

## 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  $\alpha$ -fetoprotein level  $\geq 100$   $\mu\text{g/L}$  were compared with 31 controls with a level  $\leq 15$   $\mu\text{g/L}$ . 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  $\alpha$ -fetoprotein level  $\leq 15$   $\mu\text{g/L}$  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 <sup>a</sup>
<b>Africa</b>							
Kew <i>et al.</i> (1984); South Africa	NR	107	107	0	0	0	RIA (serum), IP (liver)
Cenac <i>et al.</i> (1987); Niger	1982-85	29	21	14	NT	67	RIA (serum)
<b>Americas</b>							
Govindarajan <i>et al.</i> (1984b); USA	1971-82	39	39	1	1	3	Solid-phase blocking RIA (serum)
<b>Asia</b>							
Chen <i>et al.</i> (1984); Taiwan, China	NR	11	11	0	0	0	Solid-phase blocking RIA (serum), IF (liver)
Yong-Yuan <i>et al.</i> (1990); China	NR	20	16	NT	0	0	IF and IP (liver) (anti-HD IgG)
Ashraf <i>et al.</i> (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 <i>et al.</i> (1987); Jordan	1978-85	15	15	10	NT	67	RIA (serum)
Rezvan <i>et al.</i> (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 <sup>a</sup>
<b>Europe</b>							
Craxì <i>et al.</i> (1983); Raimondo <i>et al.</i> (1984); Italy	1977-83	79	79	8	0/18	10.1	RIA (serum), IF (liver)
Tapalaga <i>et al.</i> (1987); Romania	NR	8	8	7	NT	87.5	NR (serum)
Oliveri <i>et al.</i> (1991); Italy	1986-89	91	35	10	NT	29	IP (liver)
Verme <i>et al.</i> (1991); Italy	1986-88	62	25	9	NT	36	
Tassopoulos <i>et al.</i> (1989); Greece	1978-85	47	20	0	0	0	RIA (serum)
Hadziyannis <i>et al.</i> (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  
<sup>a</sup>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<sup>a</sup>**

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

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