2. Studies of Cancer in Humans

2.1 Case series

Studies of hepatocellular carcinoma (HCC) and seropositivity for anti-HD in case series are summarized in Table 5. The prevalence of anti-HD seropositivity varied from 0 to 88%, but the findings are difficult to interpret because of the highly variable prevalence of HDV infection in the source populations.

2.2 Case–control studies

Kew *et al.* (1984) detected neither anti-HD nor HDAg in sera from 107 HBsAg-seropositive black South Africans with HCC (101 men, six women); testing was by radioimmunoassay. Moreover, tissue HDAg was not found in neoplastic and non-neoplastic liver samples from an additional 80 cases of HCC by the direct immunoperoxidase technique. Serum anti-HD and HDAg were not present in the HBsAg-positive chronic carriers or in the renal transplant recipients tested.

Cronberg *et al.* (1984) conducted a study of 130 clinically diagnosed cases of HCC, 83 patients with other liver disorders and 50 controls in Senegal. Most of the subjects were seen at Le Dantec Hospital; the controls were primarily healthy relatives of patients. The 88 cases who were considered 'highly probable' to have HCC on the basis of an α-fetoprotein level $\geq$ 100 μg/L were compared with 31 controls with a level $\leq$ 15 μg/L. Anti-HD was found by solid-phase radioimmunoassay in 13 (20%) of the 65 HBsAg-seropositive 'highly probable' HCC cases. The investigators compared this prevalence with that of those HBsAg-seropositive people without HCC, combining the eight controls and 26 other subjects with liver disorders who had an α-fetoprotein level $\leq$ 15 μg/L in order to obtain a figure of 21%. The anti-HD prevalence was 0 in the eight HBsAg-seropositive controls and 27% in the 26 other patients. [No further details were given as to subject selection or study timing.]

Liaw *et al.* (1987) reported a 4% prevalence of HDV seropositivity among 124 HBV-carrier cases of HCC in Taiwan, China; none had a history of drug abuse or multiple blood transfusions. Two percent of asymptomatic HBsAg carriers and 14% of HBsAg-seropositive liver cirrhosis patients were also seropositive for anti-HD. Anti-HD antibody in serum was analysed by radioimmunoassay and HDAg in liver by direct immunofluorescence.

Trichopoulos *et al.* (1987a), in a study described in the monograph on HBV (p. 88; Trichopoulos *et al.*, 1987b), tested for the presence of HDAg and anti-HD in the sera of 87 HBsAg-seropositive HCC cases and 29 HBsAg-seropositive hospital controls, using ELISA for HDAg and radioimmunoassay for anti-HD. No HDAg was detected; 10% of cases and no control were reactive to anti-HD (exact $p = 0.067$). Adjustment for age and sex had no effect on the comparison. Among HCC cases, no association was found for the presence of cirrhosis and anti-HD seropositivity. A later re-analysis of these subjects for a possible interaction between HDV and HCV found no association with respect to HCC (Tzonou

Table 5. Hepatocellular carcinoma (HCC) and HDV infection in case series

Reference and location	Period	No of HCC cases	No. HBsAg seropositive	No. anti-HD seropositive	No. HDAg seropositive	% HBsAg seropositivity among HDAg seropositives	Assay for HDAg[a]
Africa							
Kew *et al.* (1984); South Africa	NR	107	107	0	0	0	RIA (serum), IP (liver)
Cenac *et al.* (1987); Niger	1982–85	29	21	14	NT	67	RIA (serum)
Americas							
Govindarajan *et al.* (1984b); USA	1971–82	39	39	1	1	3	Solid-phase blocking RIA (serum)
Asia							
Chen *et al.* (1984); Taiwan, China	NR	11	11	0	0	0	Solid-phase blocking RIA (serum), IF (liver)
Yong-Yuan *et al.* (1990); China	NR	20	16	NT	0	0	IF and IP (liver) (anti-HD IgG)
Ashraf *et al.* (1986); Saudi Arabia	1984–85	30	30	5	NT	17	RIA (serum)
Shobokshi & Serebour (1987); Saudi Arabia	NR	116 (serum) 200 (liver)	NR NR	5 NT	NT 12	NR NR	ELISA for total antibody (serum), IF (liver)
Toukan *et al.* (1987); Jordan	1978–85	15	15	10	NT	67	RIA (serum)
Rezvan *et al.* (1990); Iran (Islamic Republic of)	1986–88	8	8	5	NT	63	EIA

Table 5 (contd)

Reference and location	Period	No. of HCC cases	No. HBsAg seropositive	No. anti-HD seropositive	No. HDAg seropositive	% HBsAg seropositivity among HDAg seropositives	Assay for HDAg[a]
Europe							
Craxì *et al.* (1983); Raimondo *et al.* (1984); Italy	1977–83	79	79	8	0/18	10.1	RIA (serum), IF (liver)
Tapalaga *et al.* (1987); Romania	NR	8	8	7	NT	87.5	NR (serum)
Oliveri *et al.* (1991); Italy	1986–89	91	35	10	NT	29	IP (liver)
Verme *et al.* (1991); Italy	1986–88	62	25	9	NT	36	
Tassopoulos *et al.* (1989); Greece	1978–85	47	20	0	0	0	RIA (serum)
Hadziyannis *et al.* (1991); Greece	1970–89	303	303	59	0	19.5	RIA, ELISA (serum)

HBsAg, hepatitis B surface antigen; anti-HD, antibody to HDV; HDAg, hepatitis D antigen; NR, not reported; NT, not tested
[a]RIA, radioimmunoassay; IP, immunoperoxidase; IF, immunofluorescence; ELISA, enzyme-linked immunosorbent assay; EIA, enzyme immunoassay

et al., 1991). Of the 75 anti-HD-seronegative HCC cases tested, 52% were seropositive for anti-HC; in contrast, of the nine anti-HD-seropositive HCC cases, 33% were positive for anti-HC.

In another study, also summarized in the monograph on HBV (p. 81; Di Bisceglie *et al.*, 1991), radioimmunoassay of 99 HCC cases and 98 controls detected none with anti-HD, regardless of seropositivity for HBsAg.

These studies are summarized in Table 6.

Table 6. Case–control studies of HDV in relation to hepatocellular carcinoma among hepatitis B virus carriers[a]

Reference	Location	Seroprevalence of HDV markers				RR	95% CI
		Cases		Controls			
		No.	%	No.	%		
Trichopoulos *et al.* (1987a)	Greece	87	10	29	0	∞	[0.9–∞]
Cronberg *et al.* (1984)	Senegal	65	20	8	0	∞	[0.4–∞]
Liaw *et al.* (1987)	Taiwan, China	124	4.0	137	2.2	[1.9]	[0.4–12]

[a]In the studies of Kew *et al.* (1984) and Di Bisceglia *et al.* (1991), none of the cases or controls were anti-HD seropositive.