

Medical History and Primary Liver Cancer¹

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ABSTRACT

The relationship between selected aspects of medical history and the risk of primary liver cancer was analyzed in a hospital-based case-control study conducted in Northern Italy on 242 patients with histologically or serologically confirmed hepatocellular carcinoma and 1169 controls in hospital for acute, nonneoplastic, or digestive diseases. Significant associations were observed for clinical history of hepatitis [odds ratio (OR), 3.7; 95% confidence interval (CI), 2.3-5.9], cirrhosis (OR, 16.8; 95% CI, 9.8-28.8), and three or more episodes of transfusion in the past (OR, 2.2; 95% CI, 1.4-4.1). Among other diseases considered, there was a significant association with diabetes (OR, 2.5; 95% CI, 1.7-3.8), and a protection by history of drug allergies (OR, 0.5; 95% CI, 0.2-0.9). These associations were not appreciably modified by allowance for major identified potential confounding factors and were observed for diseases occurring less than 5 or 5 or more years before liver cancer diagnosis, although for cirrhosis the risk was higher in the short term occurrences (OR, 50). For hepatitis, the association was more evident at older ages, confirming the long lead time between infection and cancer occurrence, while for diabetes it was stronger (or restricted) to cases aged less than 60, suggesting a possible specific role of type I diabetes. While for hepatitis, cirrhosis, and blood transfusion this study offers further quantitative estimates of risk in a European population, the possible direct association with diabetes and protection by drug allergy were unexpected, lacked plausible biological or previous epidemiological support, and should be simply regarded as working hypotheses for further work.

INTRODUCTION

Primary liver cancer is associated with several liver diseases, including hepatitis (1-9), cirrhosis (2, 10), as well as disturbances of heme synthesis and hence porphyrin metabolism related to porphyrias (11). There is, however, still uncertainty about the strength of the association in different populations. With reference to hepatitis B virus infection, for instance, the relative risks reported from Taiwan are on the order of 100 (1, 7), with a range of variation between 20 and 200, while in European and Northern American populations the relative risks are on the order of 10 and range between 5 and 15 (2-5, 8). Only scanty information, moreover, is available on other aspects of past medical history and liver cancer.

To shed further light on the issue, we consider in this article selected aspects of medical history in the risk of primary liver cancer, using data from a case-control study from Northern Italy.

SUBJECTS AND METHODS

The data considered were derived from an ongoing study of digestive tract neoplasms, based on a network of teaching and general hospitals in the Greater Milan area. Recruitment of cases of liver cancer started in January 1984, and the present article is based on data collected up to December 1989.

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The general structure of this investigation has already been described (12). Briefly, trained interviewers identified and questioned cases and controls in the major teaching and general hospitals of the Greater Milan area. The structured questionnaire included information on sociodemographic characteristics, smoking habits, alcohol drinking, intake of coffee and 14 selected indicator foods, and a problem-oriented medical history including 12 selected diseases or interventions. By definition, the diseases or interventions considered had to anticipate by at least 1 year the onset of the symptoms of the disease which led to admission. Age at onset of each condition was recorded. On the average, less than 2% of cases and controls refused to be interviewed.

The cases included in the present analysis were patients below the age of 75 years with histologically or serologically (elevated α -fetoprotein levels) confirmed hepatocellular carcinoma diagnosed within the year preceding the interview, after specific exclusion of all metastatic or undefined liver neoplasms, admitted to the National Cancer Institute, several university clinics (chiefly of surgery), and the Ospedale Maggiore of Milan. A total of 242 cases (180 males, 62 females) ages 22 to 74 years (median age, 57 years) were interviewed.

The comparison group consisted of 1169 subjects (875 males, 294 females) admitted to the same network of hospitals for acute, nonneoplastic or digestive diseases, unrelated to alcohol or tobacco consumption. The age range was 21 to 74 years, and the median age was 55 years. Thirty-two % were admitted for trauma, 15% were seen for nontraumatic orthopedic conditions, 39% had acute surgical diseases, and 14% had other miscellaneous disorders, including acute infections, skin, eye diseases, etc. The catchment area of cases and controls was comparable: 80% of the cases and 83% of the controls resided in the same region, Lombardy; 90% of the cases and 94% of the controls came from Northern Italy.

ORs² and the corresponding 95% CI (13) according to various aspects of medical history were first computed from data stratified for sex and decade of age using stratification and the Mantel-Haenszel procedure (14). Secondly, to account simultaneously for the potential confounding effect of various risk factors, unconditional multiple logistic regression, with multiple likelihood fitting, was used (13, 15). All the regression equations reported included terms for age, sex, area of residence, education, smoking, and alcohol consumption.

RESULTS

Table 1 gives the distribution of liver cancer cases and the comparison group according to sex, age group, education, and alcohol consumption. Cases were slightly older than controls, significantly less educated (χ^2 , for trend, 12.71; $P < 0.001$), and more frequently heavy drinkers (OR for >6 drinks/day, 1.6; 95% CI, 1.1-2.2).

In Table 2, the relationship between liver cancer and selected aspects of medical history is considered. Twelve % of cases *versus* 4% of the controls gave a clinical history of hepatitis; the corresponding odds ratio was 3.7, with 95% CI 2.3-5.9. Serological markers of hepatitis B virus were not determined in this study. Liver cirrhosis was reported by 15% of the cases *versus* 1% of the controls, for an OR of 16.8 (95% CI 9.8-28.8).

Significantly more cases than controls (15% *versus* 6%) had a history of diabetes mellitus. The age-adjusted OR was 2.5, and the 95% CI was 1.7-3.8. No significant association was observed between thyroid disease, gastroduodenal ulcer, pan-

² The abbreviations used are: OR, odds ratio; CI, confidence interval.

Table 1 *Distribution of 242 cases of liver cancer and 1169 controls according to sex, age group, education, and alcohol consumption, Milan, Italy, 1984-1989*

	Liver cancer		Controls	
	No.	%	No.	%
Sex				
Males	180	74.4	875	74.9
Females	62	25.6	294	25.1
Age (yr)				
<45	36	14.9	235	20.1
45-54	47	19.4	330	28.2
55-64	98	40.5	353	30.2
65-74	61	25.2	251	21.5
Education				
<7	151	62.4	552	47.2
7-11	52	21.5	349	29.9
≥12	37	15.3	260	22.2
Unknown	2	0.8	8	0.7
Total alcohol consumption (drinks/day)				
0	60	24.8	205	17.5
<4	76	31.4	525	44.9
4-6	46	19.0	237	20.3
>6	58	24.0	198	16.9
Unknown	2	0.8	4	0.3

Table 2 *Relation of liver cancer with selected aspects of medical history among 242 cases and 1169 controls, Milan, Italy, 1984-1989*

Type of disease or intervention	No. (%) of subjects with the disease		Relative risk estimates (95% CI)	
	Liver cancer	Controls	M-H ^a	MLR
Cholelithiasis	22 (9.1)	82 (7.0)	1.3 (0.8-2.1)	1.2 (0.7-2.0)
Hepatitis	30 (12.4)	45 (3.8)	3.7 (2.3-5.9)	3.1 (1.8-5.2)
Liver cirrhosis	36 (14.9)	11 (0.9)	16.8 (9.8-28.8)	14.1 (6.8-28.9)
Diabetes	37 (15.3)	68 (5.8)	2.5 (1.7-3.8)	2.4 (1.5-3.7)
Thyroid disease	8 (3.3)	34 (2.9)	1.1 (0.5-2.6)	1.1 (0.5-2.6)
Gastric ulcer	13 (5.4)	46 (3.9)	1.4 (0.7-2.6)	1.5 (0.8-2.8)
Duodenal ulcer	18 (7.4)	95 (8.1)	0.9 (0.5-1.5)	0.9 (0.5-1.5)
Gastrectomy	7 (2.9)	24 (2.1)	1.4 (0.6-3.3)	1.4 (0.6-3.6)
Pancreatitis	5 (2.1)	16 (1.4)	1.6 (0.6-4.3)	1.7 (0.6-5.0)
Appendectomy	84 (34.7)	374 (32.0)	1.2 (0.9-1.6)	1.2 (0.8-1.6)
Drug allergy	10 (4.1)	99 (8.5)	0.5 (0.2-0.9)	0.5 (0.3-1.0)
Blood transfusions	32 (13.2)	108 (9.2)	1.4 (0.9-2.2)	1.3 (0.9-2.1)

^a M-H, Mantel-Haenszel estimates adjusted for age and sex; MLR, estimates from multiple logistic regression equations including terms for age, sex, area of residence, education, smoking, and alcohol consumption.

creatitis or appendectomy, and primary liver cancer. Drug allergy was apparently protective, being reported by 4% of the cases and 9% of the controls, with an odds ratio of 0.5 (95% CI, 0.2-0.9). Subjects who ever had received blood transfusions had an OR of 1.4 (95% CI, 0.9-2.2). None of the estimated odds ratios was appreciably modified by allowance for major identified potential confounding factors using multiple logistic regression.

The four diseases showing significant associations with primary liver cancer (hepatitis, cirrhosis, diabetes, and drug allergy) were further considered in Table 3 in relation to time elapsed since diagnosis. For liver cirrhosis, the risk was higher among subjects whose diagnosis dated since less than 5 years (OR = 50 *versus* 11 for ≥5 years), confirming the frequent short-term occurrence in diagnosis of hepatocarcinoma and cirrhosis. In contrast, for hepatitis, diabetes and drug allergy,

Table 3 *Relation of liver cancer with selected diseases according to time since diagnosis among 242 cases and 1169 controls, Milan, Italy, 1984-1989*

Disease	Yr since diagnosis	No. (%) of subjects with the disease		Relative risk estimates (95% CI)	
		Liver cancer	Controls	M-H ^a	MLR
Hepatitis	<5	6 (2.5)	8 (0.7)	4.4 (1.6-12.1)	4.0 (1.3-12.0)
	≥5	21 (8.7)	37 (3.2)	3.4 (1.9-5.9)	2.5 (1.4-4.6)
Liver cirrhosis	<5	20 (8.3)	2 (0.2)	50.3 (20.8-121.3)	44.7 (10.9-183.8)
	≥5	16 (6.6)	8 (0.7)	11.0 (5.2-23.0)	8.5 (3.4-20.8)
Diabetes	<5	12 (5.0)	21 (1.8)	2.9 (1.4-5.8)	2.8 (1.3-6.0)
	≥5	25 (10.3)	46 (3.9)	2.4 (1.4-3.9)	2.2 (1.3-3.8)
Drug allergy	<5	3 (1.2)	22 (1.9)	0.6 (0.2-2.1)	0.7 (0.2-2.2)
	≥5	7 (2.9)	70 (6.0)	0.6 (0.3-1.4)	0.5 (0.2-1.2)

^a M-H, Mantel-Haenszel estimates adjusted for age and sex; MLR, estimates from multiple logistic regression equations including terms for age, sex, area of residence, education, smoking, and alcohol consumption, plus the above listed diseases.

Table 4 *Relation of liver cancer with selected conditions according to age among 242 cases and 1169 controls, Milan, Italy, 1984-1989*

Disease	Patients' age (yr)	No. (%) of subjects with the disease		Relative risk estimates (95% CI)	
		Liver cancer	Controls	M-H ^a	MLR
Hepatitis	<60	12 (9.2)	28 (3.7)	2.7 (1.4-5.2)	2.9 (1.4-6.1)
	≥60	18 (16.1)	17 (4.1)	5.1 (2.6-9.9)	4.1 (1.9-8.9)
Liver cirrhosis	<60	14 (10.8)	6 (0.8)	14.3 (6.8-30.0)	12.6 (4.5-35.6)
	≥60	22 (19.6)	5 (1.2)	19.1 (8.9-41.1)	13.2 (4.7-37.0)
Diabetes	<60	16 (12.0)	19 (2.5)	5.7 (3.1-10.4)	4.9 (2.4-10.3)
	≥60	20 (17.9)	49 (11.7)	1.6 (0.9-2.8)	1.6 (0.9-2.9)
Drug allergy	<60	3 (2.3)	71 (9.5)	0.2 (0.1-0.6)	0.2 (0.1-0.7)
	≥60	7 (6.3)	28 (6.7)	0.9 (0.4-2.3)	1.1 (0.4-2.7)
Blood transfusion(s)	<60	18 (13.8)	63 (8.3)	0.7 (0.4-1.5)	0.8 (0.4-1.5)
	≥60	14 (12.5)	45 (10.8)	2.1 (1.2-3.8)	2.2 (1.2-4.0)

^a M-H, Mantel-Haenszel estimates adjusted for age and sex; MLR, estimates from multiple logistic regression equations including terms for age, sex, area of residence, education, smoking, and alcohol consumption, plus the above listed diseases.

the association was comparable for diagnoses dating back for short or long periods before the appearance of liver cancer.

Similar analyses were reproduced in Table 4 according to strata of age at diagnosis of liver cancer or interview. For cirrhosis and, chiefly, for blood transfusions and hepatitis, the association was apparently stronger at older ages (above 60 years). In contrast, the elevated risk for diabetes and the protection for drug allergy were more evident in patients less than 60 years old. When age at diagnosis of the disease was considered, the risk was higher for diabetes diagnosed below age 40 (OR, 5.4; 95% CI, 1.8-16.5).

In relation to the number of episodes of blood transfusion (Table 5), compared with subjects who never reported transfusions in the past, the risk was not elevated up to two episodes,

Table 5 *Relation of liver cancer with number of blood transfusion among 242 cases and 1169 controls, Milan, Italy, 1984-1989*

No. of blood transfusions	No. (%) of subjects reporting transfusions		Relative risk estimates (95% CI)	
	Liver cancer	Controls	M-H ^a	MLR
0	210 (86.8)	1061 (90.8)	1	1
1	9 (3.7)	37 (3.2)	1.2 (0.6-2.6)	1.0 (0.5-2.2)
2	9 (2.5)	31 (2.7)	0.9 (0.4-2.1)	0.9 (0.4-2.2)
≥3	17 (7.0)	40 (3.4)	2.2 (1.2-4.1)	2.0 (1.1-3.7)
χ^2 (trend)			3.88 (p = 0.05)	3.64 (p = 0.06)

^a M-H, Mantel-Haenszel estimates adjusted for age and sex; MLR, estimates from multiple logistic regression equations including terms for age, sex, area of residence, education, smoking, and alcohol consumption and clinical history of hepatitis.

but rose to 2.2 (with 95% CI 1.2-4.1) for three or more episodes. The trend in risk with number of blood transfusions was of borderline statistical significance. As for previous variables, simultaneous allowance for a number of identified potential distorting factors, including history of hepatitis, by multiple logistic regression did not materially change any of the estimates. The fact that clinical history of hepatitis failed to largely account for the association with blood transfusions is probably due, at least in part, to the imprecise information available on this variable.

DISCUSSION

The findings from this investigation confirm that hepatocellular carcinoma is strongly associated to liver cirrhosis and hepatitis (1-10) and suggest that diabetes may be directly related to primary liver cancer while drug allergy may be protective. Further, repeated episodes of blood transfusion are an indicator of elevated risk, which is not totally explained by clinical history of hepatitis and hence probably explicable in terms of subclinical hepatitis B, or other hepatitis virus, infection.

This study has some obvious limitations, including the fact that it was not population based; therefore we had no information on total number of incident liver cancers, and on cases that died before they could be approached for interview. Nonetheless, its hospital-based design probably represents an optimal framework for investigating medical histories. Cases and controls, in fact, are similarly sensitized towards recalling diseases which occurred in the past; a reliability analysis of personal interview data from a large hospital-based case-control study conducted in the United States, Canada and Israel, for instance, found an intraclass correlation between repeated interviews of 0.93 for diabetes and good reliability for all medical conditions or procedures requiring hospital admission or continuing medical care (16). Further, the estimated disease prevalences in this study were comparable with those obtained from the 1983 Italian National Health Survey, based on a sample of 90,000 subjects representative of the whole Italian population (17). Among other strengths of the study, there was the almost complete participation rate and the comparable catchment area of cases and controls, as well as the absence of important confounding by a number of selected covariates.

Still, the absence of information on hepatitis B virus serology probably led to imprecise definition of exposure, and hence to underestimation of the true risk. Nonetheless, the relative risk of 3.7, with an upper confidence limit of 5.9, is comparable with other estimates from European populations, based on

hepatitis B surface antigen or other serum markers of hepatitis B infection (2, 5, 8). This further confirms that the risk of hepatocellular carcinoma for exposure to hepatitis B is lower in European [and, probably, in American (4)] populations as compared to East Asia, where relative risks of the order of 20-100 are observed. This suggests that there is some important modifying effect of dietary factors, or other covariates, in the hepatitis B-liver cancer association. In a subset of this study, in fact, a diet deficient in several aspects, including vitamin A and proteins, was associated with elevated risk of hepatocellular carcinoma (12). Of further interest is the higher relative risk at older ages, which may be taken as a further confirmation of an initiating (early stage) (18) effect of hepatitis B virus on liver carcinogenesis, requiring a long time between exposure and occurrence of the disease.

For cirrhosis, the estimates of this study were in close agreement with those observed in a case-control study from Greece (OR, 13.7; 95% CI, 8.0-23.5) (8). Although the relative risk was highest (OR, 70.5; 95% CI, 25.1-198) for subjects reporting history of both hepatitis and cirrhosis, it is difficult to disentangle the separate effect of each factor, since cirrhosis may represent one step of hepatitis-induced liver damage.

If for hepatitis or cirrhosis the present data eventually provide further quantitative assessment of well known associations, the two other significant results which emerged (the elevated risk for diabetes, the protection for drug allergy) should be essentially viewed as working hypotheses for further study.

Only scattered information is available on the potential relationship between diabetes and primary liver cancer. No association was found in a case-control study from Taiwan (7), and in a cohort of diabetics the incidence of liver cancer was not higher than expected [although the statistical power of the latter study was limited, with a standardized mortality ratio of 0.9 for males, based on 15 deaths, and 1.2 for females, based on 35 deaths (19)]. Similarly, no association emerged in a smaller cohort of diabetics from Rochester, MN (20), or in a prospective study of individuals of higher post-load plasma glucose level (21). Further, no obvious biological interpretation is available and selection bias is possible, if patients with diabetes who develop liver cancer tend to die earlier and therefore cannot be interviewed. Nonetheless the time-risk relationships of this study deserve some attention, since the OR was similarly elevated for diabetes occurring less than 5 or 5 or more years before liver cancer diagnosis (or interview), hence excluding a role of impaired liver functionality due to the neoplastic process. Further, the elevated risk for diabetes was restricted to younger ages, the estimates were significantly heterogeneous below or above age 60 years and the risk was higher for diabetes diagnosed before age 40 years. This would suggest that the association is specific for type I insulin-dependent diabetes.

Likewise, little published information is available in favor of or against the possible protection of allergies on liver cancer risk, and the sole potential interpretation could be linked to aspecific immunological stimulation induced by allergic conditions. Similar protective effects are seen for asthma, allergic skin reactions, or allergic diseases in general in relation to pancreatic cancer risk (22, 23), but these results still require confirmation. Thus, it is important, although probably superfluous, to stress again that this possible protection, as well as the direct association with diabetes, should be interpreted with great caution at the present time.

In conclusion, this study has offered further quantitative assessment of the relationship between blood transfusion, hepatitis and cirrhosis, and hepatocellular carcinoma in an Euro-

pean population, as well as finding unexpected associations with diabetes (direct) and drug allergy (inverse), which may be worth further investigation.

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