

A Case-control Study of Pancreatic Carcinoma*

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Summary. The hospital records of 60 female and 56 male pancreatic cancer patients and 232 age-, race-, sex-, and hospital-matched controls were reviewed for evidence of prior thyroid disease, cholecystectomy, appendectomy, alcohol consumption and among females, for diseases of the endometrium and ovary. No statistically significant differences were detected between case and control groups. It may be of interest, however, that there were four patients with a history of thyrotoxicosis among the pancreatic cancer patients and only one in the control group. In females, a history of thyroidectomy was somewhat more common among the patients than the controls.

Key words: Adenocarcinoma of the pancreas – Thyroid diseases – Cholecystectomy – Appendectomy – Hysterectomy

Pancreatic carcinoma is the fourth most frequent cause of death due to malignancy in the United States, accounting for 18,000 deaths per year (Fraumeni 1975). US pancreatic cancer mortality has been increasing in both sexes for blacks and whites since 1950 (Bernarde and Weiss 1977). Other western countries and Japan have also experienced an increase in mortality from this tumor (Levin and Connelly 1973).

Several studies (Wynder et al. 1973; Hammond 1966) have shown a twofold increased risk of pancreatic cancer in cigarette smokers. There is also evidence that diabetics have an increased risk of this tumor and that for females this risk extends for many years after the diagnosis of diabetes, suggesting that the association is not due to the destruction of functioning pancreatic tissue by tumor (Kessler 1970).

Some studies (Burch and Ansari 1968; Lin and Kessler 1981) have suggested an association between alcohol consumption and pancreatic cancer but other investigations (Wynder et al. 1973; MacMahon et al. 1981; Blot et al. 1978) have failed to confirm this observation. Consumption of coffee and decaffeinated coffee has

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been implicated in this disease (MacMahon et al. 1981; Lin and Kessler 1981). In females, a positive relationship to history of uterine myoma, oophorectomy, and spontaneous abortion has been noted (Lin and Kessler 1981). Furthermore, an autopsy study (Soloway and Sommers 1966) has shown a high incidence of endometrial and ovarian hyperplasia as well as neoplasms of the ovary, breast, and uterus in patients with pancreatic cancer. Associations with previous cholecystectomy (Wynder et al. 1973) and appendectomy (Howson and Asal 1976) have also been suggested. There appears to be no relationship between pancreatic cancer and pancreatitis except for the rare condition, familial relapsing pancreatitis (Appel 1974).

Persons exposed to naphthylamine (Mancuso and El-Attar 1967) and gasoline (Lin and Kessler 1981), workers in the dry-cleaning industry (Lin and Kessler 1981), and printing pressmen (Lloyd et al. 1977) have all been found to be at an excess risk of pancreatic cancer. A survey of death certificates of members of the American Chemical Society shows an increase in deaths from pancreatic cancer although no relationship to specific chemical exposure could be detected (Li et al. 1969).

The present study was motivated by a high prevalence of thyroid disease noted by one of us (JQ) in patients with pancreatic cancer referred for radiotherapy to the Lawrence Berkeley Laboratory, Berkeley, California. Six of 36 male patients and six of 17 female patients had a history of thyroid disease. In addition to investigating the possible existence of an association between thyroid disease and pancreatic cancer, we have also attempted to confirm previous suggestions of associations with prior cholecystectomy, appendectomy, diseases of the endometrium and ovary, and alcohol consumption.

Methods

The study was based upon review of medical records for patients referred to Stanford University Medical Center and the University of California in San Francisco between the years of 1973 and 1978. Pancreatic cancer cases included 60 females (52 whites, 4 blacks, 3 orientals, and 1 Filipino) and 56 males (51 whites, 2 blacks, and 3 orientals).

A pancreatic cancer case was included in the study if he or she fulfilled one or more of the following four criteria; (1) biopsy-proven adenocarcinoma of the pancreas with the biopsy taken from the main tumor mass at operation; (2) typical findings of pancreatic neoplasm at operation, the operation being available in the patient's chart and in addition a typical clinical course with evidence of extension of the primary tumor or metastatic spread on followup; (3) autopsy evidence of pancreatic cancer; (4) abnormal endoscopic retrograde cholangiopancreatography suggestive of pancreatic cancer with malignant cells in the pancreatic fluid. In 65 cases included in this analysis, the diagnosis was histologically confirmed by a biopsy of the pancreas or immediately adjacent lymph node. An additional 39 cases had histological confirmation of metastatic adenocarcinoma in the liver, lung, bone, peritoneum, or distant lymph node. Twelve cases were included without histological confirmation of adenocarcinoma. This group of patients had classical surgical findings and a clinical course consistent with progressive tumor.

For each case two control patients were randomly selected from those admissions who matched the case on age (± 2.5 years), sex, race (black, white, oriental), hospital, and year of admission. Of each pair of controls, one patient had malignant disease not arising in the pancreas and the other had non-malignant disease. Controls admitted for thyroid disease were excluded. As the study was not designed to investigate the relationship between pancreatic cancer and either smoking or diabetes, patients with smoking- or diabetes-related diseases were not excluded from the control groups.

Information concerning age, sex, ethnic group, smoking, alcohol consumption, previous history of thyroid disease, diabetes, pancreatitis, and a past history of cholecystectomy, appendectomy, hysterectomy, oophorectomy, and dilatation and curettage were recorded on a standardized form. Alcohol con-

Table 1. Thyroid disease history

	N	Mean age (yr)	All thyroid diseases ^a	Thyroid replacement	Known hypothyroidism	Known thyrotoxicosis	History of partial or total thyroidectomy
Females							
Pancreatic cancer cases	60	64.3	12	6	2	3	5
Malignant controls	60	64.2	9	8 ^b	3	0	2
Nonmalignant controls	60	64.8	10	9	4	1	1
Males							
Pancreatic cancer cases	56	60.0	4	2	0	1	0
Malignant controls	56	59.8	5	4	2	0	1
Nonmalignant controls	56	60.1	2	0	0	0	0

^a The sum of patients over all categories of thyroid disease exceeds the number of patients with any thyroid disease because some patients were in more than one category

^b Includes one case given thyroid extract for weight reduction

sumption was recorded on a three-point scale representing alcohol intake less than once a day, regular daily consumption, and a history of medical problems related to alcohol ingestion. A matched case-control analysis was used (Miettinen 1969).

Results

Table 1 shows the number of cases and controls with thyroid disease. Since no significant differences were detected between the malignant and nonmalignant control groups, the groups were combined in the analyses. Only two patients were recorded as having had Hashimoto's disease; both were in the female nonmalignant control group. Case and control groups did not differ significantly in prevalence of all thyroid diseases combined. This was also true when the analysis was restricted to patients with histological confirmation of adenocarcinoma and their controls. The only category of thyroid disease showing a consistent excess in the pancreatic cancer cases was thyrotoxicosis; however, this difference was based on small numbers and was not significant ($p=0.08$ by two-tailed test). A history of thyroidectomy was somewhat more frequent among the female pancreatic cancer cases than controls. Similar results were obtained by Wynder (1973).

No differences were seen between case and control groups with respect to a previous history of cholecystectomy, appendectomy, hysterectomy, dilatation and curettage, or oophorectomy (Table 2). Similarly, no consistent differences could be detected between the three groups with respect to alcohol consumption, and restriction of the comparison to those without alcohol-related diseases did not change this negative finding. None of the patients with pancreatic cancer had a history of pancreatitis which antedated the symptoms of their tumor.

Table 2. Surgical history

	<i>N</i>	Cholecystectomy ^a	Appendectomy ^a	Hysterectomy (partial and total combined)	Oophorectomy (unilateral or bilateral)	Dilatation and curettage
Females						
Pancreatic cancer cases	60	6	14	17	7	2
Malignant controls	60	6	16	27	10	2
Nonmalignant controls	60	7	20	27	5	6
Males						
Pancreatic cancer cases	56	2	14	—	—	—
Malignant controls	56	0	9	—	—	—
Nonmalignant controls	56	5	15	—	—	—

^a Five or more years prior to diagnosis

Discussion

Although there has been some evidence of associations between various neoplasia and thyroid disorders (Wynder 1973; Itoh and Maruchi 1975; Hedley et al. 1981; Yamashita et al. 1977), no previous study has specifically attempted to relate pancreatic cancer to thyroid disease. The excess of thyrotoxicosis, suggested here among pancreatic cancer cases of both sexes, may be worthy of further examination in a larger series, perhaps in the form of a followup study of patients treated for thyrotoxicosis. This is particularly appropriate in view of the evidence from animal studies of the carcinogenicity of propylthiouracil and other antithyroid compounds (IARC Monograph 1974). In the present study only one patient (the male patient with thyrotoxicosis shown in Table 1) was recorded as having received propylthiouracil. Information on past history of antithyroid medication was not available for other cases of thyrotoxicosis.

This study has not found a relationship between pancreatic cancer and prior cholecystectomy or appendectomy. We have included in our analysis only those whose cholecystectomies and appendectomies were performed five years or more prior to the patient's diagnosis. More recent operations could be related to symptoms caused by pancreatic or other abdominal neoplasms among the cases and malignant controls. An association between large bowel cancer and prior cholecystectomy has been reported (Capron et al. 1978). However, none of the malignant control group with prior cholecystectomy were suffering from large bowel cancer, so the association is unlikely to explain our failure to find an excess of cholecystectomy.

We have also failed to find a relationship between pancreatic cancer and either hysterectomy, oophorectomy, or dilatation and curettage. This is evidence against the association of pancreatic cancer with uterine and ovarian disorders noted in previous studies (Lin and Kessler 1981; Soloway and Sommers 1966).

The absence of a relationship between alcohol consumption and pancreatic cancer in this study is consistent with the results of several other investigations (Wynder et al. 1973; MacMahon et al. 1981; Blot et al. 1978).

The results of this study are limited by small numbers and by the limited information available in the patients' medical records. The relationship of thyroid disease to pancreatic cancer could be clarified in a large case-control series, with medical histories obtained by personal interview.

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