Pergamon

European Journal of Cancer Vol. 33, No. 4, pp. 629–634, 1997

Printed in Great Britain
0959-8049/97 $17.00 + 0.00

PII: S0959-8049(96)00500-X

Original Paper

Attributable Risks for Hepatocellular Carcinoma in Northern Italy

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The population attributable risks (ARs) for hepatocellular carcinoma (HCC) were estimated in relation to low education level, heavy alcohol consumption, low vegetable and fruit intake, history of hepatitis, diabetes, liver cirrhosis and oral contraceptive use, using data from a case-control study conducted between 1984 and 1993 in Northern Italy. Cases were 320 patients (235 males and 85 females) with histologically or serologically confirmed HCC, and controls were 1408 patients (1031 males and 377 females) admitted to the same network of hospitals for acute, non-neoplastic or non-digestive tract conditions, unrelated to any of the known or likely risk factors for primary liver cancer. The ARs were 40% for low vegetable and fruit consumption, 31% for low education, 18% for liver cirrhosis, 16% for hepatitis, 8% for diabetes and 7% for heavy alcohol consumption. Together, these factors explained 74% of hepatocellular cancer cases. Compared with females, males had higher ARs for cirrhosis (21% versus 11%), diabetes (10% versus 2%) and heavy alcohol consumption (9% versus 1%). The percentage of HCC attributable to all factors considered together was 78% for males and 67% for females. Thus, even if available information on hepatitis and dietary factors was limited, and the AR estimates were based on several arbitrary assumptions, available knowledge could, in principle, reduce the burden of the disease in Italy from 3300 deaths to approximately 750 for males, and from 1600 to approximately 500 for females. © **1997 Elsevier Science Ltd. All rights reserved.**

Key words: liver neoplasms, attributable risks, case-control studies

Eur J Cancer, Vol. 33, No. 4, pp. 629–634, 1997

INTRODUCTION

PRIMARY LIVER cancer is one of the most common neoplasms in the world [1]. On a worldwide scale, however, there is a substantial variation in its incidence and mortality, with highest rates observed in the Far East, particularly in China, but also in Japan [2]. The geographical distribution of hepatocellular carcinoma (HCC), and the pattern of its occurrence in migrant populations [3], indicate that this neoplasm is caused, in the majority of cases, by environmental agents. Incidence and mortality are much lower in Western countries, but in Italy liver neoplasia is the ninth cause of cancer mortality in the two sexes combined, with overall age-standardised (world) rates of 7.5/100 000 males and 2.4/100 000 females in 1991 [4].

Most epidemiological studies have focused on HCC, the histological type that accounts for over 90% of all cases of primary liver cancer worldwide, leading to the identification of a number of well-defined risk factors [5, 6]. There are strong associations with hepatitis B and C viruses (HBV, HCV) [7], with perinatal and early childhood infections, major risk factors for chronicity and indicators of long-term exposure to the agent, explaining, at least in part, the stronger relationship observed in Asia, as compared to Europe and North America, where infections are believed to occur later in life [5].

Dietary factors play an important role in liver carcinogenesis also. These include aflatoxin [8–10], alcohol [11–13], and a diet poor in several aspects, including selected micro-

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Received 25 Jul. 1996; revised 11 Oct. 1996; accepted 28 Nov. 1996.

nutrients [14, 15]. Evidence has also been collected that oral contraceptives (OC) increase the risk of primary liver cancer among women from developed countries [6, 16, 17].

However, from a public health viewpoint, the impact of various risk factors depends not only on the strength of the associations, but also on the distribution of the exposures in the population [18]. Moreover, some of the risk factors are more prevalent among men than among women, suggesting that the ratio of male to female incidence and mortality is, at least in part, explainable through the different risk patterns of exposure in the two sexes.

To provide further quantitative data on this issue, we analysed the role of education, alcohol, selected indicator foods, oral contraceptives, hepatitis, diabetes and cirrhosis on the attributable risk of hepatocellular carcinoma in males and females in Northern Italy, using data from a case-control study.

MATERIALS AND METHODS

The data were derived from a case-control study of several 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 report is based on data collected up to February 1993. The general design of this investigation has already been described [19].

Cases

Cases were patients below the age of 75 years with histologically or serologically (elevated alpha-fetoprotein levels) confirmed hepatocellular carcinoma diagnosed within the year before the interview, after specific exclusion of all metastatic or undefined liver neoplasms. They were admitted to the National Cancer Institute, to several university clinics (chiefly of surgery) and to the Ospedale Maggiore of Milan. A total of 320 cases (235 males, 85 females) aged 24–74 years (median age 60 years) were interviewed.

Controls

Controls were patients below 75 years of age admitted for a wide spectrum of acute conditions to the Ospedale Maggiore and to several specialised university clinics. Specifically excluded from the comparison group were patients whose diagnosis, leading to the current admission, was of malignant disorders, of any digestive tract disease, and of any condition related to tobacco and alcohol consumption, or which might have resulted in long-term modification of the diet. A total of 1408 controls aged between 22 and 74 years (median age 56 years) were interviewed. Of these, 1031 were males and 377 females; 34% were admitted for traumatic conditions (mostly fractures and sprains), 17% for non-traumatic orthopaedic diseases (mostly low back pain and disc disorders), 37% for acute surgical conditions, and 12% for other miscellaneous illnesses, such as ear, nose and throat, skin and dental disorders. The catchment areas of cases and controls were comparable: over 80% resided in Lombardy, and over 90% came from Northern Italy. Information was collected only through direct interview, and no proxy was searched for deceased or subjects too ill to be interviewed. Less than 3% of eligible subjects (cases and controls) refused to be interviewed.

Trained interviewers used a structured questionnaire to collect data on sociodemographic indicators, personal characteristics and habits, such as smoking, alcohol and coffee consumption, selected indicator foods, a problem-oriented personal and family medical history (including age at first diagnosis), history of use of selected drugs and, for women, menstrual and reproductive history. Diagnoses (e.g. liver cirrhosis) that coincided or were prompted by examinations connected with the diagnosis of HCC were not considered.

Information on alcohol included the number of days per week and the number of drinks per day for each type of alcoholic beverage (wine, beer, spirits) and the duration of the habit in years. As an indicator of alcohol consumption, the average number of all alcoholic drinks per day was derived. As an index of the quality of the diet, the total frequency of consumption per week of carrots, green vegetables and fresh fruit was computed.

Data analysis

Odds ratios (ORs) of HCC, and the corresponding 95% confidence intervals (CIs), were computed, for all subjects and in separate strata of sex, using two unconditional logistic regression models [20]. Both included terms for sex (whenever appropriate), age, area of residence (Lombardy versus other) and smoking status (never/current/ex). In addition, model A included terms for education ($<7/\geq 7$ years), clinical history of hepatitis (no/yes), total alcoholic beverage consumption ($\leq 6/>6$ drinks per day for males, $<4/\geq 4$ for females), and oral contraceptive use (never/ever), while model B included additional terms for total carrots, green vegetables and fresh fruit consumption (approximate tertiles on cases and controls combined), clinical history of diabetes (no/yes) and liver cirrhosis (no/yes).

Using the distribution of the risk factors in the cases and the risk estimates from the two models, population attributable risks (ARs) were computed, i.e. the proportion of HCC that would have been avoided if a given exposure had not been present in the population. The method, described by Bruzzi and associated [21], implies knowledge of the risks estimates and of the joint distribution of the risk factors among cases only, and thus can be used for data of hospital-based case-control studies, provided that cases are representative of the whole diseased population. The corresponding variance calculations and 95% confidence intervals (CIs) were obtained, whenever computable [22, 23]. Since the logistic model assumes a multiplicative effect of the ORs, the AR for combinations of two or more factors may not be equal to the sum of the ARs for each risk factor, whenever the cases are exposed to two or more risk factors together.

RESULTS

Table 1 gives the distribution of cases and controls in strata of sex according to age and other selected variables. Cases were less educated than controls, more frequently heavy (>6 drinks/day males; ≥4 drinks/day females) drinkers, reported a lower consumption of vegetables and fruit, and more frequently, history of hepatitis, diabetes and liver cirrhosis. Among females, a larger proportion of cases than controls reported ever use of oral contraceptives.

The corresponding ORs are given in Table 2. Low education was associated with an OR of 1.87 (95% CI 1.4–

Table 1. Distribution of 320 cases of hepatocellular carcinoma and 1408 controls according to sex and selected risk factors

	Males		Females	
	Cases No. (%)	Controls No. (%)	Cases No. (%)	Controls No. (%)
Total	235	1031	85	377
Age (years)				
<40	10 (4.3)	110 (10.7)	11 (12.9)	36 (9.6)
40–49	24 (10.2)	229 (22.2)	10 (11.8)	60 (15.9)
50–59	75 (31.9)	349 (33.9)	24 (28.2)	105 (27.9)
60–69	109 (46.4)	256 (24.8)	31 (36.5)	116 (30.8)
70–74	17 (7.2)	87 (8.4)	9 (10.6)	60 (15.9)
Smoking status				
Never smokers	66 (28.1)	265 (25.7)	74 (87.1)	261 (69.2)
Current smokers	93 (39.6)	505 (49.0)	10 (11.8)	82 (21.8)
Ex smokers	76 (32.3)	261 (25.3)	1 (1.2)	34 (9.0)
Education (years)*				
<7	151 (64.5)	473 (46.2)	58 (69.1)	196 (52.3)
⩾7	83 (35.5)	552 (53.9)	26 (31.0)	179 (47.7)
Total alcoholic beverage consumption*†				
Low	181 (78.0)	870 (84.7)	80 (94.1)	356 (94.7)
Heavy	51 (22.0)	157 (15.3)	5 (5.9)	20 (5.3)
Vegetable and fruit consumption (tertiles)*				
High	50 (21.3)	340 (33.0)	22 (25.9)	132 (35.1)
Medium	90 (38.3)	326 (31.7)	29 (34.1)	146 (38.8)
Low	95 (40.4)	363 (35.3)	34 (40.0)	98 (26.1)
Oral contraceptive use				
Never			76 (89.4)	352 (93.4)
Ever			9 (10.6)	25 (6.6)
History of hepatitis				
No	190 (80.9)	993 (96.3)	70 (82.4)	360 (95.5)
Yes	45 (19.2)	38 (3.7)	15 (17.7)	17 (4.5)
History of diabetes				
No	197 (83.8)	974 (94.5)	74 (87.1)	352 (93.4)
Yes	38 (16.2)	57 (5.5)	11 (12.9)	25 (6.6)
History of liver cirrhosis				
No	185 (78.7)	1023 (99.2)	75 (88.2)	373 (98.9)
Yes	50 (21.3)	8 (0.8)	10 (11.8)	4 (1.1)

*The totals for this variable do not add up to the overall totals because of some missing values. †Categories were ⩽6 and >6 drinks per day for males, <4 and ⩾4 drinks per day for females

2.5), heavy alcohol consumption with an OR of 1.67 (95% CI 1.2–2.4), while the OR for the lowest tertile of vegetable and fruit consumption was 2.16 (95% CI 1.5–3.1). ORs were 5.99 (95% CI 4.0–9.0) for hepatitis, 2.10 (95% CI 1.4–3.3) for diabetes and 28.78 (95% CI 14.7–56.5) for cirrhosis. A somewhat stronger effect was observed in males than females in relation to diabetes and liver cirrhosis. For females, the OR was 3.06 (95% CI 1.2–8.1) for ever versus never use of oral contraceptives. None of the interaction terms for sex was significant. The ORs were 2.07 for diabetes diagnosed before 50 years of age, and 2.10 for diabetes diagnosed at age 50 years or over.

Table 3 gives the AR percentages and the corresponding 95% CIs for the whole dataset. These were 40% for low vegetable and fruit consumption, 31% for low education, 18% for liver cirrhosis, 16% for hepatitis, 8% for diabetes and 7% for alcohol. The AR was 3% for diabetes diagnosed below the age of 50 years (i.e. most likely type I insulin-dependent diabetes) and 6% for diabetes diagnosed at the age of 50 years or over (i.e. most likely type II, non-insulin-dependent diabetes). Education, hepatitis and alcohol together accounted for 44% of cases, while low vegetable and fruit consumption, liver cirrhosis and diabetes accounted for 56% of cases. All the factors considered together accounted for 74% of cases.

The corresponding ARs in separate strata of sex are given in Table 4. Compared with females, males had higher ARs for liver cirrhosis (21% versus 11%) and diabetes (10% versus 2%). In males, alcohol accounted for 9% of cases, but had a negligible role in women (1%). In females, OC accounted for 7% of cases, and 13% below 60 years of age. On the whole, the proportions of HCC attributable to all factors considered were 78% in males and 67% in females.

DISCUSSION

According to the present estimates, approximately three-quarters of HCC cases in Northern Italy could be explained by a few risk indicators, including low vegetable and fruit consumption, low education, history of liver cirrhosis, hepatitis and diabetes, and heavy alcohol consumption. The estimated ARs were 78% in males and 67% in females including OC use.

The absence of markers for HBV and HCV infections is a major limitation of this study. Since viral hepatitis is often asymptomatic, the present estimates for hepatitis are likely to be underestimated. In any case, the relative risks of hepa-

Table 2. Estimated odds ratios (ORs) of hepatocellular carcinoma and 95% confidence intervals (CIs) for the risk factors considered

	All subjects	Sex	
		Males	Females
Education (years)*			
<7	1§	1§	1§
⩾7	1.87 (1.4–2.5)	1.84 (1.3–2.5)	1.83 (1.0–3.3)
Total alcoholic beverage consumption*‡			
Low	1§	1§	1§
Heavy	1.67 (1.2–2.4)	1.68 (1.1–2.4)	1.30 (0.4–3.8)
Oral contraceptive use*			
Never			1§
Ever			3.06 (1.2–8.1)
History of hepatitis*			
No	1§	1§	1§
Yes	5.99 (4.0–9.0)	6.53 (4.0–10.6)	5.97 (2.7–13.3)
Vegetable and fruit consumption (tertiles)†			
High	1§	1§	1§
Medium	1.97 (1.4–2.8)	2.34 (1.5–3.6)	1.40 (0.7–2.7)
Low	2.16 (1.5–3.1)	2.18 (1.4–3.3)	2.22 (1.2–4.3)
History of diabetes†			
No	1§	1§	1§
Yes	2.10 (1.4–3.3)	2.49 (1.5–4.1)	1.23 (0.5–3.0)
History of liver cirrhosis†			
No	1§	1§	1§
Yes	28.78 (14.7–56.5)	38.76 (16.9–89.1)	16.50 (4.5–60.2)

*Estimates from multiple logistic regression models including terms for sex (when appropriate), age, area of residence, smoking status, education, total alcoholic beverage consumption, oral contraceptive use (for females only) and history of hepatitis. †Estimates from multiple logistic regression models including terms for sex (when appropriate), age, area of residence, smoking status, total carrot, green vegetable and fresh fruit consumption, history of diabetes and of liver cirrhosis. ‡Categories were ⩽6 and >6 drinks per day for all subjects and males, <4 and ⩾4 drinks per day for females. §Reference category.

titis from European studies appear consistently lower than those from South East Asia, possibly due to later age at infection [7]. In spite of these limitations, a clinical history of hepatitis accounted for 16% of HCC cases in this population. The importance of this factor in Italy should decline in the future, since the prevalence of HBV infection has been declining, as suggested by the decrease in prevalence of HBV core antibodies among male army recruits from 16.8% in 1981 to 5.8% in 1990 [24].

Table 3. Attributable risks percentage of hepatocellular carcinoma in relation to selected risk factors and some combinations

Factor	Attributable risk percentage and 95% CI*
Vegetable and fruit	40 (26–54)
Education	31 (19–42)
Liver cirrhosis	18 (14–22)
Hepatitis	16 (11–20)
Diabetes	8 (3–13)
Alcohol	7 (2–12)
Vegetable and fruit + liver cirrhosis + diabetes	56
Vegetable and fruit + liver cirrhosis	54 (42–66)
Vegetable and fruit + diabetes	51 (37–65)
Education + hepatitis + alcohol	44 (32–56)
Education + hepatitis	40 (29–52)
Education + alcohol	35 (23–47)
Liver cirrhosis + diabetes	24 (18–29)
Hepatitis + alcohol	22 (15–28)
All factors	74

*Whenever possible, because of computational constraints

Liver cirrhosis, usually macronodular of postnecrotic, is found in a large proportion of HCC cases [25, 26]. The lower proportions of liver cirrhosis (22% in men and 12% in women) found in our cancer patients refer to diagnosis before cancer diagnosis or related diagnostic procedures. It

Table 4. Attributable risks percentage of hepatocellular carcinoma in strata of sex in relation to selected risk factors and some combinations

Factor	Attributable risk percentage and 95% CI*	
	Males	Females
Vegetable and fruit	44 (28–60)	32 (4–60)
Education	30 (16–43)	31 (6–57)
Liver cirrhosis	21 (15–26)	11 (4–18)
Hepatitis	16 (11–21)	15 (6–24)
Diabetes	10 (4–15)	2 (−8–13)
Alcohol	9 (2–16)	1 (−5–7)
Oral contraceptives		7 (0–15)
Vegetable and fruit + liver cirrhosis	59 (45–72)	43 (17–69)
Vegetable and fruit + diabetes	52 (36–68)	34
Education + hepatitis + alcohol (males), or oral contraceptives (females)	46 (32–60)	41 (14–68)
Education + hepatitis	40 (27–54)	39 (13–64)
Education + alcohol (males), or oral contraceptives (females)	36 (22–51)	34 (6–61)
Liver cirrhosis + diabetes	27 (21–34)	12 (2–23)
Hepatitis + alcohol (males), or Oral contraceptives (females)	24 (16–32)	22 (11–33)
All factors	78	67

*Whenever possible, because of computational constraints.

is unclear whether cirrhosis is an independent factor in the aetiology of HCC, or a step in the process. Still, the AR gives a useful indication for quantifying, on a clinical and public health level, the role of past history of cirrhosis in the prediction of HCC diagnosis in an Italian population.

An association between diabetes and HCC has been reported [27–30]. Although the interpretation of this finding is still unclear, this has been related to changes in hepatocellular activity and, perhaps, mitosis, following the metabolic alterations in diabetics. Alternatively, diabetes may be seen as a consequence of impaired liver function. We had no information on diabetes subtypes. It is, however, likely that diabetes diagnosed before the age of 50 years is type I, insulin-dependent, and that diagnosed at 50 years of age or over is type II, non-insulin dependent. However, ORs were similar for subjects diagnosed below 50 years of age and at 50 years or over, while ARs were 3% and 6%, respectively. Thus, although available data are limited, and hence any estimate open to criticism, the 10% of HCC male cases attributable to a clinical history of diabetes is of major interest on a public health level.

The role of alcohol might have been underestimated as a result of a decreased consumption by cases due to previous alcohol-related conditions. Thus, the role of alcohol in terms of population AR is probably greater than estimated in the present study. Any effect of some relevance, however, is limited to males, because of the low prevalence of heavy drinking among females. Likewise, the impact of oral contraceptive use is modest on a population level, because HCC is a very rare neoplasm in younger Italian women [4] and OC use is relatively uncommon in Italy.

The potential limitations of this study include, with reference to ORs estimates, its hospital-based design, with all the consequent limitations and strengths [20]. However, in this investigation, the participation rate was practically complete and care was taken to exclude from the comparison group any patients admitted for malignant disorders, diseases of the digestive tract, and any condition related to tobacco and alcohol consumption, or which might have resulted in a long-term modification of the diet. Moreover, its hospital-based design probably offers an optimal framework for investigating medical histories, since cases and controls are similarly sensitised towards recalling diseases which occurred in the past [31]. With reference to confounding, allowance was possible for a number of potentially relevant factors.

In the computation of the attributable risks, cases were assumed to be representative of the whole diseased population. In the area under investigation, there are no cancer registries, and it is difficult to distinguish, on death certification alone, primary versus metastatic liver cancer [32]. Thus, the exact proportion of cases reached by interview is not known. However, the major hospitals in the area were covered by our study, treatment of the condition is very rare in private structures, and there is no reason to assume any major systematic selection mechanism. However, the ARs were probably underestimated by the definition of quantiles of intake (or any arbitrary cut-off point), which does not identify an unexposed category for the variable, and consequently by the shape of the dose–risk relationship.

In conclusion, in spite of several limitations in our data, of arbitrary assumptions regarding the exposure distribution, and of the use of a simple formula to derive ARs, we were able to explain a large proportion of HCC cases in the area under study with a few, largely identifiable and potentially preventable risk factors. In the whole of Italy, this could in principle reduce liver cancer deaths from 3300 to approximately 750 for males, and from 1600 to about 500 for females [4], thus largely explaining the difference in mortality between the two sexes.

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Acknowledgements—This work was conducted within the framework of the CNR (Italian National Research Council) Applied Project 'Clinical Applications of Oncological Research' (Contract Nos. 95.00562.PF39 and 95.00504.PF39) and with the contributions of the Italian Association for Cancer Research, the Europe Against Cancer Programme of the Commission of the European Communities, and Mrs. Angela Marchegiano Borgomainerio. The authors thank Mrs. Judy Baggott, Ms. M. Paola Bonifacino and the G.A. Pfeiffer Memorial Library staff for editorial assistance.