

Table 2.2. Case-control studies of HCV and hepatocellular carcinoma

Reference, study location and period	Characteristics of cases	Characteristics of controls	Detection method	Exposure categories	No. of exposed cases	Relative risk [odds ratio] (95% CI)	Adjusted potential confounders	Comments
<i>Africa</i> Cenac <i>et al.</i> (1995) Niger, 1983–1985	26 Sahelian Africans with HCC (19 men, 7 women), hospitalized in the Department of Internal Medicine at the National Hospital in Niamey; mean age (years): 49 (±11) for men, 40 (±18) for women; participation rate NR; histological confirmation rate NR	47 Sahelian Africans (24 men, 23 women), without acute or chronic liver disease and normal serum transaminase level, hospitalized in same department as cases during same period; mean age (years): 44 (±18) for men, 39 (±13) for women; participation rate NR	Anti-HCV: second-generation enzyme-linked immunosorbent assay (ELISA)	Anti-HCV Neg Pos	20 6	1.0 [4.4 (1.0–19.4)]		Of the controls, 3 had hepatic metastasis, 3 had malignant lymphoma, and 2 had leukaemia.
Kew <i>et al.</i> (1997) South Africa [study period NR]	231 southern African blacks with HCC (201 men, 30 women), treated consecutively at 4 Johannesburg hospitals; mean age and age range: 44.8 and 18–82 years; histological confirmation rate NR	231 patients from same 4 hospitals as cases, with disease not known to be caused by HBV or HCV; matched to cases on race, sex, age (±2 years), geographic background (rural, urban, rural-urban), hospital, type of ward (medical, surgical), and tribal ethnicity when possible; age range: 16–84 years; participation rate NR	Anti-HCV: second- or third-generation ELISA assays HCV RNA: Amplicor reverse-transcription polymerase chain reaction (RT-PCR) with confirmation by in-house nested RT-PCR	No HCV markers Anti-HCV-/HCV RNA+ Anti-HCV+/HCV RNA- Anti-HCV+/HCV RNA+	172 11 14 34	1.0 4.3 (1.2–15.6) 2.8 (1.0–7.8) 14.2 (4.2–48.0)	Race, sex, age, geographic background, hospital, type of ward, and tribal ethnicity	

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Hassan <i>et al.</i> (2001) Egypt, 1995–1996	33 cases of histologically confirmed HCC (23 men, 10 women), patients at University of Cairo National Cancer Institute; mean age: 55.2 (\pm 9.2) years; participation rate, 100%	35 healthy individuals (14 men, 21 women), visiting non-relative HCC case, with no history of liver tumours; mean age: 50.5 (\pm 10.1) years; participation rate, 100%	Anti-HCV: second-generation ELISA, with confirmation by radio-immunoblot assay (RIBA)	Anti-HCV Neg Pos	8 25	1.0 5.1 (1.5–17.4)	Age and sex	
<i>Americas</i> Hassan <i>et al.</i> (2002) USA, 1994–1995	115 newly diagnosed cases of histologically confirmed HCC (87 men, 28 women), diagnosed and examined at University of Texas M.D. Anderson Cancer Center; mean age: 59.5 (\pm 10.7) years; participation rate, 100%	230 non-liver cancer controls (174 men, 56 women), diagnosed at University of Texas M.D. Anderson Cancer Center with histologically confirmed primary tumours of gastrointestinal tract (44.3%), urogenital tract (18.7%), respiratory tract (17.8%), and skin (19.1%); two controls matched to each case on sex, age (\pm 5 years), and year of diagnosis and recruited within 15 days of case enrollment; mean age: 59.1 (\pm 10.9) years; participation rate, 100%	Anti-HCV: second-generation ELISA, with confirmation by RIBA	Anti-HCV Neg Pos	89 26	1.0 14.1 (4.0–49.7)	Age, sex, year of diagnosis, HBsAg, alcohol consumption, cigarette smoking, and diabetes mellitus	

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Yuan <i>et al.</i> (2004) USA, 1984–2001	295 cases of histologically confirmed HCC (192 men, 103 women), diagnosed in black, Hispanic, and non-Hispanic white residents aged 18–74 and identified through population-based cancer registry (Los Angeles County Cancer Surveillance Program); mean age: 60.6 (\pm 10.9) years; 84% of eligible cases died prior to contact; of 473 cases contacted, 320 (68%) were interviewed of whom 25 were determined not to have HCC; 245 cases had available blood sample for anti-HCV testing	435 community controls (270 men, 165 women), up to 2 controls recruited from neighbourhoods in which HCC cases resided at time of diagnosis; matched to case by sex, age (\pm 5 years), and race; mean age: 60.1 (\pm 11.4) years; blood collected from controls beginning in 1992: of 264 requested, 198 (75%) consented; of 60 controls interviewed from 1989 to 1991, blood was collected from 22 (37%); 220 controls had available blood sample for anti-HCV testing	Anti-HCV: second-generation ELISA, with confirmation by second-generation RIBA; 43 HCC cases tested with first-generation ELISA	Anti-HCV Neg Pos	146 99	1.0 125 (17.1–909)	Age, sex, race, and level of education	111 of 295 HCC cases identified through 1994 were analyzed and reported in Yu <i>et al.</i> (1997).
<i>Asia</i> Park <i>et al.</i> (1995) Korea, 1992–1994	540 cases of HCC (433 men, 109 women), admitted to Kosin University Hospital and living in Pusan city area; mean age: 53.4 (\pm 10.3) years; histological confirmation rate NR	808 individuals (431 men, 377 women), visited Department of Health care of same hospital as cases for annual routine health check in 1992–1993; none had biochemical or clinical features of liver disease; mean age: 49.9 (\pm 15.2) years.	Anti-HCV: second-generation ELISA	Anti-HCV Neg Pos	463 77	1.0 23.9 (17.4–32.9)	HBsAg, HBsAb, and HBcAb	

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Shin <i>et al.</i> (1996) Korea, 1990–1993	203 consecutive cases of newly diagnosed HCC (159 men, 44 women), admitted to Inje University Pusan Paik Hospital; mean age: 53.0 (±8.5) years; histological confirmation: 53%	406 control subjects from 2 groups: (1) 203 inpatients from same hospital as cases, from Departments of Ophthalmology and Otorhinolaryngology without liver disease, systemic disease and malignant disorders and (2) 203 healthy people who visited Non-Communicable Disease Control Center of same hospital for routine check-up; controls from both groups recruited during same period as cases (participation rates NR) and individually matched to cases by sex and age (±4) years Control groups were combined in analysis.	Anti-HCV: second-generation ELISA [personal communication]	Anti-HCV Neg Pos	151 19	1.0 30.3 (6.1–151)	Age, sex, socioeconomic status, HBsAg positivity, <i>Clonorchis sinensis</i> in stool, transfusion history, hepatitis history, liver fluke history, drinking history, smoking history	

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Sun <i>et al</i> (1996) Taiwan, China 1991–1994	58 cases of HCC (51 men, 7 women), identified as part of community-based, 2-stage liver cancer screening programme in 7 townships in Penghu Islets and main Taiwan Island; first-stage screening was based on having one of 6 criteria: elevated aspartate transaminase, alanine transaminase, or alpha-fetoprotein, presence of HBsAg or anti-HCV, and family history of HCC or cirrhosis in first-degree relative; second-stage screening was by ultrasonography, with subsequent referral to teaching medical centres for confirmatory examinations; mean age: 55.0 (\pm 7.0) years; histological confirmation: [38%]	225 participants in same liver cancer screening programme as cases (198 men, 27 women), who were not affected with subclinical HCC based on second-stage screening with ultrasonography; individually matched to cases on age (\pm 5 years), sex, residence, and date of serum sample collection (\pm 3 months); mean age: 54.2 (\pm 6.8) years	Anti-HCV: second-generation EIA HCV RNA: Amplicor RT-PCR	Anti-HCV Neg	50	1.0	Age, sex, residence, date of serum collection, and HBsAg	The results from 3 of 7 townships were published elsewhere Chen <i>et al.</i> (1996).
				Pos	8	8.8 (1.8–43.0)		
				HCV RNA Neg	50	1.0		
				Pos	8	6.2 (1.4–26.6)		

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Tanaka <i>et al.</i> (1996) Japan, 1985–1989	91 cases of HCC (73 men, 18 women), residents aged 40–69 years of Fukuoka or Saga Prefecture who were admitted to Kyushu University Hospital within study period, had been diagnosed within past year, and had an available stored sample; median age (years): 59.0 for men, 56.5 for women; cases represent; histological confirmation: [33%]	410 residents of Fukuoka City (291 men, 119 women), aged 40–69 years who underwent health examinations at public health centre near Kyushu University Hospital between 1986 and 1989; selected so sex and age distribution was similar to cases; excluded if had definite chronic liver disease or from whom blood sample could not be obtained; median age (years): 57.0 for men, 56.0 for women; participation rate NR	Anti-HCV: second-generation immunoradiometric assay, with confirmation by second-generation RIBA	Anti-HCV Neg Pos	20 71	1.0 53.7 (27.1–106)	Age and sex	Re-tested stored samples from original study published by Tanaka et al. (1991) using second-generation assays [OR (95%CI)=52 (24-114)] in original study).
Tsai <i>et al.</i> (1996) Taiwan, China 1991–1993	361 newly diagnosed cases of histologically confirmed HCC (303 men, 58 women), consecutively admitted to Kaohsiung Medical College Hospital; mean age: 53 (±11) years	361 healthy patients came to same hospital as cases for physical check-up during same time period, with no reported history of liver disease and with normal transaminase levels; matched to cases on sex and age (±5 years); mean age: 52 (±10) years	Anti-HCV: second generation EIA, with confirmation by re-testing with same EIA as well as another second-generation EIA	Anti-HCV Neg Pos	254 107	1.0 59.3 (13.6–258)	Age, sex, HBsAg, and HBeAg,	

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Lu <i>et al.</i> (1999) Taiwan, 1991–1995	27 cases of HCC (18 men, 9 women), hospitalized at 2 medical centres in Kaohsiung and residents of Tzukung Township; mean age: 60 (± 7.3) years; histological confirmation rate NR; anti-HCV status abstracted from medical records	108 community controls, from database of community survey of HCV infection among residents of Tzukung township in 1993, all received ultrasonography to rule out HCC; 4 controls matched to each case on sex and age (± 2 years)	Anti-HCV: specific assays used NR	Anti-HCV Neg Pos	3 24	1.0 [OR=6.9 (2.0–24.3)]		
<i>Europe</i> Hadziyannis <i>et al.</i> (1995) Greece, 1991–1992	65 incident cases of HCC (49 men, 16 women), admitted to 2 teaching hospitals in Athens; age range: 35–84 years; participation rate: 89%; histological confirmation: 58%	Two control groups: (1) 65 metastatic liver cancer (MLC) patients whose primary malignancy had no etiological connection to HCV or HBV, (2) 65 other hospital control (OHC) patients hospitalized with eye, ear, nose, or throat non-cancer conditions; matched to cases on hospital, sex, and age (± 5 years); participation rate: 90% for MLC, 93% for OHC	Anti-HCV: second-generation EIA, with confirmation by second-generation RIBA	Anti-HCV Neg Pos	57 8	1.0 vs MLC: 3.8 (0.81–17.5) vs OHC: Infinite (no positive OHC) vs both: 7.7 (1.7–35.1)	Age, sex, and HBsAg	

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De Vita <i>et al.</i> (1998) Italy, 1994–1997	27 incident HIV-negative HCC patients (18 men, 9 women), newly diagnosed at Aviano Cancer Centre and Pordenone General Hospital; part of case-control study of NHL; median age: 63 years; histological confirmation NR	73 hospital-based controls without lymphohaemopoietic neoplasms (34 men, 39 women), patients from discharge lists of same hospitals during same study period with valid information on HCV status, diagnosed with histologically confirmed cancers of ovary, uterus, colon-rectum, pancreas, lung, stomach, and oesophagus, or other cancers; group matched to NHL cases on sex and age (median age: 64 years); participation rate NR	Anti-HCV: second-generation ELISA, with confirmation by RIBA	Anti-HCV Neg Pos	16 11	21.9 (4.8–99.9)	Age, sex, and birthplace	
Tagger <i>et al.</i> (1999) Italy, 1995–1998	305 incident cases of HCC (244 men, 61 women), admitted to 2 main hospitals in province of Brescia (Brescia HCC Study); all cases born in Italy, residents of Brescia, and less than 76 years of age; age range: 40–75 years; [participation rate: 94%]; histological confirmation: 85%	610 patients without liver disease or malignant neoplasms (495 men, 115 women), admitted to departments of ophthalmology, dermatology, urology, surgery, cardiology, and internal medicine of same hospitals as cases; all controls born in Italy, residents of Brescia, and less than 76 years of age; frequency matched to cases on age (± 5 years), sex, and date and hospital of admission; age range: 40–75 years; [participation rate: 96%]	Anti-HCV: third-generation ELISA, with confirmation by third-generation RIBA HCV RNA (if anti-HCV+): RT-PCR	Anti-HCV- Anti-HCV+/HCV RNA- Anti-HCV+/HCV RNA+	176 7 122	1.0 1.5 (0.5–4.5) 26.3 (15.8–44.0)	Age, sex, residence, HBV status, and alcohol intake	The results from HCC cases and hospital controls enrolled through 1996 and 2000 were published in Donato <i>et al.</i> (1997) and Donato <i>et al.</i> (2002), respectively.

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Kuper <i>et al.</i> (2000) Greece, 1995-1998	333 incident cases of HCC (283 men, 50 women), admitted to 3 teaching hospitals in Athens; mean age: 64.0 years; participation rate: 89%; histologic confirmation: 47%	Two control groups: (1) 272 metastatic liver cancer (MLC) patients (172 men, 100 women) whose primary malignancy had no etiological connection to HCV or HBV, (2) 360 other hospital control (OHC) patients hospitalized for injuries or eye, ear, nose, or throat non-cancer conditions; matched to cases on hospital, sex, and age (± 5 years); participation rate: 90% for MLC, 94% for OHC	Anti-HCV: third-generation EIA	Anti-HCV Neg Pos	281 52	1.0 vs MLC: 10.2 (4.8–21.5) vs OHC: 170.4 (22.9–999) vs both: 23.2 (11.4–47.3)	Age, sex, schooling, and HBsAg	The results from HCC cases and hospital controls enrolled, 1991-1992, were published in Hadziyannis <i>et al.</i> (1995).
Montella <i>et al.</i> (2001a) Italy, 1997-1999	114 cases of liver cancer (88 men, 26 women), incident cancer patients diagnosed at National Cancer Institute and Cardarelli Hospital in Naples, all Italian-born, HIV-negative, heterosexual, with no history of intravenous drugs or alcohol abuse, and no interferon treatment; age range: 45-82 (median: 65) years; participation rate NR; histological confirmation NR	226 patients with no history of malignant tumour (110 men, 116 women; age range: 20–97 [median: 55] years), admitted to same hospitals in same time period as cases, all Italian-born, HIV-negative, heterosexual, with no history of intravenous drugs or alcohol abuse, and no interferon treatment; participation rate NR	Anti-HCV: third-generation ELISA, with positive samples re-tested for HCV RNA by Amplicor RT-PCR assay	Anti-HCV– and anti-HCV+/HCV RNA– HCV RNA+	26 88	1.0 32.9 (16.5–65.4)	Age and sex	No details concerning diagnosis of liver cancer

Comment [SM1]: Letter distinction is missing in the list of refs

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Gelatti <i>et al.</i> (2005) Italy, 1999–2002	200 cases of HCC (158 men, 42 women), about half recruited from 3 hospitals in province of Brescia and half from 2 hospitals in province of Pordenone; all cases born in Italy and less than 79 years of age; mean age: 66.5 (±8.0) years; participation rate: >95%; histological confirmation rate NR	400 patients hospitalized for reasons other than liver disease, neoplasms, and tobacco- or alcohol-related disease (316 men, 84 women), admitted to Departments of Ophthalmology, Dermatology, Orthopedic Surgery, General Surgery, and General Medicine in same hospitals as cases; all controls born in Italy and less than 79 years of age; frequency-matched to cases on age (±5 years), sex, and date and hospital of admission; participation rate: >95%	Anti-HCV: third-generation ELISA HCV RNA (if anti-HCV+): RT-PCR	Anti-HCV– and anti-HCV+/HCV RNA– HCV RNA+ anti-HCV+)	108 92	1.0 17.1 (10.0–29.3)	Age, sex, area of recruitment, HBsAg, and alcohol consumption	Not clear if there is some overlap with Brescia HCC Study A substantial number of HCC cases and controls may have been included in the study by Franceschi <i>et al.</i> (2006a).
Franceschi <i>et al.</i> (2006a) Italy, 1999–2002	229 cases of incident HCC (183 men, 46 women), patients <85 years old at 2 national cancer institutes, 1 hospital in province of Pordenone, and 4 hospitals in Naples, not yet received treatment; age range: 43–84 (median: 66) years; participation rate: [99%], [89%] with blood sample; histological confirmation: 78%	431 hospital-based controls (292 men, 139 women), patients <85 years old admitted to same hospitals as cases, for acute conditions – exclusions: conditions related to alcohol and tobacco consumption, hepatitis, and chronic disease that might have changed lifestyle habits; frequency matched to cancer cases for larger case-control study, with restriction to persons ≥40 years of age; age range: 40–83 (median: 65) years; participation rate: [99%], [93%] with blood sample	Anti-HCV: third-generation microparticle EIA, with confirmation by Inno-LIA HCV RNA: second-generation Amplicor RT-PCR assay	Anti-HCV–/ HCV RNA– Anti-HCV+/ HCV RNA– Anti-HCV+/ HCV RNA+	80 5 144	1.0 1.5 (0.50–4.3) 26.5 (15.8–44.7)	Age, sex, centre, and education	Not clear if there is some overlap with Gelatti <i>et al.</i> (2005) A substantial number of HCC cases and controls may have been included in the study by Gelatti <i>et al.</i> (2005).