 3.3, 95% CI, 0.7–15).

A more recent analysis of pancreatic cancer mortality among 34,000 non-Hispanic, white Seventh Day Adventists in California (*28*) over a 7-yr period yielded an age- and sex-adjusted relative mortality of 3.8 (95% CI, 1.7–8.3) on the basis of 8 pancreatic cancer deaths in diabetics and 28 deaths in non-diabetics.

Results from hospital-based case control studies have been largely negative. Wynder et al. (*18*), who considered only diabetes of at least 2-yr duration and made no exclusion for diabetes from the control series, found an odds ratio of six in females and less than one in males. Lin and Kessler (*25*), who made exclusions of controls admitted for diabetes, found a negative association. Falk et al. (*35*) apparently needed to control for diabetes in their hospital-based case control study of lifestyle and pancreatic cancer in Louisiana, but they did not report the strength of the association. Mack and colleagues (*30*), using community-based controls, reported a relative risk of 1.3 (95% CI, 0.7–2.2) in association with diabetes that "antedated the first symptom of pancreatic cancer."

From both clinical and pathophysiologic observations in humans, it appears, therefore, that there is a strong association between islet cell dysfunction and clinically manifest cancer of the exocrine pancreas. The association frequently appears even when the location or the size of the tumor makes simple destruction of islets by the invading tumor an implausible explanation. All or nearly all cases of pancreatic cancer are ultimately affected. Diabetes occurs, not uncommonly, in a period of several years preceding onset of the cancer and occasionally precedes cancer onset by a decade or more. Taken together, the presently available reports of this phenomenon suggest that the distribution of intervals between onset of islet cell dysfunction and the appearance of a tumor varies in an exponentially declining manner. Very short, even negative, intervals appear with the highest frequency; intervals of greater length are progressively less common, but remain part of the same distribution.

The temporal pattern has led many investigators to dismiss the relation between diabetes and pancreatic cancer as one of secondary interest, with applications to problems of early detection, but with little import of etiological significance. We would submit, however, that islet cell failure is an intimate part of the pathogenesis of pancreatic exocrine tumors. It is not appropriate, however, to say that "diabetes" "causes" pancreatic cancer in the sense that risk factors are generally understood to operate.

CONCLUSIONS

There are difficulties in studying pancreas cancer associated with the problems of confirmation of the initial diagnosis of cancer. Taken together with the high and quick fatality rate among cases, this means that many cases are dead before they can be interviewed in a case control study, for example. Thus, population-based studies of pancreas cancer are only possible when proxy interviews are used as a replacement for a direct interview of a dead case. For these, and other reasons, most published studies of pancreas cancer have been small, based on 100 or less cases, with a few outstanding exceptions. As a result, the epidemiology of pancreas cancer is not completely understood.

There is sufficient evidence, and consistently found in all but one study, that cigaret smoking is causally related to the development of pancreatic cancer. The evidence available on coffee consumption is consistent with a small increase in risk associated with moderate to high levels of consumption. There is little evidence supporting a role for alcohol intake in the etiology of pancreatic cancer; if a risk does exist, it is likely to be very small. Dietary factors are thought to be important with a suggestive increase associated with meat consumption and the suggestion that fruit and vegetable consumption decrease the risk of this disease. A role for occupational exposures is not consistently supported by the available data. In part, this may be owing to the lack of specificity with which various risks are found in various studies. There is a suggestion of an increased risk of pancreas cancer associated with a prior gastrectomy and suggestions that the presence of allergic diseases decreases the risk of pancreatic cancer. Generalized pancreatic islet cell failure appears to be a part of the pathogenic process leading to pancreatic cancer, but this should not be interpreted as meaning that diabetes causes pancreatic cancer.

Cancer of the pancreas is a common form of cancer and yet only one risk factor (cigaret smoking) has been identified with any degree of certainty. This is an unsatisfactory situation for epidemiologists and there are many issues that remain to be addressed to clarify the etiology of this disease. Among the most important of these are going to be continued refinements of case control methodology to incorporate proxy and direct interviews into one measure of disease risk (*87*). Perhaps in depth study of the role of nutrition and nutritional practices could be most useful in contributing to our understanding of the etiology of pancreatic cancer in the coming years.

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