DOI: 10.1093/jnci/djr395
Advance Access publication on October 21, 2011.

ARTICLE

Hepatocellular Carcinoma Risk Factors and Disease Burden in a European Cohort: A Nested Case–Control Study

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Manuscript received February 28, 2011; revised September 2, 2011; accepted September 6, 2011.

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Background To date, no attempt has been made to systematically determine the apportionment of the hepatocellular carcinoma burden in Europe or North America among established risk factors.

Methods Using data collected from 1992 to 2006, which included 4409809 person-years in the European Prospective Investigation into Cancer and nutrition (EPIC), we identified 125 case patients with hepatocellular carcinoma, of whom 115 were matched to 229 control subjects. We calculated odds ratios (ORs) for the association of documented risk factors for hepatocellular carcinoma with incidence of this disease and estimated their importance in this European cohort.

Results Chronic hepatitis B virus (HBV) or hepatitis C virus (HCV) infection (OR = 9.10, 95% confidence interval [CI] = 2.10 to 39.50 and OR = 13.36, 95% CI = 4.11 to 43.45, respectively), obesity (OR = 2.13, 95% CI = 1.06 to 4.29), former or current smoking (OR = 1.98, 95% CI = 0.90 to 4.39 and OR = 4.55, 95% CI = 1.90 to 10.91, respectively), and heavy alcohol intake (OR = 1.77, 95% CI = 0.73 to 4.27) were associated with hepatocellular carcinoma. Smoking contributed to almost half of all hepatocellular carcinomas (47.6%), whereas 13.2% and 20.9% were attributable to chronic HBV and HCV infection, respectively. Obesity and heavy alcohol intake contributed 16.1% and 10.2%, respectively. Almost two-thirds (65.7%, 95% CI = 50.6% to 79.3%) of hepatocellular carcinomas can be accounted for by exposure to at least one of these documented risk factors.

Conclusions Smoking contributed to more hepatocellular carcinomas in this Europe-wide cohort than chronic HBV and HCV infections. Heavy alcohol consumption and obesity also contributed to sizeable fractions of this disease burden. These contributions may be underestimates because EPIC volunteers are likely to be more health conscious than the general population.

J Natl Cancer Inst 2011;103:1686–1695

Until about 40 years ago, very little was known about the etiology of hepatocellular carcinoma, except that it was associated with liver cirrhosis. During the 1970s, epidemiological studies, first in Africa (1) and Asia (2) and later in Europe (3), firmly documented an important role of chronic infection with hepatitis B virus (HBV) in the etiology of hepatocellular carcinoma. About 10 years later, studies that relied on clinical case series (4) followed by formal case–control studies in Africa (5) and in Europe (6) showed that chronic infection with hepatitis C virus (HCV) was also strongly linked to hepatocellular carcinoma. Both HBV and HCV have been declared to be carcinogenic to humans by the International Agency for Research on Cancer (IARC) (7). Meanwhile, evidence has emerged that tobacco smoking is strongly related to hepatocellular carcinoma (8). Following a series of publications with converging findings, IARC has included hepatocellular carcinoma among the types of cancer that are causally associated with tobacco smoking (9). Alcohol intake, mostly by causing cirrhosis, is also an established liver carcinogen (10); indeed, heavy, but not moderate, alcohol consumption has been strongly associated with the risk of the disease (11). Finally, there is considerable evidence that obesity is an important factor in the etiology of hepatocellular carcinoma (12), whereas coffee drinking has been reported to reduce the risk of the disease (13,14).

Substantial progress has been made to identify exposures that strongly increase the risk of hepatocellular carcinoma and to quantify

the strength of their association with the disease. However, there has been no systematic attempt to estimate, in a population-based multinational cohort, the fraction of the hepatocellular carcinoma burden that is attributable to all established risk factors and, thus, amendable to primary prevention. This fraction depends on the prevalence of the risk factors in a given population, which can vary over place and time. In this article, we have generated conservative estimates of the quantitative importance of the indicated risk factors for hepatocellular carcinoma in the Europe-wide cohort of the European Prospective Investigation into Cancer and nutrition (EPIC). No previous cohort-based investigation has evaluated in the same dataset, the whole range of factors that have been documented to contribute to the etiology of hepatocellular carcinoma in Europe, North America, or Australia.

CONTEXT AND CAVEATS

Prior knowledge

Chronic hepatitis B virus (HBV) infection, chronic hepatitis C virus (HCV) infection, smoking, obesity, and alcohol intake have been identified as exposures that strongly increase risk of hepatocellular carcinoma, but the contribution of each risk factor to the disease burden in Europe had not been estimated.

Study design

Using data from the European Prospective Investigation into Cancer and nutrition (EPIC) from 1992 to 2006, 115 patients with hepatocellular carcinoma were matched to 229 control subjects. Serum samples were tested for indications of HBV or HCV infection. The authors calculated adjusted odds ratios as estimates of the incidence rate ratios for the evaluated factors and the population attributable fraction of hepatocellular carcinoma for the presence of each risk factor.

Contribution

Obesity, former or current smoking, and heavy alcohol intake were all associated with risk of hepatocellular carcinoma, and chronic HBV or HCV infection were especially strongly associated with risk. In this European cohort, almost half of all hepatocellular carcinomas were associated with smoking (47.6%), more than a quarter were associated with chronic HBV (13.2%) or HCV (20.9%) infection, and many with obesity (16.1%) or heavy alcohol intake (10.2%).

Implication

Almost two-thirds of hepatocellular carcinomas in Europe are associated with preventable exposures that increase risk.

Limitations

No data were available for the presence of cirrhosis, diabetes, aflatoxin exposure, or other possible factors, and interactions among the evaluated risk factors could not be examined.

From the Editors

Methods

EPIC is a large cohort study that was established to investigate the role of biological, dietary, lifestyle, and environmental factors in the etiology of cancer and other chronic diseases (15). Approximately 500 000 healthy males and females, aged 25–70 years, were recruited between 1992 and 2000 in 23 centers from 10 European countries (Denmark, France, Germany, Greece, Italy, the Netherlands, Norway, Spain, Sweden, and the United Kingdom). Most of the participants were selected from the general adult population, but some centers recruited members of health insurance services (France; women only) or breast cancer screening participants (Utrecht, Florence; women only). In Oxford, vegetarians were recruited in addition to participants from the general population, whereas in Italy and Spain, some cohorts included members of blood donor associations. Details of the EPIC study have been published (15).

The protocol of the EPIC study was approved by the Ethical Review Board at IARC and the ethical committees of the participating centers. All participants provided informed consent, and procedures were in line with the Helsinki Declaration for human rights.

Dietary, Lifestyle, Anthropometric, and Medical Variables

At enrollment, usual dietary intakes were assessed using food-frequency questionnaires. For some centers, we also used records of food and beverage intake over 7 or 14 days that were developed and validated by each center (16). Daily intakes of foods and beverages (including coffee) were calculated in grams. Ethanol intake (g/d) and total energy intake (kcal/d) were calculated using the EPIC Nutrient Database (17).

We used a questionnaire at enrollment to record sociodemographic data (including education) and data on lifestyle (including smoking) and medical history. From these data, we calculated energy expenditure related to professional, domestic, and leisure activities and created an index for overall daily physical activity with four categories: inactive, moderately inactive, moderately active, and active (18).

At enrollment, waist and hip circumferences, weight, and height were measured according to a common protocol with slight variations among centers. We corrected body weights and waist circumference data to reduce heterogeneity associated with differences in clothing (19), and we calculated body mass index (BMI in kg/m^2).

Hepatitis Virus Testing

Blood samples from the majority of the participants were collected at recruitment and stored at −196°C in liquid nitrogen. Serum levels of hepatitis B surface antigen (HbsAg) and antibodies to hepatitis C virus (anti-HCV) were determined at the Centre de Biologie République laboratory in Lyon (France). The ARCHITECT chemiluminescent microparticle immunoassay (CMIA) HbsAg assay (Abbott Diagnostics Division, Lyon, France) and the ARCHITECT CMIA anti-HCV assay (Abbott Diagnostics Division) were used to evaluate the presence of HbsAg and of anti-HCV antibodies, respectively. The laboratory personnel were blinded as to the disease status of the subjects whose blood samples they analyzed. According to manufacturer's specifications, specimens with HbsAg concentrations that were 0.05 International Units per milliliter or higher were considered to be from HBV-positive patients, whereas specimens with anti-HCV antibodies were considered to be from HCV-positive patients when the relative light units generated from the specimen were

equal to or higher than the reference relative light units in two measurements.

Follow-up

Vital status, cause of death, and date of death were collected using record linkage with regional and/or national death registries (Denmark, France, Italy, the Netherlands, Norway, Spain, Sweden, and the United Kingdom) or by active follow-up (Germany and Greece). In most countries, cancer incidence was ascertained through record linkage with cancer registries (Denmark, Italy, the Netherlands, Norway, Spain, Sweden, and the United Kingdom). In France, Germany, and Greece, a combination of methods was used to determine cancer incidence, including health insurance records, pathology registries, and active follow-up by means of mailed questionnaires or telephone interviews of the participant or next of kin in case of a participant's death. Incident cancers that were self-reported or reported by next of kin were subsequently verified by pathology reports, medical records, discharge diagnoses, or death certificates. For this study, the latest dates of complete information for cancer incidence and vital status ranged from December 2002 to December 2006 among different centers.

The Nested Case–Control Study

Ascertainment of Case Patients. We identified all case patients who were diagnosed with a verified liver cancer after their recruitment into the study. We initially excluded 39 case patients with no blood samples or missing essential information and an additional 43 case patients with prediagnosed malignancies at other sites or metastatic liver cancer. For each of the remaining patients (*ICD*-O-2 code C22.0), we further examined the relevant histologies and the method used for the diagnosis of hepatocellular carcinoma and excluded 31 patients with types of primary liver cancer other than hepatocellular carcinoma. Eventually, a total of 125 incident hepatocellular carcinoma case patients were identified.

Selection of Control Subjects. For each hepatocellular carcinoma case patient, two control subjects were chosen. For reasons concerning preservation of biological samples, subjects who developed any other cancer or had been used as control subjects in other EPIC studies were not included in the pool of eligible control subjects. Control subjects were required to be alive as of the time of the cancer diagnosis of the corresponding case patient, hence, length of follow-up time for the control subject was required to be the same as, or longer than, that for the case patient. Control subjects were matched with case patients for study center, sex, age at the time of blood collection (±12 months), date (±2 months) of blood collection, and time of day (±3 hours) of blood collection. Women were further matched by menopausal status (pre-, post-, or perimenopausal) and by use of exogenous hormones (oral contraceptives for premenopausal women and hormone replacement therapy for postmenopausal women) at blood collection (yes or no).

For the 125 hepatocellular carcinoma case patients, we identified 250 matching control subjects, for a total of 375 subjects. Among those, 29 subjects (10 case patients and 19 control subjects) had missing values in the variables used in further analyses; two additional control subjects were excluded following the exclusion of their corresponding case patient. The remaining 344 subjects with complete data comprised 115 case–control sets. Of these, 114 case–control sets relied on two matched control subjects, whereas one set relied on one matched control subject because the second control subject was excluded due to missing information on smoking status.

Statistical Analysis

We cross-tabulated variables by case–control status for descriptive purposes. Conditional logistic regression was used to estimate the associations between established or possible causal factors for hepatocellular carcinoma and hepatocellular carcinoma risk. We studied the following factors: chronic HBV infection (yes vs no), chronic HCV infection (yes vs no), BMI (obese: ≥30 kg/m^2 vs not obese: <30 kg/m^2), education (less educated vs educated at least at a secondary or technical school level), smoking status (current smokers vs nonsmokers and former smokers vs nonsmokers), usual ethanol intake at baseline with distinct cutoff points for men and women given reports (20–22) of their differential susceptibility to ethanol effects (for men, high: ≥40 g/d, moderate: 10 to <40 g/d, low: 0 to <10 g/d; for women, high: ≥20 g/d, moderate: 5 to <20 g/d, low: 0 to <5 g/d; 12 g of ethanol correspond approximately to one glass of alcoholic beverage) and regular coffee intake (low: <250 g/d vs high: ≥250 g/d; 150 g of coffee correspond approximately to one cup). For all indicated variables, we computed odds ratio (OR) estimates by conditional logistic regression, initially without adjustment and subsequently after mutually controlling for the above indicated variables. Additional conditional logistic regression models were fitted by also adjusting for total energy intake (continuous), physical activity (inactive or moderately inactive vs moderately active or active), and both of these additional variables.

Because the indicated major hepatocellular carcinoma risk factors (HBV and HCV infection, tobacco smoking, alcohol consumption, and obesity) are modifiable, we also estimated the attributable fraction per factor. The attributable fraction denotes the proportion of hepatocellular carcinomas in the underlying population that could have been avoided if the respective exposure were removed. We used the formula suggested by Miettinen (23) and extended by Bruzzi et al. (24) for case–control studies; this formula relies on the adjusted estimates of the odds ratios and the proportion of the corresponding exposures among case patients and is estimated as follows:

$$\frac{\pi \times (RR - 1)}{RR},$$

where π is the proportion of exposed among the case patients and RR is the adjusted incidence rate ratio consistently estimated by the adjusted odds ratio. We calculated 95% confidence intervals (CIs) for the attributable fractions using the bootstrap method (25). Because we included participants in our sample who were blood donors at recruitment and our sample population might thus lead to an underestimation of the prevalence of chronic HBV and/or HCV infection in the general population, we also recalculated the attributable fractions excluding centers which relied, even partially, on blood donors (all Spanish centers, and the Ragusa and Turin centers from Italy). Finally, we calculated the attributable

fractions in the subset of subjects who were not chronically infected by HBV or HCV.

Analyses were run in STATA statistical software (26). Two-sided tests of statistical significance were used, and a *P* value less than .05 was considered to denote statistical significance. For testing the statistical significance of the estimated odds ratios, the Wald test was used, whereas statistical interaction between any two of the examined factors was tested with the likelihood ratio test.

Results

Using data collected from 1992 to 2006, which included 4 409 809 person-years, we first examined the distribution of the incident case patients of hepatocellular carcinoma and their matched control subjects, by sex, age at enrollment, and country (Table 1). Hepatocellular carcinoma was more common among older people and substantially more common among men than among women. A meaningful comparison of incidence patterns among the countries is not possible because the population samples differ by sex, age, and length of follow-up. No confirmed hepatocellular carcinoma case patients with complete information, including biomarkers, were identified in the French and Norwegian EPIC cohorts, which included women only.

The distribution of the 80 male and 35 female case patients with incident hepatocellular carcinoma and their matched control subjects was next examined by status at enrollment with respect to established or suspected risk factors, such as chronic infection with HBV, chronic infection with HCV, tobacco smoking, ethanol intake, BMI, and coffee intake, and with respect to physical activity and educational level (Table 2). The patterns in this table were not directly interpretable because mutual confounding was not accounted for. Nevertheless, the overwhelming importance of chronic HBV or HCV infection in the etiology of hepatocellular carcinoma was evident, as was the important role of tobacco smoking. For example, 17 (14.8%) of 115 hepatocellular carcinoma patients were HBV-infected vs six (2.6%) of 229 matched control subjects, and 26 (22.6%) of 115 hepatocellular carcinoma patients were HCV-infected compared with seven (3.1%) of 229 of matched control subjects. Obesity (BMI $\geq$ 30 kg/m^2), though not overweight (BMI between 25 and 30 kg/m^2), was positively associated with the risk of hepatocellular carcinoma, especially among men: 25 (31.3%) of 80 of men with hepatocellular cancer were obese vs 24 (15.1%) of 159 of their matched control subjects. High alcohol intake, but not moderate alcohol intake, also appeared to be positively associated with hepatocellular carcinoma risk; 27 (23.5%) of 115 persons with hepatocellular carcinoma were heavy drinkers vs 26 (11.4%) of 229 of matched control subjects. By contrast, there was no evidence that coffee intake, educational level, or physical activity were major hepatocellular carcinoma risk factors.

We next calculated adjusted odds ratios as estimates of the corresponding incidence rate ratios for the evaluated factors, overall and by sex (Table 3). In the presence of chronic HBV or HCV infection, hepatocellular carcinoma risk was sharply increased (for

Table 1. Case patients with incident hepatocellular carcinoma and their matched control subjects within the European Prospective Investigation into Cancer and nutrition (EPIC) study from 1992 to 2006, by sex, age at enrollment, and country*

	Hepatocellular carcinoma case patients†	Matched control subjects‡	All EPIC participants
Patient characteristic	**No. (%)**	**No. (%)**	**No. (%)**
Age (matched), y			
<50	8 (7.0)	16 (7.0)	209 604 (42.4)
50 to <60	46 (40.0)	90 (39.3)	187 490 (37.9)
≥60	61 (53.0)	123 (53.7)	97 272 (19.7)
Sex (matched)			
Men	80 (69.6)	159 (69.4)	148 376 (30.0)
Women	35 (30.4)	70 (30.6)	345 990 (70.0)
Recruitment center (matched)			
Denmark	31 (27.0)	61 (26.6)	56 230 (11.4)
Germany	19 (16.5)	38 (16.6)	50 530 (10.2)
Greece	12 (10.4)	24 (10.5)	26 429 (5.3)
Italy	20 (17.4)	40 (17.5)	46 322 (9.4)
Spain	7 (6.1)	14 (6.1)	40 810 (8.3)
Sweden	16 (13.9)	32 (14.0)	49 692 (10.1)
The Netherlands	4 (3.5)	8 (3.5)	37 171 (7.5)
United Kingdom	6 (5.2)	12 (5.2)	81 804 (16.5)
France‖	—	—	69 427 (14.0)
Norway‖	—	—	35 951 (7.3)
Total	115 (100)§	229 (100)§	494 366 (100)

* Only confirmed hepatocellular carcinoma case patients and subjects with complete information are included.

† After a median follow-up of 8.9 years and a total of 4 409 809 person-years.

‡ Control subjects had to be alive as of the time of diagnosis of the corresponding case patients and were matched with case patients for study center, sex, age at the time of blood collection (±12 months), date of blood collection (±2 months), and time of day of blood collection (±3 hours). Women were further matched by menopausal status (pre-, post-, or perimenopausal) and use of exogenous hormones (oral contraceptives for premenopausal women and hormone replacement therapy for postmenopausal women) at time of blood collection (yes or no).

§ For one hepatocellular carcinoma case patient, only one control subject was available for whom there was no missing data on the examined risk factors.

‖ No eligible case patients were identified in the cohorts of France and Norway, which include women only.

Table 2. Distribution of risk factors at enrollment for the 115 incident hepatocellular carcinoma case patients and 229 matched control subjects, by sex

	Men		Women		All subjects	
	Hepatocellular carcinoma case patients (n = 80)	Matched control subjects (n = 159)	Hepatocellular carcinoma case patients (n = 35)	Matched control subjects (n = 70)	Hepatocellular carcinoma case patients (n = 115)	Matched control subjects (n = 229)
Risk factor	**No. (%)**	**No. (%)**	**No. (%)**	**No. (%)**	**No. (%)**	**No. (%)**
Chronic hepatitis B virus infection						
No	69 (86.3)	155 (97.5)	29 (82.9)	68 (97.1)	98 (85.2)	223 (97.4)
Yes	11 (13.8)	4 (2.5)	6 (17.1)	2 (2.9)	17 (14.8)	6 (2.6)
Chronic hepatitis C virus infection						
No	65 (81.3)	157 (98.7)	24 (68.6)	65 (92.9)	89 (77.4)	222 (96.9)
Yes	15 (18.8)	2 (1.3)	11 (31.4)	5 (7.1)	26 (22.6)	7 (3.1)
Body mass index						
Under- or normal weight (<25 kg/m^2)	23 (28.8)	50 (31.5)	12 (34.3)	16 (22.9)	35 (30.4)	66 (28.8)
Overweight (25 to <30 kg/m^2)	32 (40.0)	85 (53.5)	13 (37.1)	32 (45.7)	45 (39.1)	117 (51.1)
Obese (≥30 kg/m^2)	25 (31.3)	24 (15.1)	10 (28.6)	22 (31.4)	35 (30.4)	46 (20.1)
Physical activity						
Generally active*	46 (57.5)	80 (50.3)	21 (60.0)	48 (68.6)	67 (58.3)	128 (55.9)
Generally inactive*	34 (42.5)	79 (49.7)	14 (40.0)	22 (31.4)	48 (41.7)	101 (44.1)
Education						
At least secondary or technical school level	43 (53.8)	94 (59.1)	11 (31.4)	23 (32.9)	54 (47.0)	117 (51.1)
Less educated	37 (46.3)	65 (40.9)	24 (68.6)	47 (67.1)	61 (53.0)	112 (48.9)
Smoking status						
Never	10 (12.5)	48 (30.2)	21 (60.0)	49 (70.0)	31 (27.0)	97 (42.4)
Former	32(40.0)	76 (47.8)	6 (17.1)	11 (15.7)	38 (33.0)	87 (38.0)
Current	38 (47.5)	35 (22.0)	8 (22.9)	10 (14.3)	46 (40.0)	45 (19.6)
Alcohol intake at baseline, g/d						
None to low†	41 (51.3)	69 (43.4)	22 (62.9)	44 (62.9)	63 (54.8)	113 (49.3)
Moderate†	20 (25.0)	68 (42.8)	5 (14.3)	22 (31.4)	25 (21.7)	90 (39.3)
High†	19 (23.8)	22 (13.8)	8 (22.9)	4 (5.7)	27 (23.5)	26 (11.4)
Regular coffee intake, g/d						
≥250	41 (51.3)	99 (62.3)	14 (40.0)	28 (40.0)	55 (47.8)	127 (55.5)
<250	39 (48.8)	60 (37.7)	21 (60.0)	42 (60.0)	60 (52.2)	102 (44.5)
Total	80 (100)	159 (100)	35 (100)	70 (100)	115 (100)	229 (100)

* Based on the physical activity index (18).

† None to Low: Men (0 to <10) g/d and Women (0 to <5) g/d; Moderate: Men (10 to <40) g/d and Women (5 to <20) g/d; High: Men (≥40) g/d and Women (≥20) g/d. Twelve grams of ethanol correspond to approximately one normal glass or serving of each type of alcoholic beverage.

Table 3. Conditional logistic regression–derived odds ratios (OR) and associated 95% confidence intervals (CI) for developing hepatocellular carcinoma in relation to established or suggested risk factors at enrollment

	Unadjusted*		Fully adjusted†						
	All subjects		All subjects		Males		Females		
Risk factor	OR (95% CI)	*P*§	OR (95% CI)	*P*§	OR (95% CI)	*P*§	OR (95% CI)	*P*§	$P_{interaction}$ by sex‡
Chronic Hepatitis B virus infection									.704
No	Referent		Referent		Referent		Referent		
Yes	7.80 (2.61 to 23.31)	<.001	9.10 (2.10 to 39.50)	.003	15.51 (1.99 to 120.59)	.009	4.03 (0.24 to 68.48)	.334	
Chronic Hepatitis C virus infection									.118
No	Referent		Referent		Referent		Referent		
Yes	12.14 (4.22 to 34.94)	<.001	13.36 (4.11 to 43.45)	<.001	57.46 (5.61 to 588.64)	.001	8.74 (1.55 to 49.12)	.014	
Body Mass Index									.051
Not obese (<30 kg/m^2)	Referent		Referent		Referent		Referent		
Obese (≥30 kg/m^2)	1.81 (1.06 to 3.10)	.029	2.13 (1.06 to 4.29)	.035	3.66 (1.46 to 9.14)	.006	0.57 (0.15 to 2.12)	.399	
Education									.709
At least secondary or technical school level	Referent		Referent		Referent		Referent		
Less educated	1.22 (0.75 to 1.98)	.433	1.64 (0.88 to 3.05)	.118	1.99 (0.93 to 4.28)	.076	1.60 (0.45 to 5.64)	.466	
Ethanol intake at baseline, g/d									.215
None to low¶	Referent		Referent		Referent		Referent		
Moderate¶	0.48 (0.27 to 0.85)	.012	0.48 (0.24 to 0.97)	.042	0.41 (0.17 to 0.98)	.045	0.57 (0.14 to 2.42)	.450	
High¶	2.11 (1.04 to 4.27)	.038	1.77 (0.73 to 4.27)	.205	1.17 (0.40 to 3.40)	.771	7.10 (0.69 to 73.38)	.100	
Regular coffee intake, g/d									.336
≥250	Referent		Referent		Referent		Referent		
<250	1.70 (0.94 to 3.07)	.077	1.36 (0.66 to 2.79)	.405	1.56 (0.67 to 3.64)	.306	0.70 (0.10 to 4.90)	.715	
Smoking status									
Nonsmokers	Referent		Referent		Referent		Referent		.805
Former smokers	1.73 (0.89 to 3.36)	.105	1.98 (0.90 to 4.39)	.092	1.72 (0.60 to 4.90)	.312	1.35 (0.30 to 5.95)	.695	
Current smokers	4.60 (2.23 to 9.49)	<.001	4.55 (1.90 to 10.91)	.001	5.37 (1.72 to 16.75)	.004	1.70 (0.34 to 8.54)	.520	

* Through conditional logistic regression, focusing on one risk factor at a time.

† Through conditional logistic regression, adjusting mutually for all indicated possible risk factors.

‡ Likelihood ratio test, two-sided.

§ Wald test, two-sided.

¶ None to Low: Men (0 to <10) g/d and Women (0 to <5) g/d; Moderate: Men (10 to <40) g/d and Women (5 to <20) g/d; High: Men, (≥40) g/d and Women (≥20) g/d.

HBV infection, OR = 9.10, 95% CI = 2.10 to 39.50; for HCV infection, OR = 13.36, 95% CI = 4.11 to 43.45). A substantial and statistically significant increase of hepatocellular carcinoma risk was evident among current smokers (OR = 4.55, 95% CI = 1.90 to 10.91) more than former smokers (OR = 1.98, 95% CI = 0.90 to 4.39). Obesity was also positively associated with hepatocellular carcinoma risk, although the association was only present among the more numerous male subjects (among men, OR = 3.66, 95% CI = 1.46 to 9.14; among all subjects, OR = 2.13, 95% CI = 1.06 to 4.29). Heavy drinkers appeared also to be at increased risk, but the association was not statistically significant (OR = 1.77, 95% CI = 0.73 to 4.27). By contrast, there was no evidence that moderate consumption of alcohol, simple overweight (BMI from 25 to 29.9 kg/m^2), low educational level (less than secondary or technical school), or reduced coffee intake (<250 g/d) was associated with increased hepatocellular carcinoma risk. Adjustment for energy intake and/or physical activity did not noticeably change adjusted odds ratio estimates (data not shown). There was no statistically significant interaction by sex in any of the indicated associations, although for BMI, the *P* value for interaction was close to .05 (likelihood ratio test).

We also calculated the population attributable fractions (as percentages) for the five most important hepatocellular carcinoma risk factors from both the literature and this study, that is, chronic HBV or HCV infection, obesity, high alcohol intake, and current or past tobacco smoking (Table 4). Because neither the literature nor our data indicated statistically significant interactions of the indicated five exposures with sex with respect to hepatocellular carcinoma occurrence, we used the overall mutually adjusted odds ratios from Table 3. This was particularly relevant with respect to obesity, for which the odds ratios associated with hepatocellular carcinoma appeared to differ (although not at a statistically significant level) between sexes. We estimated the prevalence of exposure to the indicated risk factors from the data in our study; while interpreting these findings, one must consider that the EPIC population comprises volunteers, who are likely characterized by lower prevalence of these risk factors. Overall, a substantial fraction (47.6%) of the burden of hepatocellular carcinoma in this European population was attributed to ever smoking (for current smoking 31.2%, 95% CI = 17.3% to 43.3%; for former smoking 16.4%, 95% CI = −5.9% to 32.0%). Other substantial contributors were chronic HCV infection (20.9%, 95% CI = 12.8% to 29.2%), chronic HBV infection (13.2%, 95% CI = 5.7% to 20.3%), obesity (16.1%, 95% CI = −0.7% to 29.3%), and heavy alcohol intake (10.2%, 95% CI = −8.6% to 22.5%). When we excluded EPIC centers in which blood donors had contributed to the formation of the respective cohorts, the overall attributable fractions changed only marginally: for HBV, from 13.2% to 12.1%; for HCV, from 20.9 % to 20.7%; for obesity, from 16.1% to 15.4%; for high regular alcohol intake, from 10.2% to 9.7%; for current smoking, from 31.2% to 33.3%; and for former smoking, from 16.4% to 16.8%. When we excluded subjects who were chronically infected with HBV or HCV, the overall attributable fractions were as follows: for obesity, 20.9%; for high regular alcohol intake, 18.0%; for current smoking, 32.2%; and for former smoking, 13.7%.

We also calculated the population attributable fraction of hepatocellular carcinoma for the presence of at least one of the five risk factors indicated above (not including former smoking). This fraction was 65.7% (95% CI = 50.6% to 79.3%), indicating that about two-thirds of hepatocellular carcinoma cases were attributable to established risk factors for this disease. Among hepatitis virus–negative hepatocellular carcinoma case patients, the population attributable fraction of hepatocellular carcinoma for the presence of at least one of the three risk factors indicated above (obesity, heavy alcohol drinking, and current smoking) was 51.6%, indicating that in the absence of chronic hepatitis virus infection, about half of the hepatocellular carcinoma cases were attributable to established risk factors for this disease.

Discussion

In an incidence density-matched case–control study nested within the EPIC cohort and comprising 115 histologically confirmed incident case patients of hepatocellular carcinoma and 229 control subjects, we identified statistically significant associations for chronic HBV infection (OR = 9.10), chronic HCV infection (OR = 13.36), obesity (OR = 2.13), and current smoking at enrollment (OR = 4.55). Plausible, but statistically not significant in these data, associations were found for high alcohol intake (OR = 1.77) and former smoking (OR = 1.98). We also calculated attributable fractions for this Europe-wide cohort. We have estimated that tobacco smoking contributed to almost half of the hepatocellular carcinoma cases in this population (47.6%; ie, 31.2% for current and

Table 4. Percentages of the hepatocellular carcinoma burden in the European Prospective Investigation into Cancer and nutrition (EPIC) population that can be attributed to each or any of the indicated factors, by sex*

Causal exposures	Men	Women	Overall	Overall excluding blood donors	Overall excluding HBV/HCV positives
Chronic HBV infection	12.2	15.3	13.2	12.1	—
Chronic HCV infection	17.3	29.1	20.9	20.7	—
Former smoking	19.8	8.5	16.4	16.8	13.7
Current smoking	37.1	17.8	31.2	33.3	32.2
Obesity (body mass index ≥30 kg/m^2)	16.6	15.1	16.1	15.4	20.9
Heavy ethanol consumption at baseline†	10.3	9.9	10.2	9.7	18.0
Any of the above	67.1	62.7	65.7	65.5	51.6

* HBV = hepatitis B virus; HCV = hepatitis C virus

† Men: alcohol intake: ≥40 g/d; Women, alcohol intake ≥20 g/d.

16.4% for former smokers), whereas chronic infection with HBV or HCV contributed to 13.2% and 20.9%, respectively. We also estimated that obesity (BMI ≥ 30 kg/m^2) and high regular ethanol intake contribute 16.1% and 10.2%, respectively, to the burden of the disease. Attributable fractions are not additive, but almost two-thirds (65.7%, 95% CI = 50.6% to 79.3%) of hepatocellular carcinomas in this European population can be accounted for by exposure to at least one of the documented strong risk factors for this disease.

Large as it is estimated to be, the apparent population attributable fraction for hepatocellular carcinoma is still likely to be an underestimate. The EPIC participants are volunteers and, as such, are expected to have relatively low prevalence of chronic infection of HBV and/or HCV, and to less often be current smokers and heavy drinkers than the general population. There is indeed convincing evidence that the prevalence of current smoking (27) and heavy drinking (28), though not systematically that of obesity (29), is higher in the general adult population of the countries that have contributed to the EPIC project than among the control subjects in this study. With respect to the prevalence of chronic infection with HBV and HCV, the population-based data in the EPIC countries have been reported to vary from less than 0.5% in northern European countries to about 4% in southern European countries for both HBV and HCV (30).

With respect to cause-specific population attributable fractions (Table 4), these are likely to vary among countries, as the prevalence of each of the six indicated exposures also varies (27–30). Nevertheless, the order of magnitude indicated in Table 4 does reflect the contribution of the established risk factors for hepatocellular carcinoma to the burden of the disease in this European cohort. With respect to tobacco smoking, we did not take into account the duration of the smoking habits, which, at least with respect to lung cancer, is a stronger determinant of risk than the daily dose of cigarette smoking (31). However, evidence has emerged that tobacco smoking may operate mostly in the late stage of hepatocellular carcinoma development (32), and the most relevant available metric of exposure to tobacco smoking in our study is captured by the information on smoking behavior at enrollment, rather than smoking behavior over a lifetime. Our estimate for the hepatocellular carcinoma population attributable fraction due to alcohol consumption is lower than those reported from other studies in economically developed countries (33) and, notably, from that reported from a study in the overall EPIC cohort (34). In the latter study, the relevant population attributable fraction was estimated at 33% (95% CI = 11% to 54%) among men and at 18% (95% CI = −3% to 38%) among women, for an average around 25%. This figure should be compared with our estimates of about 10% overall or 18% among hepatitis virus–negative hepatocellular carcinoma case patients. Although the respective confidence intervals are wide and extensively overlapping, the main reasons for the higher fractions in other studies, including the overall EPIC study, are likely to be that 1) past drinkers, who are thought to remain at high risk for hepatocellular carcinoma (33), were not specifically studied in our investigation (there were not enough control subjects to allow meaningful cross-tabulations by current and past drinking habits); 2) calculations in other studies, including the overall EPIC study (34), relied on generally higher estimates of prevalence of drinking habits in the general population, as derived from independent sources (a legitimate approach which, however, generates difficulties in the calculation of the confidence intervals); and 3) in most other studies, including the overall EPIC study, confounding generated by the coexistence of chronic infection with HBV or HCV and excessive ethanol intake could not be accounted for, as it was in our investigation.

A strength of this study is its reliance on a prospective cohort design and the coverage of several European countries with variable prevalent patterns of exposures relevant to hepatocellular carcinoma risk. Other strengths of the study include the use of a uniform protocol and the centralized laboratory determinations of markers of hepatitis B and C infections. Lastly, the sample size can be considered adequate for a cohort study in Caucasians, among whom hepatocellular carcinoma is a rare tumor.

There are also limitations to this study. We did not have adequate information on possible coexisting cirrhosis, but this condition is frequently an intermediate in the pathophysiological process that links chronic infection with HBV and particularly HCV, as well as alcohol drinking, with hepatocellular carcinoma; as such, this is a variable that should not be controlled for in the analysis. We have not evaluated the role of diabetes mellitus, but we did evaluate overweight and obesity. We did not evaluate aflatoxin exposure, an established risk factor for hepatocellular carcinoma, but this exposure is more relevant for the occurrence of the disease in Africa or South Asia rather than in Europe or the United States. We did not take into account possible occupational or pharmaceutical exposures linked to liver cancer which, however, appear to be rare and mostly related to angiosarcoma rather than hepatocellular carcinoma (11). We also did not take into account qualitative aspects of the diet, for which a role in hepatocellular carcinoma is plausible but not fully documented (35,36); thus, we cannot exclude the possibility of some residual confounding by diet or, indeed, other unidentified confounding factors. We used broad categories for exposure to tobacco smoking, alcohol drinking, and obesity, but we have used cutoffs that are widely used in the literature; moreover, using broad categories is not considered an important disadvantage when the focus of the study is the determination of the population attributable fraction (37,38). Finally, we could not explore possible interactions among these five documented risk factors for hepatocellular carcinoma because of power limitations.

In conclusion, we have shown that hepatocellular carcinoma, one of the most lethal human cancers, is largely amenable to primary prevention with existing knowledge and technology. Moreover, we have shown that although chronic infection with HBV and/or HCV was the strongest risk factor for hepatocellular carcinoma, tobacco smoking was responsible for more cases of hepatocellular carcinoma than either or both these viruses in this population. Finally, our data support existing evidence that heavy, although not moderate, alcohol consumption may increase hepatocellular carcinoma risk and that obesity, although not simple overweight, also plays a major role in the occurrence of the disease.

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Funding

This work was supported by the French National Cancer Institute (Institut National du Cancer; INCA) (grant number 2009-139). The coordination of EPIC is financially supported by the European Commission (DG-SANCO); and the International Agency for Research on Cancer. The national cohorts are supported by Danish Cancer Society (Denmark); Ligue Contre le Cancer; Institut Gustave Roussy; Mutuelle Générale de l'Education Nationale; and Institut National de la Santé et de la Recherche Médicale (INSERM) (France); Deutsche Krebshilfe, Deutsches Krebsforschungszentrum; and Federal Ministry of Education and Research (Germany); Stavros Niarchos Foundation; Hellenic Health Foundation; and Ministry of Health and Social Solidarity (Greece); Italian Association for Research on Cancer (AIRC); National Research Council; and AIRE-ONLUS Ragusa, AVIS Ragusa, Sicilian Government (Italy); Dutch Ministry of Public Health, Welfare and Sports (VWS); Netherlands Cancer Registry (NKR); LK Research Funds; Dutch Prevention Funds; Dutch ZON (Zorg Onderzoek Nederland); World Cancer Research Fund (WCRF); and Statistics Netherlands (the Netherlands); European Research Council (ERC) (grant number ERC-2009-AdG 232997) and Nordforsk; and Nordic Center of Excellence Programme on Food, Nutrition and Health (Norway); Health Research Fund (FIS); Regional Governments of Andalucía, Asturias, Basque Country, Murcia (No. 6236) and Navarra; and ISCIII RETIC (RD06/0020) (Spain); Swedish Cancer Society; Swedish Scientific Council; and Regional Government of Skåne and Västerbotten (Sweden); Cancer Research UK; Medical Research Council; Stroke Association; British Heart Foundation; Department of Health; Food Standards Agency; and Wellcome Trust (UK).

Notes

Reagents for the hepatitis infection determinations were kindly provided by Abbott Diagnostics Division, Lyon, France.

The study sponsors had no role in the design of the study, the collection, analysis and interpretation of the data, the writing of the article, and the decision to submit the article for publication.

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