Family History of Liver Cancer and Hepatocellular Carcinoma

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Familial clustering of hepatocellular carcinoma (HCC) has been frequently reported in eastern Asiatic countries, where hepatitis B infection is common. Little is known about the relationship between family history of liver cancer and HCC in Western populations. We carried out a case-control study in Italy, involving 229 HCC cases and 431 hospital controls. Data on family history were summarized through a binary indicator (yes/no) and a family history score (FHscore), considering selected family characteristics. Odds ratios (ORs) and the corresponding 95% confidence intervals (CIs) were obtained from unconditional multiple logistic regression models, including terms for age, sex, study center, education, tobacco smoking, alcohol drinking, hepatitis B surface antigen, and/or anti–hepatitis C virus positivity. We also performed a meta-analysis on family history of liver cancer and liver cancer updated to April 2011 using random-effects models. After adjustment for chronic infection with hepatitis B/C viruses, family history of liver cancer was associated with HCC risk, when using both the binary indicator (OR, 2.38; 95% CI, 1.01-5.58) and the FHscore, with increasing ORs for successive score categories. Compared to subjects without family history and no chronic infection with hepatitis B/C viruses, the OR for those exposed to both risk factors was 72.48 (95% CI, 21.92-239.73). In the meta-analysis, based on nine case-control and four cohort studies, for a total of approximately 3,600 liver cancer cases, the pooled relative risk for family history of liver cancer was 2.50 (95% CI, 2.06-3.03). *Conclusion*: A family history of liver cancer increases HCC risk, independently of hepatitis. The combination of family history of liver cancer and hepatitis B/C serum markers is associated with an over 70-fold elevated HCC risk. (HEPATOLOGY 2012;55:1416-1425)

Liver cancer is a common neoplasm, which ranks sixth in terms of incidence and third in terms of mortality worldwide.[1] Most of the new cases and deaths occur in developing countries, particularly in eastern and southeastern Asia and in sub-Saharan Africa.[2] Among Western countries, southern Europe shows the highest incidence rates of liver cancer.[1] The relatively high incidence in (southern) Italy is mostly a consequence of the high prevalence of hepatitis C virus (HCV) infection in that region.[3,4]

Hepatocellular carcinoma (HCC) is the most frequent histologic type of primary liver cancer.[5] More than 75% of cases worldwide and 85% of cases in developing countries have been attributed to hepatitis B virus (HBV) and HCV, both of which increase the risk of HCC by approximately 20-fold.[6] Other well-recognized risk factors for HCC are advanced age, male gender, heavy alcohol drinking, aflatoxin exposure, tobacco smoking, cirrhosis, and some rare monogenic syndromes (e.g, haemocromatosis, alpha1-

Abbreviations: chi-square, χ^2; anti-HCV, antibodies against hepatitis C virus; CI, confidence interval; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; FHscore, family history score; MEIA, microparticle-based enzyme immunoassay; MOOSE, Meta-analysis Of Observational Studies in Epidemiology; OR, odds ratio; RR, relative risk.

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antitrypsin deficiency, and porphyria cutanea tarda).[5] HBV and HCV transmission among family members, together with other shared environmental risk factors, may be responsible for part of the observed familial aggregation of liver cancer. Familial clustering of HCC has been frequently reported in eastern Asia,[7,8] where HBV infection is common.[9] However, family history was found to be related to HCC risk, even after adjustment for other risk factors, and in subjects without hepatitis B and C serum markers.[10-12]

Given the limited number of studies conducted on non-Asian populations, we investigated the role of family history of liver cancer on the risk of HCC in a South European country. We adopted both a standard approach, in which the exposure is defined as the number of observed affected first-degree relatives, and a continuous family history score (FHscore), which takes into account some family characteristics. We also quantitatively combined, in a systematic meta-analysis, all published data on family history of liver cancer and HCC risk from observational studies.

Patients and Methods

Italian Case-Control Study. Between January 1999 and July 2002, we carried out a case-control study on HCC in the province of Pordenone (northeastern Italy) and in the city of Naples (southern Italy).[13]

Cases included subjects younger than 85 years with incident HCC who had not received any cancer treatment at study enrollment. They were admitted to the National Cancer Institute in Aviano, the "Santa Maria degli Angeli" General Hospital in Pordenone, and the National Cancer Institute "Fondazione Pascale", the Cardarelli Hospital, and the University of Naples "Federico II", in Naples. Of the 261 HCC cases satisfying the inclusion criteria, 3 refused to participate in the study and 29 did not supply blood samples. For the remaining 229 HCC cases (median age, 66 years; range, 43-84), both questionnaire information and blood samples were available. Most of the HCC cases (78.2%) were histologically or cytologically confirmed; for the remaining HCC cases, cancer diagnosis was based on ultrasound, tomography, and elevated alpha-fetoprotein levels.

Controls were patients younger than 85 years of age, from the same cathment areas as cases, admitted for a wide spectrum of acute, non-neoplastic conditions. Controls were more often females and were younger than cases, as the matching procedure was carried out by considering the age and sex distribution of cancer cases in the entire study, which also included lymphohematopoietic cancer cases.[14] Patients whose hospital admission was the result of diseases related to alcohol or tobacco use, hepatitis viruses (e.g., hepatitis, cirrhosis, and esophageal varices), or other chronic diseases, which may have substantially modified their lifestyle, were excluded from the comparison group. Overall, 467 controls were contacted and 462 accepted to participate in the study. Blood samples were available from 431 controls, which represented the final control group for the analysis (median age, 65 years; range, 40-82). Twenty-six percent of controls were admitted to hospital for traumas, 25% for acute surgical conditions, 23% for nontraumatic orthopedic diseases, 13% for eye diseases, and 13% for other illnesses.

All study participants signed an informed consent form, according to the recommendations of the Board of Ethics of the National Cancer Institute of Aviano.

Cases and controls were interviewed during their hospital stay using a structured questionnaire, including information on sociodemographic characteristics, anthropometric measures, lifestyle habits (including tobacco smoking and alcohol drinking), usual diet, and personal medical history. Information on family history included number of brothers, sisters, sons, and daughters. For each first-degree relative (i.e., parents, siblings, and sons/daughters), we recorded the vital status, current age/age at death, history of cancer (excluding nonmelanoma skin cancer), site of cancer, and age at diagnosis.

Each case and control provided a 15-mL blood sample the same day of the interview. Sera were screened for antibodies against HCV (anti-HCV) using a third-generation microparticle-based enzyme immunoassay (MEIA) (AxSYM HCV version 3.0; Abbott Diagnostic Division, Wiesbaden, Germany) and for HBV surface antigen (HBsAg) using the MEIA (AxSYM HBsAg version 2.0; Abbott Diagnostic Division).

To assess the association between family history of liver cancer and HCC risk, we adopted two different approaches. In a standard approach, we classified each subject according to the number of first-degree relatives affected by liver cancer and identified the

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following two categories: (1) no family history of liver cancer and (2) one or more first-degree relatives with liver cancer (only 1 subject reported two relatives affected). As a second approach, each study participant was classified according to a continuous FHscore, as proposed by Silberberg et al.[15] This score compares the observed disease status of each relative to his or her expected risk, estimated from a logistic regression model. To estimate the expected risk of liver cancer for each relative, his or her disease status (i.e., affected if had liver cancer, not affected otherwise) was modelled as a function of his or her sex and age. In this model, age represents the disease-free life experience of each relative and is defined as age at diagnosis for relatives affected by HCC, current age for those free of HCC and alive, and age at death for those unaffected by liver cancer and deceased. The residuals from this model were then averaged over each family to form a score. In detail, for the jth study participant, $FHScore_j = \sum_{i=1}^{n_j} \left(\pi_{ij} - \hat{\pi}_{ij}\right)/n_j$, where π_{ij} refers to the observed disease status (1 if affected, 0 otherwise) and $\hat{\pi}_{ij}$ refers to the expected risk of liver cancer (as predicted by the model) for the ith individual in the jth family, and n_j represents the family size. Subjects with FHscore ≤ 0 were included in the minimal-risk category. Subjects having a positive FHscore were divided into two groups: the low-/intermediate-risk category group, including subjects with an FHscore lower than the median FHscore calculated among controls with a positive score (i.e., 0.1046), and the high-risk category group, including subjects with an FHscore greater than the median score.

We estimated the odds ratio (OR) and the corresponding 95% confidence interval (CI) of HCC for family history of liver cancer using unconditional multiple logistic regression models, including terms for age (categorical: <55, 55-64, 65-74, and ≥75 years), sex, study center (categorical: Pordenone, Naples) (Model 1), and also further terms for education (categorical: <7, 7-11, and ≥12 years), tobacco smoking (categorical: never smokers, former smokers, current smokers <15; and current smokers ≥15 cigarettes per day), alcohol drinking (categorical: never drinkers, <14, 14-34, and ≥35 drinks per week) (Model 2), and for HbsAg and/or anti-HCV positivity (yes or no) (Model 3). Tests for trend in risk were based on the likelihood-ratio test between models with and without a linear term for the score. To test for the presence of interaction between family history of liver cancer and HBsAg and/or anti-HCV positivity, the difference between the $-2 \times$ log (likelihood) of the models with and without the interaction term was compared with the chi-square (χ^2) distribution with 1 degree of freedom.

Meta-analysis. We performed a Medline search in PubMed up to April 2011 using the string "(liver OR hepatocellular) and (cancer OR neoplasm OR tumor OR carcinoma) and (family history)", limiting the search to the publications written in English and following the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines.[16] The PubMed search identified 232 articles. From these, we selected 14 reports giving information on the association between family history of liver cancer and HCC risk. Studies considering family history of any cancer or family history of liver diseases were not considered. Some reports were excluded as based on data later updated[17-19] or because reporting data from case-control studies nested in previously identified cohorts.[20,21] Three additional articles were identified through review of the reference lists of the publications retrieved.[22-24] Finally, besides our present case-control study, the meta-analysis included other eight case-control[10,11,22-27] and four cohort studies.[7,12,28,29]

Whenever available, we considered multivariate risk estimates, adjusted for the largest number of potential confounding factors; otherwise, we computed the crude OR (and the corresponding 95% CI) from the distribution of cases and controls according to family history of liver cancer.[26] In a study reporting the adjusted OR, but not the corresponding 95% CI,[24] we used the standard error of the crude OR. We pooled the relative risks (RRs) of HCC for family history of liver cancer from each study using random-effects models, which consider both within- and between-study variation.[30] Heterogeneity among studies was assessed using the χ^2 test (results were defined as heterogeneous for a P value <0.10).[31]

Sensitivity analysis was performed according to the quality of each study and assessed independently by two reviewers using the Newcastle-Ottawa Scale.[32]

Results

Italian Case-Control Study. The distribution of 229 HCC cases and 431 controls, according to selected HCC characteristics, has already been published.[13] Briefly, cases were more likely to have a low level of education, to smoke cigarettes, and to drink alcohol; 172 (75.1%) cases and 48 (11.1%) controls had evidence of chronic infection with HBV/HCV.

Table 1 reports the joint distribution of the study participants according to the FHscore categories and the observed number of first-degree relatives with liver

Table 1. Distribution of Study Participants According to the Silberberg's FHscore Categories and to the Observed Number of First-Degree Relatives With Liver Cancer*

FHscore†	Observed No. of First-Degree Relatives With Liver Cancer			Total	Kappa Statistic
	0	1	2		
Minimal-risk	614	0	0	614	
Low-/intermediate-risk	0	22	0	22	k = 0.749
High-risk	0	21	1	22	SE = 0.0391
Total	614	43	1	658	$P < 0.001$

Abbreviation: SE, standard error.

*Italy, 1999-2002.

†Subjects with an FHscore ≤0 were included in the minimal-risk category. Subjects with a positive FHscore were divided into two groups (the low-/intermediate-risk category and the high-risk category) on the basis of the median value of the score among controls with a positive FHscore (i.e., 0.1046). There were 2 missing for the FH score.

cancer. Of the 43 subjects with one affected relative, 22 were categorized in the low-/intermediate-risk category of the FHscore and 21 in the high-risk category. The only subject who reported two relatives with liver cancer was categorized in the high-risk category of the FHscore.

Table 2 reports information on the study subjects' family characteristics according to the two different classifications of family history of liver cancer. Considering the standard approach, no meaningful variation emerged in terms of family size, age, and sex among subjects with and without a family history of liver cancer. Considering the alternative approach, families in the high-risk FHscore category tended to be somewhat smaller than those in the low-/intermediate-risk category, whereas no significant difference emerged according to age and sex.

Table 3 gives the ORs and corresponding 95% CIs of HCC according to family history of liver cancer. After adjustment for age, sex, center, education, alcohol drinking, smoking habits, and HBsAg and/or anti-HCV positivity, the OR for subjects reporting at least one first-degree relative with liver cancer was 2.38 (95% CI, 1.01-5.58), compared to subjects with no family history. A positive association was found in males (OR, 3.21; 95% CI, 1.13-9.10), whereas no excess of risk emerged in females (OR, 1.11; 95% CI, 0.21-5.78). A higher risk of developing HCC was associated with having affected parents (OR, 6.08; 95% CI, 1.99-18.62), rather than affected siblings (OR, 0.69; 95% CI, 0.20-2.33). The OR for having a male affected relative was nonsignificantly higher than the one for a female affected relative. No difference was found according to the age of the youngest affected relative. Considering the FHscore approach, increasing ORs were obtained for increasing levels of the score: as compared to the minimal-risk category, the ORs from the fully adjusted models were 1.42 (95% CI, 0.43-4.72) for subjects in the low-/intermediate-risk category and 3.87 (95% CI, 1.20-12.55) for those in the high-risk category, with a significant trend in risk ($P = 0.02$).

Figure 1 shows the interaction between family history of liver cancer, measured with the standard method, and HBsAg and/or anti-HCV positivity. Compared to the lowest risk category (i.e., subjects without family history and with no chronic infection

Table 2. Family Characteristics of Study Subjects (Cases and Controls Combined) According to Different Methods of Classification of Family History of Liver Cancer in First-Degree Relatives*

Family History of Liver Cancer	No. of Families	Average Number of First-Degree Relatives† (SD)	Average Age of First-Degree Relatives† (SD)	Average Percentage of Males in First-Degree Relatives† (%)	Average Expected HCC Cases in First-Degree Relatives‡ (SD)	Average FHscore (SD)
Observed HCC cases						
0	616	8.5 (3.3)	55.7 (9.4)	50.2	0.0682 (0.0280)	−0.0081 (0.0014)
≥1	44	9.1 (3.3)	54.0 (8.0)	52.0	0.0714 (0.0265)	0.1200 (0.0525)
P value§		0.21	0.23	0.46	0.44	<0.01
FHscore‖						
Minimal-risk	614	8.5 (3.3)	55.7 (9.4)	50.2	0.0682 (0.0280)	−0.0081 (0.0014)
Low-/intermediate-risk	22	11.6 (2.4)	54.6 (7.4)	50.0	0.0906 (0.0208)	0.0820 (0.0167)
High-risk	22	6.7 (1.9)	53.4 (8.8)	54.0	0.0523 (0.0156)	0.1579 (0.0485)
P value§		0.01	0.45	0.53	<0.01	<0.01
All families	660	8.5 (3.3)	55.6 (9.4)	50.3	0.0684 (0.0279)	0.0004 (0.0347)

Abbreviation: SD, standard deviation.

*Italy, 1999-2002.

†Excluding the study subjects.

‡The expected HCC cases in first-degree relatives of each study participant were calculated by summing up the predicted probability of disease of their first-degree relatives, which were obtained from a logistic regression model fitted on a dataset including all the first-degree relatives. The model was adjusted for age and sex of the relatives.

§*P* value for test comparing group means (obtained by the analysis of variance procedure). The null hypothesis is that the means of the groups are equal.

‖There were 2 missing values for the FHscore.

Table 3. ORs of HCC and Corresponding 95% CIs According to Family History of Liver Cancer in First-Degree Relatives*

	Cases/Controls	Model 1 OR† (95% CI)	Model 2 OR‡ (95% CI)	Model 3 OR§ (95% CI)
Number of first-degree relatives with liver cancer				
All subjects				
0	204/412	1‖	1‖	1‖
≥1	25/19	2.64 (1.39-5.02)	3.04 (1.57-5.91)	2.38 (1.01-5.58)
Males				
0	166/280	1‖	1‖	1‖
≥1	17/12	2.19 (0.99-4.81)	2.68 (1.16-6.18)	3.21 (1.13-9.10)
Females				
0	38/132	1‖	1‖	1‖
≥1	8/7	3.79 (1.25-11.46)	3.69 (1.16-11.72)	1.11 (0.21-5.78)
Type of affected relative				
No affected relatives¶	204/412	1‖	1‖	1‖
Parents	17/8	4.86 (1.99-11.87)	5.58 (2.23-14.00)	6.08 (1.99-18.62)
Siblings	9/11	1.38 (0.55-3.50)	1.60 (0.62-4.18)	0.69 (0.20-2.33)
Age of youngest affected relative#				
No affected relatives	204/412	1‖	1‖	1‖
<60	10/11	2.29 (0.93-5.69)	2.72 (1.08-6.90)	1.58 (0.46-5.40)
≥60	9/8	2.12 (0.77-5.81)	2.19 (0.79-6.11)	2.18 (0.62-7.72)
Sex of the affected relative**				
No affected relatives	204/412	1‖	1‖	1‖
Male	16/10	3.26 (1.41-7.54)	3.28 (1.39-7.71)	2.29 (0.80-6.58)
Female	9/9	1.41 (0.86-2.39)	1.67 (1.00-2.78)	1.59 (0.80-3.14)
Family history of liver cancer using FHscore††				
Minimal-risk	204/412	1‖	1‖	1‖
Low-/intermediate-risk	12/10	1.83 (0.75-4.47)	1.89 (0.76-4.72)	1.42 (0.43-4.72)
High-risk	13/9	3.82 (1.56-9.36)	4.91 (1.95-12.33)	3.87 (1.20-12.55)
P value for trend		≤0.01	≤0.01	0.02

*Italy, 1999-2002.
†Estimated from unconditional multiple logistic regression models adjusted for age, sex, and center.
‡Further adjusted for education, alcohol drinking, and smoking habits.
§Further adjusted for HBsAg and/or anti-HCV positivity.
‖Reference category.
¶One subject reported both a parent and a sibling affected by liver cancer.
#The sum does not add to the total because of some missing values on age at liver cancer diagnosis in first-degree relatives.
**One subject had the mother and a brother affected by liver cancer
††There were two missing values for the FHscore.

with HBV/HCV), the ORs were 2.94 (95% CI, 0.94-9.21) for subjects not chronically infected by hepatitis viruses and with family history, 38.19 (95% CI, 21.97-66.39) for those with chronic infection with hepatitis viruses and no family history, and 72.48 (95% CI, 21.92-239.73) for those exposed to both risk factors. No deviation from multiplicative interaction emerged between these two factors ($P = 0.61$).

As compared to the minimal-risk category of the FHscore, ORs associated with successive categories of the score were 2.64 (95% CI, 0.48-14.47) and 3.23 (95% CI, 0.71-14.73) for subjects without chronic infection with HBV/HCV and 37.40 (95% CI, 21.50-65.07), 36.20 (95% CI, 8.82-148.64), and 201.92 (95% CI, 23.22-not estimable) for subjects with chronic infection with HBV/HCV (data not shown). No deviation from multiplicative interaction emerged between the score and chronic infection with HBV/HCV ($P = 0.63$).

Table 4 shows the distribution of cases and controls according to history of other selected cancers in first-degree relatives and the corresponding ORs. None of

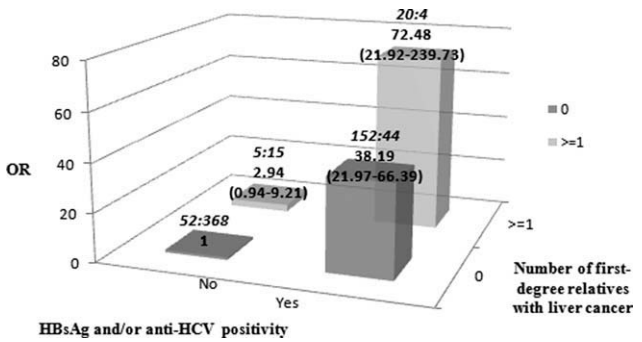

Fig. 1. Number of cases and controls, ORs* and 95% CIs of hepatocellular carcinoma according to chronic hepatitis and family history of liver cancer, measured by the standard method. Italy, 1999-2002. *Adjusted for age, sex, center, education, alcohol drinking, and smoking habits.

Table 4. ORs of HCC and Corresponding 95% CI According to Family History of Selected Cancers* Other Than Liver in First-Degree Relatives†

Cancer Site	Subjects With Family History		OR‡ (95% CI)	OR§ (95% CI)
	Cases (%)	Controls (%)		
Stomach	16 (7.0)	24 (5.6)	1.43 (0.72-2.83)	1.98 (0.81-4.79)
Colorectum	11 (4.8)	28 (6.5)	0.73 (0.35-1.53)	1.14 (0.42-3.12)
Lung	19 (8.3)	41 (9.5)	0.84 (0.47-1.52)	0.55 (0.24-1.26)
Breast	11 (4.8)	27 (6.3)	0.85 (0.40-1.77)	0.74 (0.27-2.03)
Prostate	9 (3.9)	8 (1.9)	2.23 (0.83-6.03)	2.42 (0.64-9.16)
Bladder	5 (2.2)	4 (0.9)	1.97 (0.51-7.58)	1.50 (0.27-8.24)
All lymphohematopoietic cancers	5 (2.2)	11 (2.6)	1.03 (0.34-3.08)	0.39 (0.10-1.50)
Any digestive tract cancer excluding liver‖	34 (14.9)	73 (16.9)	0.90 (0.57-1.43)	1.26 (0.68-2.35)
All sites	110 (48.0)	175 (40.6)	1.51 (1.07-2.12)	1.26 (0.79-1.98)
All sites, excluding liver	85 (37.1)	156 (36.2)	1.16 (0.82-1.65)	0.97 (0.60-1.56)

*Including sites with at least 5 cases with positive family history.
†Italy, 1999-2002.
‡Estimated from unconditional multiple logistic regression models adjusted for age, sex, centre. Reference category: no family history.
§Further adjusted for education, alcohol drinking, smoking habits, and HBsAg and/or anti-HCV positivity.
‖Including cancer of the oral cavity and pharynx, esophagus, stomach, colorectum, pancreas, and gallbladder.

the other cancer sites showed a significant association with MCC risk. The OR from the fully adjusted model was 1.26 (95% CI, 0.79-1.98) for all cancer sites combined and 0.97 (95% CI, 0.60-1.56) for all cancer sites, liver excluded. Also, among subjects without chronic infection with HBV/HCV, no association with family history of any cancer (OR, 1.29; 95% CI, 0.69-2.41) and of any cancer, liver excluded (OR, 1.00; 95% CI, 0.53-1.89), was observed (data not shown).

Meta-analysis. Besides the present study, we identified eight other case-control and four cohort studies, for a total of 3,627 liver cancer cases. The main study characteristics are reported in Table 5. Most studies were conducted in eastern Asia,[7,12,22-24,26-29] where the prevalence of HCV/HBV infection is high; only three studies, besides the present one, were carried out in Western countries.[10,11,25] Figure 2 shows the forest plot for the association between family history of liver cancer and liver cancer risk. The pooled RRs were 2.80 (95% CI, 2.19-3.58) for case-control, 2.28 (95% CI, 1.58-3.29) for cohort, and 2.50 (95% CI, 2.06-3.03) for all studies combined, with no heterogeneity between study type ($P = 0.17$). When studies not allowing for hepatitis were excluded from the analyses, the overall RR was 2.28 (95% CI, 1.85-2.18) (RR estimate based on studies either including a term for hepatitis in the logistic regression models or performed on subjects with chronic infection with HBV or HCV only). Analyses according to the sex of the subjects showed a pooled RR of 2.80 (95% CI, 2.14-3.66; P value for heterogeneity $= 0.21$) for males from nine studies (including the present study)[7,10,12,22-25,28] and of 1.55 (95% CI, 0.92-2.64; P value for heterogeneity $= 0.77$) for females from six studies (including the present study).[10,12,22,23,25] When only the six studies (including the present study) reporting risk estimates for both males and females separately were considered,[10,12,22,23,25] the pooled RR for males became 2.39 (95% CI, 2.03-2.81), whereas the pooled RR for females remained the same.

Quality score ranged between 4 and 7 for case-control and between 6 and 7 for cohort studies (median score: 6 for both case-control and cohort studies). The pooled RRs were 2.48 (95% CI, 1.84-3.35) from five high-quality studies (i.e., studies with a quality score higher than 6) and 2.56 (95% CI, 1.92-3.42) from eight low-quality studies, in the absence of significant heterogeneity ($P = 0.88$).

Discussion

We observed a significant increased HCC risk in subjects with a family history of liver cancer, after adjustment for several HCC risk factors, including HBsAg and/or anti-HCV positivity. Moreover, the FHscore showed increasing risk estimates for successive categories of the score.

To limit possible sources of bias, we included in the control group subjects admitted for a wide spectrum of acute, non-neoplastic conditions, which were unrelated to the major risk factors for HCC. The practically complete participation and the comparable catchment areas of cases and controls contributed to the strength of our study. With reference to confounding, we adjusted for the main recognized HCC risk factors, including chronic infection with HBV/HCV, tobacco smoking, and alcohol drinking. Obesity, which runs in

Table 5. Main Characteristics of the Studies on Liver Cancer and Family History of Liver Cancer Included in the Meta-analysis

Study	Country	Gender	No. of Cases	No. and Type of Controls/ Size of Cohort	Years of Study/Duration of Follow-up	Adjusting Factors and Matching Variables	Notes
Case-control studies							
Tsukuma et al., 1990[23]	Japan	Both	229	266 hb	1983-1987	Age, sex, alcohol, smoking, history of blood transfusion, HBsAg	
Chen et al., 1991[24]	Taiwan	Male	200	200 pb	1985-1987	Age, sex, ethnic group, residence, alcohol, smoking, HBsAg/HBeAg	95% CI for the adjusted OR was calculated on the distribution of cases and controls according to family history
Tanaka et al., 1992[22]	Japan	Both	204	410 pb	1985-1989	Age, sex	
Fernandez et al., 1994[25]	Italy	Both	320	1,408 hb	1983-1992	Age, sex, residence, education, alcohol, smoking, history of cirrhosis and hepatitis	
Donato et al., 1999[11]	Italy	Both	287	450 hb	1996-1998	Age, sex, date of admission to hospital, residence, education, alcohol, HCV and HBV infection, family history of all cancer excluding liver	
Zhu et al., 2005[26]	China	Both	246	549 pb	2001-2003	Age, sex	OR and 95% CI calculated on the distribution of cases and controls according to family history.
Hsu et al., 2006[27]	Taiwan	Both	225	225 hb	1999-2001	Age, sex, alcohol, TCR-γ STR genotype 16	Cases were HBV- or HCV-related cirrhosis patients with HCC; controls were HBV- or HCV-related cirrhosis patients without HCC
Hassan et al., 2009[10]	United States	Both	347	1,075 pb	2000-2008	Age, sex, ethnic group, education, alcohol, smoking, diabetes, anti-HCV, HBsAg, anti-HBc	
Turati et al., 2011 (present study)	Italy	Both	229	431 hb	1999-2002	Age, sex, centre, education, alcohol, smoking, HBsAg and/or anti-HCV	
Cohort studies							
Sun et al., 1999[28]	China	Male	22	145 pr	1988-1998 10 years	Age, aflatoxin, anti-HCV	The cohort consisted of men with chronic HBV hepatitis
Yu et al., 2000[7]	Taiwan	Male	132	4,808 pr	1988-1992 8.9 years (average)	Age, education, alcohol, smoking, number of siblings	The cohort consisted of men HBV carriers. The article also reports data from a case-control familial study.
Chen et al., 2002[29]	Taiwan	Both	94	4,843 pr	1991-1998 7 years (average)	Age, sex, HBsAg, HCV, AFP, AST, ALT	The cohort consisted of subjects selected among members of a screened population who were positive for at least one of six investigated risk factors of HCC (i.e., HBsAg, anti-HCV, AFP $\geq$20 ng/mL, AST $\geq$40 IU/L, ALT $\geq$45 IU/L. and family history of HCC). We selected ORs for incidence rather than mortality
Evans et al., 2002[12]	China	Both	1,092	83,794 pr 434,718 py	1992-2000 8 years	Males: age, occupation, alcohol, tea, well water, history of acute hepatitis, HBsAg; females: age, alcohol, smoking, history of acute hepatitis, HBsAg	The article reported results from a cohort of males and one of females; results were stratified by sex. The outcome was death for HCC

Abbreviations: hb, hospital-based controls; pb, population-based controls; pr, persons at risk; py, person-years; HBeAg, hepatitis B surface antigen; TCR-γ, T-cell receptor-gamma; STR, short tandem repeat; anti-HCV, antibodies against hepatitis C virus; anti-HBc, hepatitis B core antibody; AFP, alpha-fetoprotein; AST, aspartate transaminase; ALT, alanine transminase.

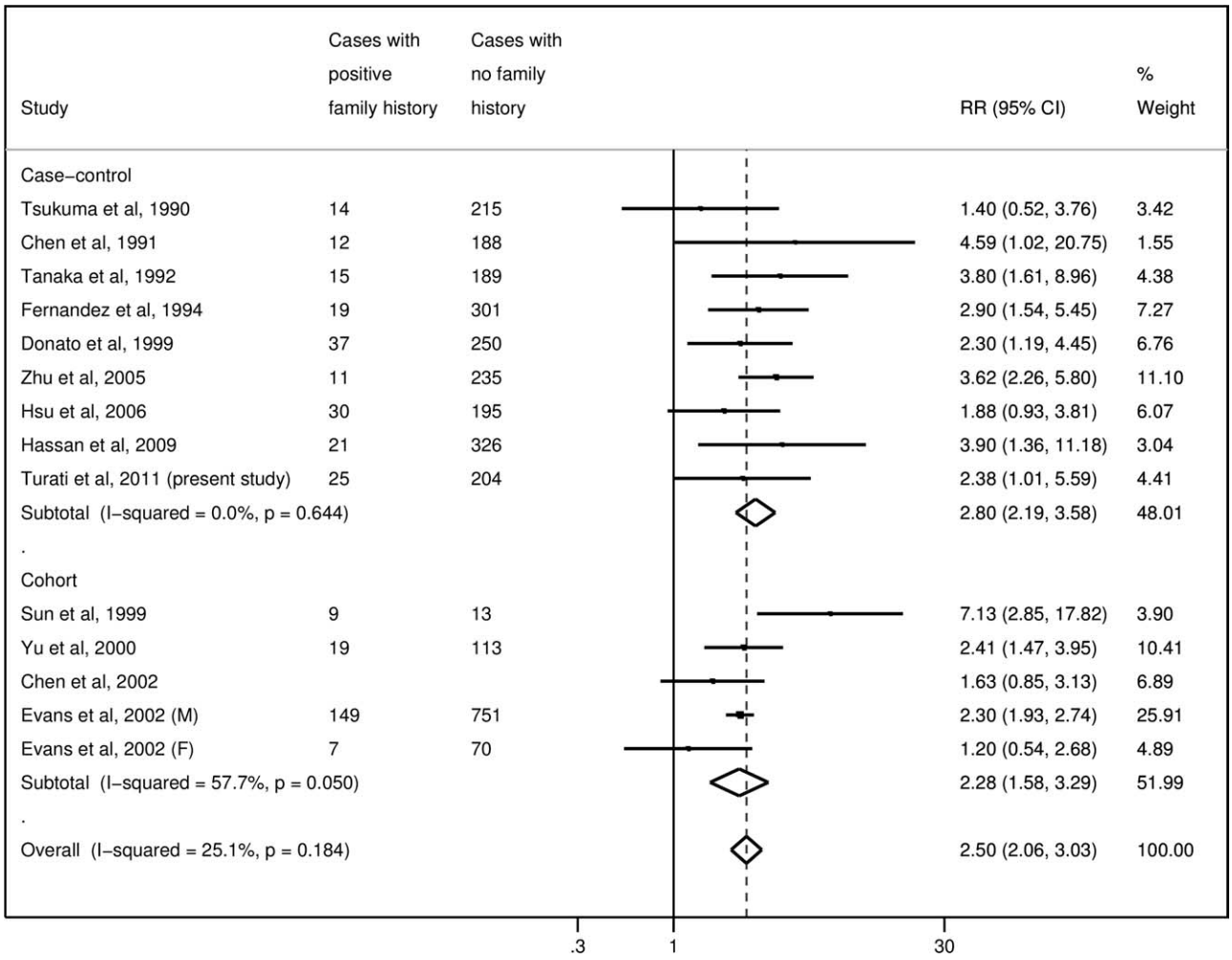

Fig. 2. Forest plot for the association between family history of liver cancer and HCC risk. Abbreviations: M, males; F, females.

families, and diabetes have been positively associated with HCC risk.[33-35] However, further adjustment for these factors did not substantially change our results.

This study was based on information on family history reported by the subjects, and it is therefore possible that HCC cases may recall family history of liver cancer or other cancers better than controls.[36] However, the similar hospital setting for cases and controls should have improved the comparability of information.[37,38] In the Connecticut Family Health Study, reports from first-degree relatives were more accurate than those from second-degree relatives, with positive predictive values between 78% and 80% for lung and breast cancer.[39] Thus, we considered only first-degree relatives. An analysis in our population showed a good reliability of data on family history of all cancers provided by hospital controls, with a kappa statistic of 0.70 for all cancers, 0.70 for liver cancer, and 0.80 for any digestive tract cancers.[37] Furthermore, the lack of association between HCC risk and family history of any cancer site, liver excluded, indicates that differential reporting of familial cancer in general did not occur.

Another possible limitation in our study was the lack of information on alcohol drinking and smoking habits (two of the main recognized HCC risk factors) among family members and also on family history of chronic hepatitis,[5] cirrhosis,[40] and other inherited diseases known to be related to HCC risk, such as genetic hemochromatosis and alpha-1-antitrypsin deficiency,[5] which may partly explain the observed familial HCC aggregation.

Our risk estimates are consistent with the overall evidence from a meta-analysis of published data. The studies included were conducted in countries with different population baseline characteristics and HCV/HBV prevalence; moreover, RR estimates were adjusted for different factors. However, when we restricted the analysis to studies allowing for hepatitis,

our results did not materially change. Furthermore, the association was of similar magnitude when only high-quality studies[32] were considered.

We observed a nonsignificantly stronger association between HCC risk and family history of liver cancer for males. This is in agreement with results obtained from our meta-analysis, which estimated pooled RRs of 2.80 and 1.55 for males and females, respectively. In particular, the study by Hassan et al.[10] reported an OR of 9.2 (95% CI, 1.9-45.3) for males and of 1.6 (95% CI, 0.3-8.7) for females. Similar results were also shown in a Chinese cohort investigating HCC mortality (RR for males = 2.3, 95% CI: 1.9-2.7; RR for females = 1.2, 95% CI: 0.5-2.5)[12] and in a case-control study from Italy (OR for males = 3.1, 95% CI: 1.5-6.3; OR for females = 1.6, 95% CI: 0.5-5.6).[25] Conversely, two Japanese studies found similar risk estimates for males and females.[22,23] In any case, the test for heterogeneity between the two sex-specific pooled RRs gave a *P* value of 0.05, suggesting a borderline difference in HCC risk related to family history between males and females.

A family history of any cancer and of any cancer, excluding liver, was not associated with HCC risk. This is against the hypothesis of a genetic mutation of a widely expressed tumor-suppressor gene.[41]

Family history of liver cancer was an important HCC risk factor independently from the presence of hepatitis. However, HBsAg and/or anti-HCV positivity was a much stronger risk factor for developing HCC than family history of liver cancer, with related RRs of approximately 38 and 3, respectively. Using the standard approach, the OR of subjects with family history and chronic infection with HBV/HCV predicted by a model assuming an additive effect would be over 40, and over 100 by assuming a multiplicative model. Our point estimate for the combination of family history and hepatitis is 72.48, which did not suggest a specific pattern of interaction.

In conclusion, this study shows that subjects with a positive family history of liver cancer have a 2- to 3-fold increase in their HCC risk, and that a continuous FHscore can identify subjects with high and low/moderate HCC risk among those with a family history of this cancer. Furthermore, the combination of family history of liver cancer and hepatitis B/C serum markers leads to an over 70-fold elevated HCC risk, as compared to subjects without family history and hepatitis.

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