3. Studies of Cancer in Experimental Animals

Primate

A seven-year-old male chimpanzee (*Pan troglodytes*), seronegative for HBsAg, anti-HBs and anti-HBc and seropositive for antibodies to hepatitis A virus, was inoculated with 40 ml of serum from a human patient with chronic non-A, non-B hepatitis, who was seronegative for markers of HBV and hepatitis A virus, and 10 months thereafter with 10 ml of the chimpanzee's own acute-phase serum (taken at day 34 after inoculation). Over the next six years, the chimpanzee received inoculations of several different plasma-derived products, including concentrates of coagulation factors II, VII, VIII, IX and XIII, and anti-thrombin III. Serum levels of aspartate and alanine transferase, γ glutamyl transferase and HBV markers were monitored and liver biopsies were performed. Serum transferase levels increased after the first inoculation of the human serum and the animal's acute-phase serum. Over the next six years, the levels fluctuated above normal, and serial liver biopsies showed changes ranging from histologically normal to moderate hepatitis (which included focal hepatocellular necrosis and chronic portal inflammation). The chimpanzee remained seronegative for hepatitis B markers throughout the study. Seven years after the first inoculation, liver masses were palpable, and necropsy revealed two large (16 × 8 cm and 5 × 7 cm)

Table 9. Summary of results of case–control studies of hepatocellular carcinoma and the presence of antibody to HCV as measured by second-generation assays

Reference and location	Subjects	Seroprevalence of antibodies to HCV				OR[a]	95% CI	Study period and comments
		Cases		Controls				
		No.	%	No.	%			
Africa								
Dazza *et al.* (1993); Mozambique	NR	178	6	194	2	1.1	0.4–3.1	Blood donor controls; adjusted for age; mean age of cases, 40.8 years; controls, 31.3 years
Coursaget *et al.* (1992); Senegal	NR	49	4	134	1	[5.7]	[0.5–69]	General population controls
Asia								
Tanaka *et al.* (1991); Japan	Men and women	91	51	410	3	52	24–114	Cases, 1985–89; controls, 1986–89; general population controls; adjusted for age, sex, occupational class and education; initial screening by first-generation with confirmation by RIBA
Cordier *et al.* (1993); Viet Nam	Men	152	2	241	1	2.0	0.3–17	1989–92; hospital controls
Europe								
Stroffolini *et al.* (1992); Italy	Men and women	65	66	99	13	27	9.9–73	1990; all cases had cirrhosis and controls had non-hepatic chronic disease; adjusted for age, sex, hospital and HBV markers
	HCV antibody seropositive and HBsAg seropositive *versus* neither					77	3.8–1421	Adjusted for age, sex and hospital; 0.5 added to each entry; confirmation by RIBA
Zavitsanos *et al.* (1992); Greece	Men and women	181	13	446	1	10	4.2–26.0	1976–84; same subjects as Tzonou *et al.* (1991); unadjusted

[a]Cornfield limits

Table 10. Separate effects of HBV and HCV on risk for hepatocellular carcinoma

Reference and location	HBsAg seronegative HCV Ab seronegative		HBsAg seronegative HCV Ab seropositive			HBsAg seropositive HCV Ab seronegative			HBsAg seropositive HCV Ab seropositive		
	Cases	Controls	Cases	Controls	OR	Cases	Controls	OR	Cases	Controls	OR
First-generation tests											
Yu *et al.* (1990); USA	24	110	5	5	4.8	12	13	4.4	10	0	∞
Kaklamani *et al.* (1991); Greece	71	373	29	29	[5.3]	42	29	[7.6]	43	1	[226]
Yu *et al.* (1991)[a]; China	12	104	5	2	16	101	21	22	9	0	∞
Chuang *et al.* (1992)[a]; China	16	267	13	8	27	87	104	14	12	5	40
Simonetti *et al.* (1992); Italy	46	197	133	11	[52]	15	4	[16]	18	0	[∞]
Di Bisceglie et al. (1991a); USA	80	56	12	2	[7.2]	6	0	[∞]	1	0	[∞]
Xu *et al.* (1990); China	11	46	1	0	∞	35	4	[37]	3	0	∞
Second-generation tests											
Stroffolini *et al.* (1992); Italy	11	80	38	13	[21]	11	6	[13]	5	0	[∞]
Cordier *et al.* (1993); Viet Nam	8	194	3	2	38	138	44	[76]	0	0	-
Tanaka *et al.* (1991); Japan	27	390	45	12	[54]	18	8	[33]	1	0	[∞]
Coursaget *et al.* (1992); Senegal	23	82	4	0	[∞]	20	50	[1.4]	2	2	[3.6]
Dazza *et al.* (1993); Mozambique	52	163	8	4	1.4	115	27	[13]	3	0	[∞]

[a]Partially overlapping

hepatic neoplasms interspersed with areas of haemorrhage, necrosis and fibrosis; a smaller tumour (4 × 4 cm) was also seen. Frozen sections of liver stained with a monoclonal antibody against non-A, non-B-infected hepatocytes revealed positive immunostaining, but no specific staining for HBV surface or core antigens was observed. Histological examination of liver tumours revealed trabecular, well-differentiated HCC. The adjacent liver tissue contained hyperplastic nodules and severely dysplastic hepatocytes, as well as chronic hepatitis, characterized by portal inflammation and bile duct proliferation (Linke *et al.*, 1987; Muchmore *et al.*, 1988). [HCV markers were not evaluated.]