A Case-Control Study of Pancreatic Cancer and Cigarettes, Alcohol, Coffee and Diet

GEARY W. OLSEN, DVM, PHD, JACK S. MANDEL, PHD, ROBERT W. GIBSON, PHD, LEE W. WATTENBERG, MD, AND LEONARD M. SCHUMAN, MD

Abstract: A pancreatic cancer case-control study was conducted in the Minneapolis-St. Paul area. Family members were interviewed about the subject's usage of cigarettes, alcohol, coffee, and other dietary factors in the two years prior to death (cases, n = 212) or prior to interview (controls, n = 220). The adjusted odds ratio for two packs or more of cigarettes per day was 3.92 (95% CI = 1.18, 13.01) and four or more drinks per day OR 2.69 (95% CI = 1.00, 7.27). Coffee was not a risk factor (seven cups or more per day; OR 0.58 (95% CI = 0.27, 1.27). A positive trend was observed for beef and pork consumption, and a negative trend from cruciferous vegetables. (*Am J Public Health* 1989; 79:1016–1019.)

Introduction

Cigarette smoking is the only currently known etiologic factor for pancreatic cancer.[1] While some epidemiologic studies have shown a positive association between alcohol consumption and pancreatic cancer,[2–4] most have not.[5–11] A positive association between pancreatic cancer and coffee consumption was reported in one study,[5] but was not substantiated by other studies.[6–10] Four case-control studies have reported inconsistent findings regarding meat and vegetable consumption.[7–10] The present case-control study was designed to evaluate further the role of cigarettes, alcohol, and coffee as well as to explore other dietary factors.

Methods

Cases were White males ages 40 to 84 whose deaths occurred between January 1, 1980 and June 30, 1983 with pancreatic cancer (exocrine only) listed on the death certificate; place of residence at the time of death was within the seven-county Minneapolis-St. Paul area.

There were 262 pancreas-identified cancer deaths. An informant was located for 250 cases and 212 (84.8 percent) were interviewed. Of those interviewed, 140 cases (66.0 percent) had pathological confirmation.

Population-based controls were White males, ages 40–84, ascertained through random digit dialing and frequency matched within five year groups. A total of 94.2 percent of all households screened provided data.[12] The following are the percentages (in parentheses) of eligible controls whose respondents agreed to participate in the study: less than 60 years of age (80.2), ages 60–64 (82.2), 65–69 (92.6), 70–74 (72.7), 75 and older (69.5).

The widow (case) or spouse (control) was interviewed at home. If unavailable, the next closest relative (e.g., daughter) was sought. The spouse was the primary respondent for 73 percent of the cases and 92 percent of the controls. The subject's wife or daughter provided the information for 88 percent of the cases and 97 percent of the controls.

Questions on smoking, drinking, and diet pertained to the subject's usage two years prior to death for the cases and two years prior to the interview for the controls. Individual dietary information was obtained by a frequency-of-use questionnaire. Frequency categories ranged from no use to daily use (two or more packs of cigarettes, four or more drinks of beer, wine, or hard liquor, and seven or more cups of coffee). An index of alcohol consumption was computed using the combined frequencies of beer, wine, and hard liquor. In-season and out-of-season consumption was asked for selected vegetables and fruit. Reported are the the monthly consumption indices for beef, pork, poultry, cruciferous vegetables (cabbage, broccoli, brussel sprouts, and cauliflower) and noncruciferous vegetables, fruits and juices, bread and cereals, and dairy products.

Logistic regression was employed to obtain maximum likelihood point estimates and 95 percent confidence intervals of the odds ratio.[13] Odds ratios were adjusted for the potential confounding variables of age, educational status, reported history of diabetes mellitus, cigarettes, alcohol as well as other dietary life-style factors where applicable, i.e., frequency of meat (beef, pork and poultry) and vegetable (cruciferous and noncruciferous) consumption.

Analyses were performed using all cases and only histologically confirmed cases. Since there were no differences, the results are reported for all cases combined. Data were also analyzed and reported separately for all respondents and spouse only respondents.

Results

An increased risk for pancreatic cancer was observed for current cigarette smoking and, to a less extent, smoking duration (Table 1). An index of total alcohol consumption (Table 2) showed a greater than two-fold risk for pancreatic cancer for heavy alcohol consumption (four or more drinks per day), primarily due to heavy beer and hard liquor consumption. There was weakly decreased risk for coffee consumption. A positive trend was observed for the consumption of beef and pork but not poultry (Table 3). Consumption of cruciferous vegetables showed a negative trend but this was not observed with the consumption of noncruciferous vegetables or fruits and juices. Increased risks were associated with dairy products and breads and cereals. However, a strong difference was observed in the consumption of white versus whole wheat bread. The upper quartile

Address reprint requests to Geary W. Olsen, DVM, PhD, Health and Environmental Sciences, Epidemiology Department, Dow Chemical Company, 1803 Building, Midland, MI 48674. He is also affiliated with the Department of Epidemiology, University of Minnesota School of Public Health, Minneapolis, as are Drs. Gibson and Schuman. Dr. Gibson is also affiliated with the University of Minnesota School of Medicine, Department of Behavioral Sciences, Duluth; Dr. Mandel is with the Division of Environmental and Occupational Health, U-MN SPH, Minneapolis; Dr. Wattenberg is with the Department of Laboratory Medicine and Pathology, U-MN School of Medicine, Minneapolis. This paper, submitted to the Journal August 8, 1988, was revised and accepted for publication February 26, 1989.

TABLE 1—Adjusted Odds Ratios* and 95 Percent Confidence Intervals for Cigarette Smoking by Type of Respondent

Current Smoking Status	All Respondents			Spouses Only		
	Cases/ Controls	Adjusted Odds Ratio	95% CI	Cases/ Controls	Adjusted Odds Ratio	95% CI
Nonsmokers	132/178	1.00	—	94/164	1.00	—
Current Packs/Day						
<1 pack	22/17	1.77	0.87–3.61	16/16	1.68	0.77–3.69
1–2 packs	42/21	2.90	1.55–5.43	33/21	2.83	1.47–5.46
≥2 packs	16/4	3.92	1.18–13.01	11/4	2.65	0.72–6.20
Years smoked**						
1–15	11/6	2.06	0.70–6.05	7/6	1.75	0.54–5.68
16–29	30/16	2.58	1.26–5.28	25/16	2.55	1.21–5.39
≥30	34/19	2.37	1.25–4.49	24/18	2.15	1.06–4.35
Never Smoked	44/54	1.00	—	30/49	1.00	—
Ex smokers	88/124	0.76	0.46–1.28	64/115	0.76	0.43–1.37

*Adjusted for age, education level, reported diabetes mellitus history, and alcohol, meat and vegetable consumption.
**Five spouse and one non-spouse respondents were unable to recall smoking duration.

TABLE 2—Adjusted Odds Ratios* and 95 Percent Confidence Intervals for Total Alcohol, Beer, Hard Liquor, Wine and Coffee Consumption by Type of Respondent

Drinks/Day	All Respondents			Spouses Only		
	Cases/ Controls	Adjusted Odds Ratio	95% CI	Cases/ Controls	Adjusted Odds Ratio	95% CI
Total alcohol						
0	56/44	1.00	—	40/39	1.00	—
1	104/149	0.77	0.47–1.30	77/140	0.73	0.41–1.28
2–3	28/20	1.42	0.67–3.03	20/19	1.30	0.57–2.97
≥4	24/7	2.69	1.00–7.27	17/7	2.33	0.81–6.67
Beer						
0	89/80	1.00	—	63/72	1.00	—
1	100/132	0.87	0.56–1.35	77/125	0.84	0.52–1.36
2–3	10/7	1.09	0.35–3.39	5/7	0.62	0.16–2.31
≥4	13/1	8.25	1.01–67.54	9/1	6.92	0.80–59.52
Hard Liquor						
0	95/78	1.00	—	65/67	1.00	—
1	86/126	0.66	0.42–1.01	64/123	0.60	0.37–0.98
2–3	24/14	1.24	0.56–2.71	19/13	1.34	0.57–3.11
≥4	7/2	3.49	0.65–18.72	6/2	3.53	0.63–19.70
Wine						
0	119/78	1.00	—	85/69	1.00	—
1	89/138	0.63	0.41–0.97	65/132	0.55	0.36–0.88
2–3	2/3	0.69	0.09–5.43	2/3	0.83	0.11–6.40
≥4	2/1	2.72	0.24–31.37	2/1	2.97	0.26–34.13
Coffee						
<1	29/25	1.00	—	19/24	1.00	—
1–3	60/84	0.50	0.26–1.00	42/77	0.59	0.28–1.26
4–6	74/68	0.72	0.37–1.45	54/62	0.83	0.39–1.77
≥7	49/43	0.58	0.27–1.27	39/42	0.68	0.30–1.57

*Adjusted for age, education level, reported diabetes mellitus history, cigarette smoking, meat and vegetable consumption.

of cases ate more white bread (OR 2.42, 95% CI = 1.52, 3.84) and less whole wheat bread (OR 0.44, 95% CI = 0.26, 0.76).

Discussion

The reporting of pancreatic cancer on the death certificate has been shown to be quite accurate.[14] The use of death certificates allowed for the virtually complete ascertainment of all cases in the defined geographic area and justified the use of a population-based control group.

In this study, live rather than deceased controls were selected. The use of deceased controls may introduce a bias since their use of alcohol and cigarettes may be greater than the general population.[15] To keep data collection procedures comparable in cases and controls, we asked surrogates for the information for the controls. Disparaties in recall could still exist, but several features of our method minimized the influence that a live control could have had on a surrogate: the surrogate was not informed about the nature of the interview until the interviewer was present; controls were not allowed to be present during the interview; potentially sensitive questions (e.g., alcohol consumption) were asked toward the end of the interview.

Diseases such as pancreatic cancer which are rapidly fatal are difficult to study because many patients die before the interview can be completed or are too debilitated to participate. Previous case-control studies have suffered from this problem. Wives and daughters can provide reasonable estimates of a man's dietary habits, although the data on alcohol are less certain.[16–18]

The risk estimates and trends observed in this study are consistent with other results for cigarette smoking[2–11] and

TABLE 3—Adjusted Odds Ratio and 95 Percent Confidence Intervals for Selected Food Groups by Type of Respondent

Food Group Times/Month	All Respondents			Spouses Only		
	Cases/ Controls	Adjusted Odds Ratio	95% CI	Cases/ Controls	Adjusted Odds Ratio	95% CI
Beef						
≤8	43/53	1.00	—	22/50	1.00	—
9–17	89/112	1.05	0.62–1.78	67/106	1.57	0.84–2.92
≥18	80/55	1.81	1.00–3.28	65/49	3.02	1.50–4.89
Pork						
≤2	29/43	1.00	—	21/39	1.00	—
3–8	106/119	1.42	0.78–2.57	80/112	1.43	0.74–2.76
≥9	77/58	1.90	1.00–3.61	53/54	1.66	0.81–3.39
Poultry						
≤2	45/42	1.00	—	28/39	1.00	—
3–5	106/120	0.80	0.47–2.23	83/111	1.09	0.60–1.99
≥6	61/58	0.95	0.52–1.73	43/55	1.09	0.55–2.14
Cruciferous vegetables						
≤2	62/49	1.00	—	38/39	1.00	—
3–8	102/114	0.71	0.43–1.18	72/111	0.56	0.31–1.01
≥9	48/57	0.57	0.31–1.04	44/55	0.55	0.28–1.09
Noncruciferous vegetables						
≤16	71/56	1.00	—	44/51	1.00	—
17–31	78/113	0.55	0.33–0.91	57/104	0.58	0.33–1.03
≥32	63/51	0.95	0.52–1.73	53/50	1.07	0.55–2.06
Fruits and juices						
≤21	68/53	1.00	—	47/49	1.00	—
22–52	98/112	0.90	0.54–1.49	67/102	0.91	0.51–1.61
≥53	46/55	0.88	0.48–1.62	40/54	1.06	0.54–2.06
Breads and cereals						
≤24	32/52	1.00	—	23/48	1.00	—
25–36	95/110	1.22	0.68–2.12	66/104	1.34	0.70–2.58
≥37	85/58	2.19	1.18–4.08	65/53	2.66	1.33–5.33
Dairy						
≤16	50/56	1.00	—	31/50	1.00	—
17–38	97/102	1.21	0.72–2.03	70/94	1.26	0.70–2.27
≥39	65/62	1.51	0.85–2.71	53/61	1.59	0.84–3.01

*Adjusted for age, education level, reported diabetes mellitus history, cigarette smoking, alcohol and when appropriate meat and/or vegetable consumption. The frequency level was determined by the 25th and 75th percentile values of the controls in order to categorize low, moderate and high consumption patterns.

Beef = hamburger, pot roast, roast beef, steak, beef ribs.
Pork = pork chops, ham, ribs, roast, bacon.
Poultry = chicken, turkey.
Cruciferous vegetables = cabbage, broccoli, brussel sprouts, cauliflower.
Noncruciferous vegetables = spinach, carrots, lima beans, peas, tomatoes, corn, green and yellow beans.
Fruits and juices = oranges, apples, bananas, peaches, grapefruit, strawberries, orange juice.
Breads and cereals = white, whole wheat, rye bread, cereal.
Dairy = cheese, cottage cheese, ice cream, milk.

further support its role as an etiologic factor for pancreatic cancer.

Heavy alcohol consumption adjusted for several potential confounding variables was positively associated with pancreatic cancer. The consumption of beer and hard liquor contributed to this association, but there were few wine drinkers among the subjects. These results are supported by some[2–4] but not all epidemiologic studies on pancreatic cancer. This discrepancy, reviewed by Velema, *et al*,[19] may be due, in part, to differences in case selection, hospital versus population-based controls, the use of living or deceased controls when cases are deceased, and whether the vital status of the case affects the accuracy of information provided by a family member. Studies of alcohol abusers have not reported an excess risk for pancreatic cancer;[20,21] however, these studies did not allow for an adequate latency period and many abusers died of other causes.

Heavy alcohol consumption may induce chronic calcifying pancreatitis which may, perhaps in the presence of other dietary modifiers (e.g., high fat), lead to pancreatic cancer.[22] Animal models, however, have not shown pancreatic cancer to be produced by high concentrations of ethanol.[23] At this time there is no clear biologic mechanism to link alcohol consumption to pancreatic cancer.

It is probably premature to suggest, as some investigators have,[1,9] that alcohol does not have an important role in the development of pancreatic cancer. We agree with Velema, *et al*,[19] that the consumption of alcohol in relation to pancreatic cancer should remain under close observation.

Our findings concur with most epidemiologic[6–11] and laboratory[24] studies that coffee is not a risk factor for pancreatic cancer. In fact, after adjusting for major dietary life-style factors as recommended by Falk, *et al*,[10] we observed a negative association for coffee usage even at seven or more cups per day.

Ecologic studies have examined national food consumption patterns and pancreatic cancer mortality rates and have shown a positive correlation between pancreatic cancer and meat and fat consumption;[25,26] of four recent case-control studies, three have reported positive associations with meat. Mack, *et al*, observed a high level of beef consumption among directly interviewed subjects.[9] Falk, *et al*, showed a dose response for pork products.[10] Norell, *et al*, reported a positive association with meat that was fried or grilled.[8] However, Gold, *et al*, in their case-control study, did not find a relation with beef, deep-fried foods, smoked or barbequed

beef, bologna, or salami.[7] Laboratory data have suggested high fat diets may cause pancreatic hyperplasia which may subsequently lead to neoplasia.[27] Our findings support the hypothesis that diets high in animal fat may be associated with pancreatic cancer.

Our results showed a decreased risk of pancreatic cancer with an increased consumption of cruciferous vegetables. Indoles and aromatic isothiocyanates, found in cruciferous vegetables, have been shown to increase glutathione S-transference activity and inhibit experimentally induced neoplasia in laboratory animals.[28] The lack of a decreasing risk trend for consumption of noncruciferous vegetables was due to cases consuming more of the common vegetables (peas, corn, green bean and yellow beans). Unlike Norell, *et al*,[8] we did not observe a negative trend with carrots.

The risk estimates for fruit consumption showed at best a weak negative association. Others have reported much stronger negative associations.[7-10]

The increased risk for white bread has also been observed elsewhere.[7,9] This association may be due to a change from white to whole wheat bread by controls which may parallel their preference for a diet of more vegetables, less meat.

Based on the results of our study and those from previously published studies, we believe a cessation of cigarette smoking will result in a decreased incidence of pancreatic cancer in the adult male population. Furthermore, a decrease in heavy alcohol and meat consumption and a corresponding increase in vegetables may also contribute to a decline. Our results lend additional support to the conclusion that coffee is not a risk factor for pancreatic cancer.

ACKNOWLEDGMENTS

This study was supported by grant SIG5 from the American Cancer Society. The authors wish to acknowledge the assistance of Sheila Richter, Sue Harmon, Ann Berry and Virginia Sykes to this study.

REFERENCES

1. MacMahon B: Risk factors for cancer of the pancreas. Cancer 1982; 50:2676–2680.
2. Heuch I, Kvale G, Jacobson BK, *et al:* Use of alcohol, tobacco and coffee, and risk of pancreatic cancer. Br J Cancer 1983; 48:637–643.
3. Durbec JP, Chevillotte G, Bidart JM, *et al:* Diet, alcohol, tobacco and risk of cancer of the pancreas: A case-control study. Br J Cancer 1983; 47:463–470.
4. Hinds MW, Kolonel LN, Lea AJ, *et al:* Associations between cancer incidence and alcohol and cigarette consumption among five ethnic groups in Hawaii. Br J Cancer 1980; 41:929–940.
5. MacMahon B, Yen S, Trichopolous D, *et al:* Coffee and cancer of the pancreas. N Engl J Med 1981; 304:630–633.
6. Wynder EL, Hall NE, Polansky M: Epidemiology of coffee and pancreatic cancer. Cancer Res 1983; 43:3900–3906.
7. Gold EB, Gordis L, Diener MD, *et al:* Diet and other risk factors for cancer of the pancreas. Cancer 1985; 55:460–467.
8. Norell SE, Ahlbom A, Erwarld R, *et al:* Diet and pancreatic cancer: A case-control study. Am J Epidemiol 1986; 124:894–902.
9. Mack TM, Yu MC, Hanish R, *et al:* Pancreas cancer and smoking, beverage consumption, and past medical history. JNCI 1986; 6:49–60.
10. Falk RT, Pickle LW, Fontham ET, *et al:* Life-style risk factors for pancreatic cancer in Louisiana: A case-control study. Am J Epidemiol 1988; 123:324–336.
11. Hsieh C, MacMahon B, Yen S, *et al:* Coffee and pancreatic cancer (Chapter 2). (Letters) N Engl J Med 1986; 315:587–588.
12. Olsen GW, Mandel JS: Elderly control selection using random digit dialing. Am J Public Health 1988; 78:1487–1488.
13. Sas Institute Inc: SAS User's Guide: Statistics, Version 5 Edition. Cary, NC: SAS Institute Inc., 1985.
14. Percy C, Stanek E, Gloeckler L: Accuracy of cancer death certificates and its effect on cancer mortality statistics. Am J Public Health 1981;71:242–250.
15. McLaughlin JK, Blot J, Mehl E, *et al:* Problems in the use of dead controls in case-control studies. I. General results. Am J Epidemiol 1985; 121:131–139.
16. Kolonel LN, Hirohata T, Nomura AM: Adequacy of survey data collected from substitute respondents. Am J Epidemiol 1977; 101:476–484.
17. Marshall JR, Priore R, Haughey B, *et al:* Spouse-subject interviews and the reliability of diet studies. Am J Epidemiol 1980; 112:675–683.
18. Sandler DP, Shore DL: Quality of data on parents' smoking and drinking provided by adult offspring. Am J Epidemiol 1986; 124:768–778.
19. Velema JP, Walker AM, Gold EB: Alcohol and pancreatic cancer. Insufficient epidemiologic evidence for a causal relationship. Epidemiol Rev 1986; 8:28–41.
20. Hakulinen T, Lehtimaki L, Lehtonen M, *et al:* Cancer morbidity among two male cohorts with increased alcohol consumption in Finland. JNCI 1974; 52:1711–1714.
21. Robinette CD, Hrubec Z, Fraumeni JF: Chronic alcoholism and subsequent mortality in World War II veterans. Am J Epidemiol 1979; 109:687–700.
22. Ischii AJ, Nakamura K, Hirayama T, *et al:* Chronic calcifying pancreatitis and pancreatic carcinoma in Japan. Digestion 1973; 9:429–437.
23. Pour PM, Reber HA, Stepan K: Modification of pancreatic carcinogenesis in hamster model. XII. Dose-related effect of ethanol. JNCI 1983; 71:1085–1087.
24. Takayama S, Nagao M, Suwa L, *et al:* Long-term carcinogenicity studies on caffeine, instant coffee, and methyl glyoxal in rats. MacMahon B, Sugimura T (eds): Coffee and Health. Banbury Report 17. Cold Springs Harbor, Cold Springs Harbor Laboratory 1984; 99–106.
25. Hirayama T: A large-scale cohort study on the relationship between diet and selected cancers of digestive organs. Bruce WR, Correa P, Lipkin M, *et al* (eds): Gastrointestinal Cancer: Endogenous Factors. Banbury Report 7. Cold Springs Harbor, Cold Springs Harbor Laboratory, 1981; 409–426.
26. Armstrong B, Doll R: Environmental factors and cancer incidence and mortality in different countries with special response to dietary practices. Int J Cancer 1975; 15:617–631.
27. Longnecker DS, Wiebkin P, Schaeffer BK, *et al:* Experimental carcinogenesis in the pancreas. Int Rev Exp Pathol 1984; 26:177–229.
28. Wattenberg LW: Inhibition of carcinogens-induced neoplasia by sodium cyanate, tert-butyl isocyanate and benzyl isothiocyanate administered subsequent to carcinogen exposure. Cancer Res 1981; 41:2991–2994.