

Family History and the Risk of Liver, Gallbladder, and Pancreatic Cancer¹

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Abstract

The relationship between family history of selected neoplasms in first-degree relatives and the risk of pancreatic, liver, and gallbladder cancer was investigated using data from a case-control study conducted in northern Italy on 320 histologically confirmed incident cases of liver cancer, 58 of gallbladder cancer, 362 of pancreatic cancer, and 1408 controls admitted to the hospital for acute, nonneoplastic, nondigestive tract disorders. Significant associations were observed between family history of hepatocellular carcinoma and primary liver cancer [relative risk (RR) = 2.4; 95% confidence interval (CI), 1.3 to 4.4], between family history of pancreatic cancer and pancreatic cancer (RR = 3.0; 95% CI, 1.4 to 6.6), and between family history of gallbladder cancer and gallbladder cancer (RR = 13.9; 95% CI, 1.2 to 163.9). The elevated risk of liver cancer associated with family history was not materially modified by adjustment for tobacco, alcohol, and personal history of cirrhosis and hepatitis (RR = 2.9; 95% CI, 1.5 to 5.3). Similarly, the risk for pancreatic cancer did not appreciably change after allowance for tobacco, alcohol, dietary factors, and medical history of diabetes and pancreatitis (RR = 2.8; 95% CI, 1.3 to 6.3). This pattern of risk would support the existence of a genetic component in the familial aggregation of liver and pancreatic cancer. In terms of population attributable risk, approximately 3% of the newly diagnosed liver and pancreatic cancers would be related to this familial component.

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Introduction

Although several case reports and some formal epidemiological studies have addressed the issue of familial aggregation of pancreas (1–6), liver (7–11), and gallbladder cancer (12, 13), few of them have provided relative or population attributable risk estimates according to selected indicators of family history of cancer, after allowance for major recognized potential confounding factors.

Further, since there is consistent evidence that a few digestive tract cancers share some common risk factors, either environmental (14) or potentially genetic (15), combined analyses of the pattern of risk for different cancers may provide useful information.

We decided therefore to analyze family histories of selected neoplasms in a case-control study of pancreatic, liver, and gallbladder cancer conducted in northern Italy.

Subjects and Methods

The data were derived from an ongoing series of case-control studies, on the basis of a network of teaching and general hospitals in the Greater Milan area (*i.e.*, the largest urban area in northern Italy, with approximately 4 million inhabitants). Recruitment of cases of several digestive tract neoplasms and of the corresponding controls began in January 1983, and the present analysis is based on data collected before December 1992.

The general design of this investigation has been previously described (16, 17). In summary, trained interviewers identified and questioned cases of selected cancer sites and controls admitted to hospital using a structured questionnaire, including information on sociodemographic factors, personal characteristics, and lifestyle habits (such as smoking, alcohol, coffee, and other methylxanthine-containing beverage consumption), frequency of consumption of a few selected indicator foods, a problem-oriented medical history, and history of use of oral contraceptives and other female hormone preparations. A family history of cancer, including major digestive tract neoplasms (esophageal, stomach, large bowel, liver, gallbladder, and pancreatic), was specifically investigated for first-degree relatives.

Cases. The cases included in the present analysis were patients under 75 years of age with histologically confirmed incident (*i.e.*, diagnosed within the year before interview) cancers of the liver ($n = 320$: 235 males and 85 females), gallbladder ($n = 58$: 27 males and 31 females), and pancreas ($n = 362$: 229 males and 133 females). They were admitted to the National Cancer Institute, to several university hospitals, and to the Ospedale Maggiore of Milan, which includes the four largest teaching and general hospitals in Milan. All the interviews were conducted in hospital and restricted to identified surviving patients, in the absence of search for proxies for deceased ones. No information was collected on patients without pathological confirmation, or

Table 1 Distribution of 320 cases of liver cancer, 58 cases of gallbladder cancer, 362 cases of pancreatic cancer, and 1408 controls according to sex and age. Milan, Italy 1983–1992

	Liver cancer	Gallbladder cancer	Pancreatic cancer	Controls
	No. (%)	No. (%)	No. (%)	No. (%)
Sex				
Males	235 (73.4)	27 (46.6)	229 (63.3)	1031 (73.2)
Females	85 (26.6)	31 (53.4)	133 (36.7)	377 (26.8)
Age group (yr)				
<45	40 (12.5)	5 (8.6)	24 (6.6)	264 (18.8)
45–54	56 (17.5)	11 (19.0)	84 (23.2)	382 (27.1)
55–64	140 (43.8)	20 (34.5)	136 (37.6)	459 (32.6)
65–74	84 (26.2)	22 (37.9)	118 (32.6)	303 (21.5)
Total	320 (100)	58 (100)	362 (100)	1408 (100)

outside the network of participant hospitals. This, however, includes the major public hospitals in the area under investigation, where the large majority of patients with serious neoplasms is admitted. The median age was 60 years for liver, 61 years for gallbladder, and 60 years for pancreatic cancer cases.

Controls. The comparison group included 1408 patients (1031 males and 377 females) younger than 75 years (median age, 56 years) admitted for a wide spectrum of acute, nonneoplastic, nondigestive disorders to the Ospedale Maggiore and the same teaching hospitals where cases were recruited. Thirty-four % had traumatic conditions, 17% had nontraumatic orthopedic disorders, 37% had acute surgical conditions, and 12% had other miscellaneous diseases, such as ear, nose, and throat, skin, or dental disorders. The catchment area of cases and controls was comparable: more than 80% of cases and controls resided in the same region, Lombardy, and more than 90% came from Northern Italy. Participation rate was over 95% for both cases and controls. As for cases, all the data were collected by direct interview in hospital. The distribution of cases of various cancer sites and controls according to sex and age group is shown in Table 1.

Data Analysis. RR³ and the corresponding 95% CI of pancreatic, liver and gallbladder cancer, according to history of selected cancers among first-degree relatives were first computed using unconditional multiple logistic regression (18), including terms for age, sex, area of residence, and education. In addition, when significant associations were observed, further allowance was also made for selected variables (smoking habits, alcohol consumption, and selected medical history).

Results

The distribution of cases of liver, pancreatic, and gallbladder cancer, and of the comparison group, according to history in first-degree relatives of cancers of the esophagus, stomach, intestines, liver, gallbladder, and pancreas is shown in Table 2. Thirty-eight (2.8%) individuals in the control group

Table 2 Distribution of selected cancers in first degree relatives of 320 cases of liver cancer, 58 of gallbladder cancer, 362 of pancreatic cancer, and 1408 controls.^a Milan, Italy 1983–1992

Site of cancer in relatives	Liver cancer	Gallbladder cancer	Pancreatic cancer	Controls
	No. (%)	No. (%)	No. (%)	No. (%)
Esophagus	5 (1.6)		4 (1.1)	7 (0.5)
Stomach	16 (5.1)	3 (5.4)	14 (3.9)	38 (2.8)
Colorectum	9 (2.9)		6 (1.7)	22 (1.6)
Liver	19 (6.1)	2 (3.6)	9 (2.5)	34 (2.5)
Gallbladder		1 (1.8)	4 (1.1)	2 (0.1)
Pancreas		1 (1.8)	14 (3.9)	15 (1.1)

^a Information is missing for some individuals.

Table 3 RR^a and 95% CI of liver, gallbladder and pancreatic cancer according to history of selected cancers in first-degree relatives. Milan, Italy 1983–1992

Site of cancer in relatives	Liver cancer	Gallbladder cancer	Pancreatic cancer
	RR (95% CI)	RR (95% CI)	RR (95% CI)
Esophagus	2.4 (0.7–7.6)		2.4 (0.7–8.3)
Stomach	1.7 (0.9–3.2)	1.9 (0.5–6.5)	1.4 (0.7–2.7)
Intestines	2.0 (0.9–4.5)		1.2 (0.5–3.0)
Liver	2.4 (1.3–4.4)	1.2 (0.3–5.4)	0.9 (0.4–1.9)
Gallbladder		13.9 (1.2–163.9)	9.9 (2.4–41.8)
Pancreas		1.4 (0.2–11.7)	3.0 (1.4–6.6)

^a Adjusted for age, sex, area of residence, and education by multiple logistic regression.

reported a family history of stomach cancer, 34 (2.5%) of liver cancer, and 22 (1.6%) of large bowel cancer. Among cases, the highest proportions were observed for family history of liver cancer among patients with primary liver cancer (6.1%), for family history of stomach cancer among cases of liver cancer (5.1%), gallbladder cancer (5.4%), and pancreatic cancer (3.9%), and for family history of pancreatic cancer among pancreatic cancer cases (3.9%).

The corresponding RRs are given in Table 3. Statistically significant increased risks were observed between family history of hepatocellular carcinoma and family history of liver cancer (RR = 2.4) and between family history of pancreatic cancer and pancreatic cancer (RR = 3.0). A tendency of excess risk was observed for a family history of a number of other digestive sites, specifically for liver cancer with RRs of 1.7, 2.0, and 2.4 for family history of stomach, intestine, and esophageal cancer, respectively. None of these estimates, however, was significant. History of gallbladder cancer was reported by one case of gallbladder cancer and two controls, yielding a RR of 13.9, which, however, had a very wide confidence interval. The relationships between family history of liver cancer and the risk of hepatocellular carcinoma and between family history of pancreatic cancer and the risk of pancreatic cancer are further analyzed in terms of simultaneous allowance for several known or potential confounding factors and in separate strata of sex and age (Table 4). With reference to liver cancer, adjustment for smoking, alcohol consumption, history of cirrhosis, and hepatitis did not appreciably modify the risk estimate (RR = 2.9). No significant interaction emerged with sex or age. Similarly, for pancreatic cancer, adjustment for smoking habits, alcohol consumption, history of pancreatitis, and diabetes did not

³ The abbreviations used are: RR, relative risk estimate; CI, confidence interval.

Table 4 RR (and 95% CI) of liver cancer and pancreatic cancer according to family history of liver and, respectively, pancreatic cancer, sex, and age group. Milan, Italy 1983–1992

	Cases	Controls	RR (95% CI)
	No. (%)	No. (%)	
Liver cancer*			
Total	19 (6.1)	34 (2.5)	2.9 (1.5–5.3)
Sex			
Males	15 (6.4)	21 (2.0)	3.1 (1.5–6.3)
Females	4 (4.7)	13 (3.4)	1.6 (0.5–5.6)
Age group (yr)			
<60	9 (5.8)	22 (2.5)	2.3 (1.0–5.1)
≥60	10 (6.0)	12 (2.3)	3.0 (1.2–7.3)
Pancreatic cancer**			
Total	14 (3.9)	15 (1.1)	2.8 (1.3–6.3)
Sex			
Males	5 (2.2)	9 (0.9)	2.5 (0.8–7.9)
Females	9 (6.8)	6 (1.6)	3.9 (1.3–11.9)
Age group (yr)			
<60	6 (3.4)	11 (1.2)	2.2 (0.8–6.5)
≥60	8 (4.4)	4 (0.8)	4.0 (1.1–14.3)

* Adjusted for sex, age, area of residence, education, smoking habits, alcohol consumption, history of cirrhosis and hepatitis by multiple logistic regression.

** Adjusted for sex, age, area of residence, education, smoking habits, alcohol consumption, history of pancreatitis and diabetes by multiple logistic regression.

appreciably modify the overall estimate (RR = 2.8). Likewise, no interaction was observed with sex or age.

Discussion

The present analysis provides additional quantitative information on the existence of a familial component for liver, gallbladder, and pancreatic cancer. Liver and pancreatic cancers appear to be approximately 3-fold more frequent among patients with a positive history of the corresponding cancers. In terms of population attributable risk (19), approximately a 3% of the pancreatic and liver cancers would be related to this familial component. There was also some evidence of a familial aggregation for gallbladder cancer, although it is based on very small absolute numbers.

These findings are consistent with risk estimates from various other studies. Besides few reports of families or clusters of cancer (9, 11), a case-control study conducted in Taiwan (7) reported an elevated risk (RR = 4.6) of borderline significance for liver cancer associated with a positive family history of this cancer; the estimated population attributable risk was 3.5%. For pancreatic cancer, Ghadirian *et al.* (1) in a case-control study in Canada found an increased risk for the familial component (RR = 15.1; 95% CI, 2.0–311.2), in the absence of apparent differences in environmental risk factors between familial and nonfamilial cases.

Although an apparent association between the cancer sites studied and family history of the same neoplasms in first-degree relatives was observed in this as well as in previous studies (1–6), these results may be influenced by various sources of bias. Recall bias may have produced some overestimation of risk, since patients suffering from a specific cancer are more sensitized than noncancer patients toward recalling episodes of cancer in their relatives. Information

was restricted to first-degree relatives and collected through interview only, in the absence of a clinical or histological evidence of the diagnosis of cancer among relatives. Additional sources of information (from other relatives, or clinical notes) were searched only in the case of uncertainty on the presence and type of neoplasms. The absence of a generalized increased risk between various different cancer sites is suggestive of the existence of a real association for specific sites. In principle, cancer patients might tend to selectively assign the primary site of their cancer to tumors in relatives. However, most cancer patients in Italy have no precise information on their diagnoses during their hospital stay, and several patients even after hospital discharge. This potential bias, therefore, is unlikely to have played any major role.

The excess risk for liver and pancreatic cancer might be partly explained by misclassification, due to the difficulties in diagnosis of these neoplasms, and particularly, to the possibility of misclassification of liver metastasis as primary liver tumors. For these reasons, too, case identification was restricted to pathologically confirmed neoplasms, since serious misclassification can be induced by inclusion of clinical diagnosis of liver cancer. Among other strengths of the study, there are the practically complete participation, the comparable catchment area of cases and controls (*i.e.*, control individuals would have been referred, if affected by liver, gallbladder or pancreatic cancer, to the same hospitals where cases were identified), and the comparable setting of data collection (20). With reference to confounding, we were able to adequately allow for age, and a number of other potentially relevant covariates.

The present findings, therefore, indicate and quantify the presence of a significant family aggregation for both liver and pancreatic cancer. However, using this study design it was not possible to distinguish clearly between the environmental or genetic component of such a familial aggregation. For instance, with reference to liver cancer, the familial risk could be partly or largely due to family aggregation of hepatitis B infection, which is a major determinant of primary liver cancer (17, 21–23). For pancreatic cancer, at least part of the association could be related to tobacco smoking, which is a recognized risk factor for the disease (24) and tends to aggregate in families, too.

The risk estimates, however, were not materially modified after adjustment for major identified covariates, including tobacco, alcohol, and past medical conditions related to liver cancer (cirrhosis and hepatitis) or pancreatic cancer (pancreatitis and diabetes). This would, therefore, support, although indirectly, the existence of a genetic component in the familial aggregation of liver and pancreatic cancer.

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