2.9 Cancer of the pancreas

2.9.1 *Cohort studies*

(a) Special populations (Table 2.47)

Ten cohort studies of men and women with a high alcoholic beverage intake (i.e. among alcoholics or brewery workers) have reported on the risk for pancreatic cancer. Four studies (Carstensen *et al*., 1990; Tønnesen *et al*., 1994; Sigvardsson *et al*., 1996; Karlson *et al*., 1997) found a significant excess risk among heavy alcoholic beverage drinkers compared with the national population, although all of these studies were based on small numbers of cases (i.e. <50). One study of men employed in a brewery in Sweden (and who were allowed a ration of 1 L of beer per day) and who were followed-up for nearly 20 years reported a significant excess rate of pancreatic cancer. The authors noted that a large reduction in the number of breweries occurred during the

Table 2.47 Cohort studies of pancreatic cancer in special populations

Reference, location, name of study	Cohort description	Exposure assessment	Exposure categories	No. of cases	Relative risk (95% CI)	Adjustment factors	Comments
Hakulinen *et al.* (1974), Finland, Alcohol Misuse Records and Alcoholics	205 000 male 'alcohol misusers' registered for convictions for drunkenness, 1944–59; 4370 alcoholic men on Social Welfare Register, aged ≥30 years, 1967–70; follow-up until 1970	Incidence rates compared with national population rates	Population rate (Exp) Alcoholics (Obs)	2.2 4	NS		Results not stated for cohort of alcoholics on Social Register; no individual exposure data; no information on potential confounders
Monson & Lyon (1975), Massachusetts, USA	1382 men and women hospitalized with alcoholism in 1930, 1935, 1940; mortality follow-up until 1971	Mortality rates compared with US whites	Population rate (Exp) Alcoholics (Obs)	5.1 3	1.0 0.6	Age, sex, calendar time	Half lost to follow-up; no individual exposure data; no information on potential confounders
Dean *et al.* (1979), Ireland, Dublin Brewers	1628 deaths recorded 1954–73 in male brewery workers (average intake, 58 g/day)	Mortality rates compared with local population rates	Population rate (Exp) Brewers (Obs)	14 17	1.0 1.09 (NS)		Predominantly beer intake; no individual exposure data; no information on potential confounders

Table 2.47 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Exposure categories	No. of cases	Relative risk (95% CI)	Adjustment factors	Comments
Jensen (1979), Denmark, Danish Brewery Workers Union	14 313 brewers (free 2-L daily ration of beer) and 1063 mineral water factory workers, recruited from 1943; follow-up until 1973; 44 cases identified through registry/death certificates	Incidence and mortality rates compared with national rates			*Incidence*	Age, sex, area, time	No individual exposure data; no information on potential confounders
			Population rate (Exp)	40	1.0		
			Brewers (Obs)	44	1.09 (0.80–1.47)		
					Mortality		
			Population rate (Exp)	41	1.0		
			Brewers (Obs)	44	1.08 (0.78–1.44)		
Robinette *et al.* (1979), US Army Veterans	4401 men hospitalized with alcoholism and 4401 with nasopharyngitis recruited 1944–45; matched by age; follow-up of mortality until 1975	None	Nasopharyngitis	5	1.0	Age	Mortality only; ~50% aged <30 years at entry; no individual exposure data; no information on potential confounders
			Alcoholism	4	0.87 (0.22–3.25)[a]		
Schmidt & Popham (1981), Ontario, Canada	9889 men hospitalized for alcoholism, 1951–70; follow-up until 1971	Mortality rates compared with regional rates	Population rate (Exp)	9.24	1.0		No individual exposure data; no information on potential confounders
			Alcoholics (Obs)	11	1.19 (NS)		

Table 2.47 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Exposure categories	No. of cases	Relative risk (95% CI)	Adjustment factors	Comments
Carstensen *et al.* (1990), Sweden, Cancer Environment Register	6230 male brewers listed in 1960 census, aged 20–69 years (ration of 1 L/day); follow-up until 1979; 38 cases identified through registry	Incidence rates compared with national rates	Population rate (Exp) Brewers (Obs)	23 38	1.0 1.66 (1.18–2.28) p-value <0.01	Age, follow-up period, region	Reduction in breweries in 1960–80 so potential misclassification of jobs probable, no individual exposure data; no information on potential confounders
Tønnesen *et al.* (1994), Denmark, Copenhagen Alcoholics	18 307 male and female alcoholics, recruited 1954–87 from outpatient clinics (~200 g ethanol/day); follow-up until 1987	Incidence rates compared with national rates	Population rate (Exp) Alcoholics (Obs)	31 41	1.0 1.3 (1.0–1.8) p-value ≤0.05	Age, sex, calendar time	Most drank beer; not adjusted for smoking; no individual exposure data; no information on potential confounders
Sigvardsson *et al.* (1996), Sweden	15 508 alcoholic women (Temperance Board records/ convictions) in 1947–77 and comparison group of 15 508 women, matched by age and region (population register); follow-up not stated; 48 cases identified by registry	Incidence rates in alcoholics compared with rates in matched comparison group	Comparison group Alcoholics	18 48	1.0 2.7 (1.6–4.6)	Matching factors	Excluded ~6000 older women with no identity number; large changes in alcoholic beverage availability and attitudes during follow-up; no individual exposure data; no information on potential confounders

Table 2.47 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Exposure categories	No. of cases	Relative risk (95% CI)	Adjustment factors	Comments
Karlson *et al.* (1997); Ye *et al.* (2002), Sweden, Inpatient Hospital Register (retrospective cohort)	Karlson *et al.* (1997): Analytical cohort of 4043 patients discharged with pancreatitis associated with alcoholism, 1965–83; mean age, 46 years; follow-up until 1989; 15 cases (13 men, 2 women) (excluding 1 year of follow-up) Ye *et al.* (2002): 178 688 male and female patients with hospital discharge of alcoholism, 1964–95; 305 cases identified through cancer registry (excluding 1 year of follow-up)	Incidence rates compared with national rates	Population (Exp) Alcoholics (Obs) Population (Exp) Alcoholics (Obs)	Not stated 15 222 305	1.0 2.9 (1.6–4.8) 1.0 1.4 (1.2–1.5)	Age, sex, calendar year	No individual exposure data; no information on potential confounders Increased risk in men and women separately, but not adjusted for smoking; increased risk among younger patients

CI, confidence interval; Exp, expected; NS, not significant; Obs, observed; SIR, standardized incidence ratio; SMR, standardized mortality ratio

[a] 90% confidence interval

follow-up period (1960–80), and that potential misclassification of exposure is probable (Carstensen *et al*., 1990). Three cohort studies of alcoholics in Sweden and Denmark also reported significant excess rates of pancreatic cancer compared with national incidence rates (Tønnesen *et al*., 1994; Sigvardsson *et al*., 1996; Ye *et al*., 2002), matched by age, sex and calendar time.

None of these studies provided individual exposure data and thus dose–response relationships could not be examined and potential confounding factors such as cigarette smoking could not be taken into account. Finally, it must be noted that high alcoholic beverage consumption may induce chronic pancreatitis, a known risk factor for pancreatic cancer. One study based on hospital discharge records in Sweden found that the rate of pancreatic cancer among patients with pancreatitis associated with alcoholism was higher than that among the national population, but similar to the rates found among patients with chronic or recurrent pancreatitis as a whole (Karlson *et al*., 1997).

(b) General population (Table 2.48)

Twelve cohort studies examined alcoholic beverage consumption and the subsequent risk for pancreatic cancer in the general population. Three studies reported a significant excess risk with increased alcoholic beverage intake (Klatsky *et al*., 1981; Heuch *et al*., 1983; Zheng *et al*., 1993). An early report from the Kaiser-Permanente study found a significantly increased risk for men and women who drank ≥6 drinks per day compared with non-drinkers (Klatsky *et al*., 1981), although this was not confirmed in a subsequent follow-up (Hiatt *et al*., 1988; Friedman & van den Eeden, 1993). Another study reported an excess risk among those with a frequent intake (i.e. ≥14 times per month) compared with none or very limited use (Heuch *et al*., 1983). [Data on smoking history were only available for a sub-sample of the cohort (~5000 men) and this relative risk estimate was therefore based on small numbers. Further, the excess risk appeared to be weaker among cases without histological confirmation, which suggests that some selection bias may have occurred.] A cohort study conducted among the Lutheran Brotherhood in the USA also reported a significant threefold excess risk for death from pancreatic cancer among men who drank 10 or more times per month compared with never drinkers after adjustment for age and smoking, based on 57 deaths (Zheng *et al*., 1993).

The majority of the studies, most of which were conducted in the USA and Japan among populations with low to moderate alcoholic beverage intake, have not found a significant association between alcoholic beverage intake and pancreatic cancer. One cohort study in Japan reported a significant excess risk among former drinkers compared with never drinkers (Inoue *et al*., 2003), which was seen in both men and women. [Former drinkers may have ceased drinking because they are ill, causing a spuriously high relative risk in this category.]

All of these cohort studies adjusted for cigarette smoking, and some incorporated adjustments for other potential confounders such as diet, diabetes and family history.

Table 2.48 Cohort/nested case–control studies of pancreatic cancer and alcoholic beverage consumption in the general population

Reference, location, name of study	Cohort description	Exposure assessment	Exposure categories	No. of cases	Relative risk (95% CI)	Adjustment factors	Comments
Klatsky *et al.* (1981); Hiatt *et al.* (1988); Friedman & van den Eeden (1993), USA, Kaiser-Permanente Medical Care Program	Klatsky *et al.* (1981): Nested case–control study of 8060 men and women in health plan; recruited 1964–68; high-intake group (2084) matched to 3 controls with varying intake (age, date, race, sex, smoking, location); follow-up till 1976; 16 deaths identified from death certificates	Self-administered questionnaire	*Usual drinks/day* 0 ≤2 3–5 ≥6	16 deaths 2 5 3 6	 Not stated ≥6 versus ≤2, *p*=<0.01	Matching factors	

Table 2.48 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Exposure categories	No. of cases	Relative risk (95% CI)	Adjustment factors	Comments
(contd)	Hiatt *et al.* (1988)/ Analytical cohort of 122 984 men and women receiving health check-ups; baseline at 1978; follow-up until 1984; 48 cases identified through hospital discharge data and cancer registry. histologically confirmed, 76%		*Drinks/day* None Past <1 >1	48	 1.0 2.6 (0.8–8.6) 1.3 (0.5–3.1) 0.9 (0.3–2.7)	Age, sex, race, blood glucose level, smoking, coffee	

Table 2.48 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Exposure categories	No. of cases	Relative risk (95% CI)	Adjustment factors	Comments
(contd)	Friedman & van den Eeden (1993): Nested case–control study from original recruitment date of 1964; aged 15–94 years; follow-up until 1988; 450 cancers identified through hospital discharge data and cancer registry verified through medical records; 2687 controls matched on age, sex, site, date of recruitment		*Use in last year (drinks/day)* None <3 ≥3	450	 1.0 1.12 (0.85–1.48) 1.35 (0.90–2.03)	Age, race, smoking	35% of cases diagnosed within 1 year of entry; no association with getting drunk on workdays, drinking in the morning, heavy alcohol user (yes versus no) or spouse having a drinking problem

Table 2.48 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Exposure categories	No. of cases	Relative risk (95% CI)	Adjustment factors	Comments
Heuch *et al.* (1983), Norway, 1960–67	Analytical cohort of 16 713 men and women, aged 45–74 years (4995 had information on alcohol intake and smoking); based on 3 groups: men from 1960 census (48%); brothers of migrants (20%); relatives of gastrointestinal cases from a previous case–control study (32%); follow-up until 1973; 63 cases identified via cancer registry; histologically confirmed, 29%	Self-administered questionnaire (1964 to groups 1 and 2, and 1967 to group 3); frequent use equivalent to beer or spirits 14 times/ month	*Alcohol use* None or very limited use Frequent use *p* for trend	18 *p* for trend	 1.0 10.82 0.001	Age, sex, region, urban/rural, smoking	Results presented for 18 histologically confirmed cases (men) with smoking data; weaker (but still significant) association in cases with no histological confirmation

Table 2.48 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Exposure categories	No. of cases	Relative risk (95% CI)	Adjustment factors	Comments
Kono *et al.* (1986), Japan, Japanese Physicians	Analytical cohort of 5135 men recruited in 1965; follow-up until 1983; 14 deaths identified from death certificates; response rate, 51%	Self-administered questionnaire	*Intake in last 20 years* None Former Occasional <2 go (sake)/day ≥2 go (sake)/day	 3 2 5 1 3	 1.0 1.9 (0.3–11.7) 1.4 (0.3–5.9) 0.4 (0.0–4.0) 1.5 (0.3–7.9)	Age, smoking	No association for daily versus none; low response rate
Zheng *et al.* (1993), USA, Lutheran Brotherhood Insurance Society	Analytical cohort of 17 633 men, aged ≥35 years, recruited 1966; follow-up until 1986; 57 deaths identified from death certificates	Self-administered questionnaire	*Total intake (times/month)* Never <3 3–9 ≥10	 7 13 13 18	 1.0 2.0 (0.5–5.2) 3.6 (1.4–9.3) 3.1 (1.2–8.0)	Age, smoking	Low alcohol intake (26% ≤2.5 drinks/week); significant increased risk for beer and spirits
Shibata *et al.* (1994), USA, Laguna Hills Residents, Los Angeles	Analytical cohort of 13 976 men and women recruited 1982; 80% aged 65–80 years; follow-up until 1990; 65 cases identified from pathology reports from participating hospitals	Self-administered questionnaire	*Drinks/day* <1 1–2 >2	 24 27 12	 1.0 1.01 (0.58–1.77) 0.91 (0.44–1.88)	Age, sex, smoking	

Table 2.48 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Exposure categories	No. of cases	Relative risk (95% CI)	Adjustment factors	Comments
Harnack *et al.* (1997), USA, Iowa Women's Health Study	Analytical cohort of 33 976 women, aged 55–69 years, recruited 1986; follow-up for incidence and mortality through registry until 1994; 66 cases (verification not stated)	Self-administered questionnaire	*Drinks/week* None 0.5–2 >2 *p* for trend	 29 18 19	 1.0 1.46 (0.81–2.63) 1.65 (0.90–3.03) 0.11	Age, smoking	Increased risk for spirits (>1 unit/ week, 2.1) and also seen in never smokers, but small numbers
Coughlin *et al.* (2000), USA, Columbia, Puerto Rico, American Cancer Society, Cancer Prevention Study-II	Analytical cohort of 1.2 million men and women, recruited 1982, aged ≥30 years; mortality follow-up until 1996; 3751 deaths (1967 men, 1784 women) identified from death certificates	Self-administered questionnaire	*Drinks/day* None Some 1 >1 None Some 1 >1	 329 198 226 564 390 194 151 244	*Men* 1.0 0.9 (0.8–1.1) 0.9 (0.8–1.1) 0.9 (0.8–1.1) *Women* 1.0 0.9 (0.8-1.1) 0.8 (0.7-1.0) 0.9 (0.8-1.1)	Age, race, education, family history, gallstones, diabetes, body-mass index, smoking, red meat, citrus fruit and juices, vegetable intake	Cases not verified; no interaction with smoking

Table 2.48 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Exposure categories	No. of cases	Relative risk (95% CI)	Adjustment factors	Comments
Michaud *et al.* (2001), USA, HPFS and NHS	Analytical cohort of 136 593 men and women, using data from 1980 and 1986; follow-up until 1996 (women, aged >30 years); and 1998 (men, aged 40–75 years); self-reported cases verified by pathology and medical records	Self-administered questionnaire	*Intake (g/day)* 0 0.1–1.4 1.5–4.9 5–29.9 ≥30 *p* for trend	288	 1.0 0.78 (0.47–1.30) 1.15 (0.78–1.69) 1.0 (0.69–1.44) 1.0 (0.57–1.76) 0.94	Age, smoking, body-mass index, diabetes, cholecystecomy, energy intake, time period	No association for type of beverage or with past heavy drinking; no association by body mass index, age or smoking
Stolzenberg-Solomon *et al.* (2001), Finland, ATBC Cancer Prevention Study	Analytical cohort of 27 101 male smokers, aged 50–69 years, recruited 1985; follow-up until 1997; 157 cases identified through cancer registry; histologically confirmed, 79%	Self-administered questionnaire	*Intake (g/day)* None <5.4 5.4–13.4 13.5–27.7 ≥27.8 *p* for trend	 14 39 38 32 34	 1.0 1.39 (0.75–2.56) 1.39 (0.75–2.56) 1.24 (0.66–2.32) 1.40 (0.75–2.62) 0.71	Age, intervention arm, adjustment for other factors made little difference	

Table 2.48 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Exposure categories	No. of cases	Relative risk (95% CI)	Adjustment factors	Comments
Isaksson *et al.* (2002), Sweden, Swedish Twin Regsitry	Analytical cohort of 21 884 men and women recruited in 1961, aged 36–75 years; followed-up between 1969 and 1997; 176 cases identified through cancer registry; histologically confirmed, 90%	Self-administered questionnaire; alcohol consumption derived from 1967 questionnaire	*Alcohol intake (g/month)* None 1–209 ≥210	 52 86 11	 1.0 0.89 (0.61–1.30) 0.78 (0.39–1.55)	Age, sex, smoking	
Lin *et al.* (2002), Japan, Japan Collaborative Cohort	99 527 men and women, recruited 1988–90, undergoing health check, aged 40–79 years; follow-up until 1997 for mortality; 191 deaths (94 men, 97 women) with information on alcoholic beverages	Self-administered questionnaire	*Intake (g/day)* None Former 0–29 30–69 ≥60 *p* for trend	*Men* 26 6 35 20 7	*Men* 1.0 0.74 (0.30–1.82) 1.16 (0.66–2.04) 1.07 (0.56–2.06) 0.98 (0.39–2.46) 0.76	Age, smoking	No association in women; no association by duration or lifetime intake

Table 2.48 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Exposure categories	No. of cases	Relative risk (95% CI)	Adjustment factors	Comments
Inoue *et al.* (2003), Japan, HERPACC	Nested case–control study of hospital patients, aged 32–85 years, recruited 1988–99: follow-up until 2000; 200 cases (122 men, 78 women), 2000 controls (non-malignant), matched by age, sex	Self-administered questionnaire	*Alcohol drinking* Never Former Current	 111 37 52	 1.0 3.70 (2.28–6.00) 0.50 (0.34–0.73)	Age, sex, family history, diabetes, physical activity, bowel habits, raw vegetable intake	Increased risk in men and women, separately; the increased risk in former drinkers may be due to ill-health.

ATBC, α-Tocopherol β-Carotene; CI, confidence interval; HERPACC, Hospital-based Epidemiologic Research Program at Aichi Cancer Center; HPFS, Health Professionals Follow-up Study; NHS, Nurses' Health Study

However, where crude and multivariate data were presented together, adjustment for these factors appeared to make little difference to the estimates for alcoholic beverage intake.

There are very limited data on the effect of duration of alcoholic beverage drinking or cessation of drinking on the risk for pancreatic cancer; those studies that have reported risks for former drinkers compared with never drinkers have shown highly inconsistent results.

2.9.2 *Case–control studies (Table 2.49)*

Twenty-nine case–control studies have published quantitative data on the association of alcoholic beverage intake and the risk for pancreatic cancer. Most studies found no association (see Table 2.49). Several studies suggested that heavy alcoholic beverage consumption (≥15 drinks/week) may be associated with an increased risk for pancreatic cancer (Falk *et al*., 1988; Cuzick & Babiker, 1989; Ferraroni *et al*., 1989; Olsen *et al*., 1989; Silverman, 2001). Other studies have reported significant reductions in risk with increasing alcoholic beverage intake (Gold *et al*., 1985; Baghurst *et al*., 1991; Talamini *et al*., 1999).

There is no consistent evidence that intake of any specific type of beverage is associated with risk for pancreatic cancer.

The difference in findings may be partly due to differences in study design. In many of these case–control studies, a large proportion of cases were deceased, which resulted in interviews being conducted among the next of kin. Although some studies suggest that spouse proxies give reasonable estimates of alcoholic beverage intake, many interviews were conducted with a child, friend or other relative, which may result in substantial exposure misclassification and/or recall bias. Further, studies that only included cases that were histologically verified may not be representative of all cases and may lead to bias if high alcoholic beverage intake is associated with reduced access to medical care. In addition, selection bias due to low response rates, possible confounding by tobacco smoking, failure to exclude controls who had tobacco- and alcohol-related diseases and chance findings as a result of small sample size may also contribute to these discrepant results.