2.5 Cancer of the liver

Hepatocellular carcinoma (HCC) is the third most common cause of mortality from cancer and the sixth most common cause of cancer incidence worldwide (Parkin *et al*., 2005). Although it is relatively rare in developed countries compared to the developing world, the incidence of primary liver cancer has increased during the last few decades in the USA (Howe *et al*., 2001) and in several European countries, although it has levelled off and subsequently declined in most of southern Europe over the last decade (La Vecchia *et al*., 2000).

In 1988, the IARC Monograph on alcohol drinking concluded that there was "sufficient evidence for the carcinogenicity of alcoholic beverages" and that "the occurrence of malignant tumours of the liver is causally related to consumption of alcoholic beverages" (IARC, 1988). Since that time, further evidence has been presented on the risk of liver cancer associated with prolonged alcoholic beverage consumption, the increased risk of associated liver cancer among cirrhotics and the modifying effects of the infectious agents hepatitis B virus (HBV) and hepatitis C virus (HCV).

Table 2.21 Selected cohort and case–control studies of oesophageal cancer in nonsmokers and smokers by level of alcoholic beverage intake

Reference	Exposure categories	Nonsmokers		Smokers					
Cohort studies									
Kato *et al.* (1992c)		*Never smokers*		*Former and current smokers*					
		Cases	RR (95% CI)	Cases	RR (95% CI)				
	<30 mL/day	5	1.0	29	3.3 (1.3–8.4)				
	≥30 ml/day	3	8.6 (2.1–36.0)	34	17.3 (6.7–44.2)				
Sakata *et al.* (2005)		*Never smokers*		*Former smokers*		*Smokers*			
		Deaths	HR (95% CI)	Deaths	HR (95% CI)	Deaths	HR (95% CI)		
	Non-drinkers	4	1.0	1	0.34 (0.04–3.12)	4	0.74 (0.18–3.02)		
	Former drinkers	1	1.10 (0.12–10.24)	3	1.47 (0.31–7.08)	4	2.19 (0.51–9.40)		
	Drinkers	2	0.18 (0.03– 1.02)	21	1.39 (0.47–4.10)	60	2.37 (0.85–6.58)		
Case–control studies									
Franceschi *et al.* (1990)		*Never smokers*		*Light smokers*		*Intermediate smokers*		*Heavy smokers*	
		Cases	Odds ratio	Cases	Odds ratio	Cases	Odds ratio	Cases	Odds ratio
		9	1.0	11	1.1	47	2.7	16	6.4
		3	0.8	19	7.9	78	8.8	14	11.0
		5	7.9	13	6.4	60	16.7	6	17.5
Negri *et al.* (1992)		*Never smokers*		*Ex/Moderate smokers*		*Heavy smokers*			
		Cases	Odds ratio	Cases	Odds ratio	Cases	Odds ratio		
	<4 drinks/day	7	1.0	10	2.8	11	4.3		
	4–6 drinks/day	2	1.6	4	4.5	6	6.9		
	>6 drinks/day	1	3.5	9	3.8	12	15.3		
Kabat *et al.* (1993)		*Never smokers*		*Ever smokers*					
			Odds ratio		Odds ratio				
	Non drinker/ occasional		1.0		1.5 (0.5–4.2)				
	≥1 oz WE/day		4.3 (1.4–12.5)		7.6 (3.1–18.6)				

Table 2.21 (continued)

Reference	Exposure categories	Nonsmokers		Smokers	
Gallus *et al*. (2001)		*Never and former smokers*		*Current smokers*	
		Cases	Odds ratio (95% CI)	Cases	Odds ratio (95% CI)
	<1 drink/day	18	1.0	11	2.25 (0.95–5.33)
	1–2 drinks/week	27	1.66 (0.85–3.25)	23	5.52 (2.57–11.85)
	≥3 drinks/week	16	5.79 (2.48–13.50)	19	12.75 (5.09–31.96)
Znaor *et al*. (2003)		*No smoking*		*Smoking*	
		Cases	Odds ratio (95% CI)	Cases	Odds ratio (95% CI)
	No drinking	45	1.00	155	3.57 (2.51–5.06)
	Drinking	7	3.41 (1.46–7.99)	164	7.33 (5.06–10.62)
Wu *et al*. (2006a)		*No smoking*		*Smoking*	
		Cases	Odds ratio (95% CI)	Cases	Odds ratio (95% CI)
	No alcohol	3	1.00	11	6.5 (1.9–29.8)
	Alcohol	4	23.3 (4.3–142.2)	54	108.0 (35.1–478.0)
Hashibe *et al*. (2007c)		*Nonsmokers*		*Smokers*	
		Cases	Odds ratio (95% CI)	Cases	Odds ratio (95% CI)
	Alcohol				
	No	4	1.0	1	0.71 (0.07–7.00)
	Yes	12	0.96 (0.28–3.28)	174	6.42 (2.03–20.30)

CI, confidence interval; HR, hazard risk; RR, relative risk; WE, whiskey-equivalent

Table 2.22 Selected cohort and case–control studies of oesophageal cancer in men and women by level of alcoholic beverage intake

Reference	Exposure categories	Men		Women	
		Cases/ deaths	Relative risk (95% CI)	Cases/ deaths	Relative risk (95% CI)
Cohort studies					
Adami *et al*. (1992b)	Alcoholics	26	6.9 (4.5–10.0)	1	5.9 (0.1–32.6)
Kinjo *et al*. (1998)	None	56	1.0	93	1.0
	1–3 times/month	24	0.8 (0.5–1.3)	7	0.6 (0.3–1.3)
	1–3 times/week	67	1.1 (0.7–1.6)	9	1.3 (0.6–2.5)
	≥4 times/week	181	2.4 (1.8–3.3)	3	2.0 (0.6–6.2)
Case–control studies			**Odds ratio (95% CI)**		**Odds ratio (95% CI)**
DeStefani et al. (1990)	0 mL/day	26	1	38	1
	1–24 mL/day	16	0.85 (0.4–1.8)	12	1.04 (0.4–2.4)
	25–49 mL/day	12	0.71 (0.3–1.6)		
	50–149 mL/day	50	1.37 (0.8–2.4)		
	150–249 mL/day	46	3.57 (1.9–6.7)	12	1.89 (0.7–4.9)
	≥250 mL/day	49	5.27 (2.7–10.2)		
Negri *et al*. (1992)	<4 drinks/day	63	1	48	1
	4–6 drinks/day	50	1.5 (0.9–2.2)	8	2.2 (1.0–4.3)
	>6 drinks/day	131	3.5 (2.4–5.1)		*p*=0.05
			p<0.001		
Kabat *et al*. (1993)	Non-drinker	7	1.0	16	1.0
	Occasional	15	1.4 (0.6–3.5)	17	1.4 (0.7–2.9)
	1–3.9 oz WE/day	27	2.3 (1.0–5.4)	25	4.4 (2.2–8.7)
	≥4 oz WE/day	86	10.9 (4.9–24.4)	20	13.2 (6.1–28.8)
Gallus *et al*. (2001)	<1 drink/day			29	1.0
	1–2 drinks/day			50	1.99 (1.15–3.44)
	≥3 drinks/day			35	5.40 (2.70–10.80)
					p<0.001

Table 2.22 (continued)

Reference	Exposure categories	Men		Women	
		Cases/ deaths	Relative risk (95% CI)	Cases/ deaths	Relative risk (95% CI)
Yokoyama *et al*. (2006)	Never/rare			24	1.0
	Light			11	1.81 (0.81–4.05)
	Moderate			6	3.97 (1.40–11.26)
	Heavy			7	15.35 (4.85–48.62)
	Former drinker			4	4.58 (1.25–16.79)
					p<0.0001
	Strong alcoholic beverages				
	Never			46	1.0
	Sometimes			4	2.58 (0.80– 8.33)
	Frequently			2	12.47 (0.97–160.06)
					p=0.012

CI, confidence interval; WE, whiskey-equivalent

2.5.1 *Cohort studies*

(a) Special populations (Table 2.23)

Most HCCs occur in cirrhotic livers, and cirrhosis is a pathogenic step in liver carcinogenesis (La Vecchia *et al*., 1998). In alcoholics, prolonged, excessive alcohol consumption results in alcoholic cirrhosis. The risk of HCC has been examined among alcoholic and cirrhotic subjects. In western countries, a few cohort studies have provided information regarding these special populations. Results from these cohort studies are presented in Table 2.23. Since 1988, two cohort studies conducted in Sweden have assessed the risk of primary liver cancer. One cohort comprised alcoholic and cirrhotic subjects (Adami *et al*., 1992a) and the other cohort included male and female alcoholics (Adami *et al*., 1992b). An additional cohort study in Denmark was conducted among patients with cirrhosis (Sørensen *et al*., 1998). The number of cases ranged from four to 182 within these three populations. Each of the three studies showed evidence of a strong association between alcoholism, cirrhosis and liver cancer. Two of these studies reported statistically significant SIRs greater than 35 among alcoholics and cirrhotics (Adami *et al*., 1992a; Sørensen *et al*., 1998). The Swedish cohort, which included alcoholics and cirrhotics, was based on a total of 83 cases and the Danish cohort of cirrhotics was based on a total of 245 cases. In contrast, a cohort study of 5332 Norwegian teetotallers reported a SIR for liver cancer of 0.31. However, this was based on only one observed case (Kjaerheim *et al*., 1993).

(b) General population (Table 2.24)

Two cohort studies have been conducted among the general population since 1988 (Yuan *et al*., 1997; Wang *et al*., 2003b). Neither study observed an association between alcoholic beverage consumption and liver cancer. In a study of male residents from communities in Shanghai, Yuan *et al*. (1997) reported a non-statistically significant reduction in risk among moderate (relative risk 0.68) and heavy (relative risk 0.84) drinkers of alcohol compared with non-drinkers. Similarly, Wang *et al*. (2003b) found no significant associations with the risk for HCC among drinkers compared with non-drinkers in a study of male residents from Taiwan.

2.5.2 *Case–control studies (Table 2.25)*

Ten case–control studies published since the last evaluation (IARC, 1988) provide information related to alcoholic beverage consumption and liver cancer: four were conducted in Italy (La Vecchia *et al*., 1998; Donato *et al*., 2002; Gelatti *et al*., 2005; Franceschi *et al*., 2006), two in the USA (Yuan *et al*., 2004; Marrero *et al*., 2005), and one each in Greece (Kuper *et al*., 2000a), Japan (Tanaka *et al*., 1992), South Africa (Mohamed *et al*., 1992) and Spain (Vall Mayans *et al*., 1990). All of these studies, with the exception of Yuan *et al*. (2004), used hospital-based controls. Tanaka *et al*. (1992) used city residents who visited a local public health centre for a routine health

Table 2.23 Cohort studies of liver cancer and alcoholic beverage consumption in special populations

Reference, location, study name	Cohort description	Exposure assessment	Organ site	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment	Comments
Adami *et al* (1992a), Sweden	Cohorts were selected from the in-patient registry containing diagnostic codes for alcoholism and/ or liver cirrhosis; 12 942 patients included in the study. 8511 alcoholics (7609 men, 911 women), 3589 cirrhotics (1961 men, 1628 women), 836 alcoholics/ cirrhotics (734 men, 102 women); follow-up 1965–1983; 90% histology confirmed	Hospital discharge-diagnosis	Liver (155.0, 155.1, 155.2, 155.3, 155.8, 155.9)			**SIR**	Age, sex	Risk for liver cancer 10 times higher among cirrhotics than among alcoholics
				Alcoholics	13	3.1 (1.6–5.3)		
				Cirrhotics	59	35.1 (26.7–45.3)		
				Alcoholics and cirrhotics	11	34.3 (17.1–61.3)		

Table 2.23 (continued)

Reference, location, study name	Cohort description	Exposure assessment	Organ site	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment	Comments
Kjaerheim *et al*. (1993)	5332 members of the International Organization of Good Templars, Norwegian teetotalers; followed-up 1980–1989	Cancer Registry	Liver (155.0)	Teetotalers		**SIR** 0.31 (0.1–1.7)	Age, sex	
Adami *et al*. (1992b), Sweden	Population-based cohort of 9353 (8340 men; 1013 women) alcoholics diagnosed in 1965–1983, followed-up for 19 years; 90% diagnosed	Discharge diagnosis of alcoholism	Liver (ICD-7 307, 322; ICD-8 291, 303	Alcoholics (men, women)	Men 23 Women 4	5.4 (3.4–8.1) 12.5 (3.4–32.0)	Age, years follow-up	No age related trends were seen with relation to liver cancer. Patients without a discharge diagnosis of cirrhosis experienced a 3-fold increase in risk for primary liver cancer.

Table 2.23 (continued)

Reference, location, study name	Cohort description	Exposure assessment	Organ site	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment	Comments
Sørensen *et al*. (1998), Denmark	Danish National Registry of Patients; patients with a diagnosis of alcoholic cirrhosis, primary biliary cirrhosis, non-specified cirrhosis, chronic hepatitis or other type of cirrhosis, alcoholism not indicated between 1977 and 1989; 205 cases (182 men, 103 women); follow-up until 1993	Discharged diagnosis	Liver (ICD-8 571.09, 571.90, 571.92, 571.93, 571.99, 303)	Cirrhotics	Men 82 Women 63 Both 245	 40.2 (NG) $p<0.05$ 27.8 (NG) $p<0.05$ 36 (31.6–40.8)	Age, sex	Excess risk for liver cancer observed among cirrhotics: 40-fold increase risk among men and 28-fold increase among women; risk further exaggerated among cases of hepatocellular carcinoma

CI, confidence interval; ICD, International Classification of Diseases; NG, not given; SIR, standardized incidence ratio

Table 2.24 Cohort studies of liver cancer and alcoholic beverage consumption

Reference, location, study name	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment	Comments
Yuan *et al.* (1997), Shanghai, China, 1986–1989	18 244 male residents living in 4 small communities in the city of Shanghai, aged 45–64 years; no history of cancer; follow-up until 1995	Structured questionnaire	Liver (ICD-9 155)	Non-drinkers 1–28 drinks/ week ≥29 drinks/ week	61 32 9	1.0 0.68 0.84	Age, level of education, cigarette smoking	No association between alcohol consumption and risk for liver cancer in men; CI not given, *p* values not given
Wang et al. (2003b); Taiwan 1990-2000	Residents of seven townships in Taiwan; 11 937 born between 1926 and 1960; follow-up until 2000	Personal interview; serum samples	Liver	Non-drinkers Drinkers	84 31	1.00 1.46 (0.97–2.21)	Age, residence, HBV, HCV markers	Elevated risk for HCC among users of alcohol although not significant

CI, confidence interval; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; ICD, International Classification of Diseases

Table 2.25 Case–control studies of liver cancer and alcoholic beverage consumption

Reference, location, study name	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment	Comments
Mayans *et al*. (1990), Catalonia, Spain, 1986-88	96 hospital-based cases were diagnosed with primary liver cancer in 1986–88; 77% histologically confirmed as HCC	190 matched 2:1 on age (within 5 years), sex; selected from same hospital as cases	Structured interview	Non-drinker 1–20 g/day 21–40 g/day 41–60 g/day 61–80 g/day >80 g/day	3 27 16 18 12 20	1.00 1.78 1.97 6.22 7.89 12.0 $p<0.001$	Age, sex, HBV status	Alcohol consumption significantly associated with HCC; risk did not significantly change with HBV status; CI not given
Yuan *et al*. (2004), Los Angeles County, CA, USA, 1984-2002	Population-based; 295 HCC cases, 18–74 years old; LA County Cancer Surveillance Program (1984–2002); 100% histologically confirmed	435 (age, gender, race) controls; Hispanic and non-Hispanic 2% match; age (within 5 years)	Personal interview; blood specimen	Non-drinker >0–2 drinks/day >2–4 drinks/day >4 drinks/day	91 66 43 95	1.00 0.6 (0.4–0.9) 1.4 (0.8–2.4) 3.2 (1.9–5.3) $p<0.001$	Age, gender, race, level of education, smoking status, history of diabetes	Risk for HCC increased with increased drinking: reduction in risk for patients that consumed >2 drinks/day (40% reduction)

Table 2.25 (continued)

Reference, location, study name	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment	Comments
Gelatti *et al*. (2005), Brescia and Pordenone, Italy	200 cases of HCC, up to age 79 years; born in Italy; Caucasian	400 hospitalized for other reasons not related to liver disease, neoplasms, tobacco- or alcohol-related disease; frequency-matched with cases on age (± 5 years), sex, date of hospital admission	Interview; blood sample	0–60 g/day 61–100 g/day >100 g/day	86 48 66	1.00 1.2 (0.8–1.9) 2.6 (1.7–4.0)	Age, sex, HBV and HCV markers, area of recruitment	Heavy alcohol consumption related to increased risk for HCC; no other alcohol related findings reported
Franceschi *et al*. (2006), Pordenone and Naples, Italy, 1999–2002	279 cases, aged 43–84 years; diagnosed with HCC without treatment; 78.2% histologically confirmed; enrolled from hospitals and cancer institutes in Naples and Pordenone (1999–2002)	431 hospital-based 40–83 years old; admitted for reasons other than alcohol- and tobacco-related use or hepatitis; distribution matched on age, sex	Questionnaire; HBV, HCV testing	Never <7 drinks/ week 7–13 drinks/ week 14–20 drinks/ week 21–34 drinks/ week ≥35 drinks/ week	20 16 26 38 53 76	1 1.67 (0.55–5.13) 0.81 (0.35–2.38) 1.04 (0.41–2.65) 1.61 (0.61–4.29) 5.94 (2.25–15.67)	Gender, age, center, education, HBV, HCV markers	Significant increase in risk for HCC among heaviest drinkers

Table 2.25 (continued)

Reference, location, study name	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment	Comments
Marrero *et al*. (2005), Michigan, USA, 2002–03	70 cases of HCC from liver or general medicine clinics; 81.4% histologically confirmed	70 with cirrhosis and 70 with no liver disease; 2:1 match on age (± 5 years) and sex: 80% histologically confirmed for cirrhosis controls	Validated questionnaire by trained interviewer	None <1500 g–years ≥1500 g–years	11 11 48	1.0 1.4 (0.8–1.9) 23.8 (7.3–79)	Body mass index, smoking, age	24-fold increased risk for HCC among heavy consumers of alcohol (HCC versus no liver disease); risk not as excessive in comparison with cirrhotics
Kuper *et al*. (2000a); Athens, Greece, 1995-98	333 cases enrolled from 3 teaching hospitals in Athens (283 men, 50 women); 99% confirmed diagnosis	360 (298 men, 62 women) hospital controls; matched 1:1 on gender, age (±5 years)	Hospital interview; blood test	Non-drinkers <20 glasses/week 20–39glasses/week ≥40 glasses/week	135 71 46 81	1.0 0.8 (0.4–1.4) 0.7 (0.3–1.5) 1.9 (0.9–3.9) *p*=0.13	Age, gender, years of education, HBV, HCV markers	Increased risk of HCC among heavy consumers of alcohol not significant.

Table 2.25 (continued)

Reference, location, study name	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment	Comments
Mohamed *et al*. (1992), Johannesburg, South Africa	101 (77 men, 24 women) Southern African blacks with HCC, 20–87 years old; enrolled from a hospital outside Johannesburg;	101 controls; 1:1 matched on ethnic origin, sex, age (±2 years); same hospital as cases with diagnosis other than HCC	Interview	*Men* Non-drinkers Light/ moderate Heavy *Women* Non-drinkers Light/ moderate Heavy	 Not reported 18 39 Not reported 1 7	 0.8 (0.2–2.6) 4.4 (1.4–14.1) p=0.0005 0.6 (0.0–8.8) 1.4 (0.3–9.3) p=0.81	HBV status, smoking	Significant increased risk for HCC found only among men >40 years of age

Table 2.25 (continued)

Reference, location, study name	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment	Comments
Tanaka *et al*. (1992), Fukuoka, Japan, 1985–89	204 HCC patients aged 40–69 (168 men, 36 women); residents of Fukuoka or Saga Prefecture, Japanese nationality, enrolled from Kyushu University Hospital; 40% histologically confirmed enrolled in 1985–89	410 residents (291 men, 119 women) of Fukuoka city who visited a public health center near Kyushu University Hospital between January 1986 and July 1989 for a health examination; matched on age, sex	In-person interview; blood sample	*Men* Non-drinker 0.1–33.9 drink–years 34.0–76.6 drink–years >76.6 drink–years *Women* Non-drinkers 0.1–33.9 drink–years 34.0–76.6 drink–years >76.6 drink–years	 37 31 36 64 27 5 2 2	 1.0 (reference) 0.9 (0.5–1.6) 0.9 (0.5–1.7) 1.7 (1.0–2.9) *p*=0.03 1.0 (reference) 2.1 (0.6–7.0) – 2.4 (0.6–9.1) *p*=0.11	Age, sex	History of heavy drinking significantly associated with increased risk for HCC
La Vecchia *et al*. (1998), Milan, Italy, 1984–96	499 (276 men, 123 women) with HCC, aged 23–74 recruited from major teaching and general hospitals in the greater Milan area	1552 (1141 men, 411 women); aged 20–74 years; patients admitted to area hospitals; with no history of cancer	Interview	0 drink/day 1–4 drinks/day >4 drinks/day (cases with history of cirrhosis)	26 24 37	13.4 (4.1–43.8) 15.2 (3.2–72.9) 24.9 (8.2–76.0)	Age, sex, tobacco smoking, hepatitis, diabetes, body mass index, family history	Association between heavy alcohol consumption and HCC among patients with a history of cirrhosis

Table 2.25 (continued)

Reference, location, study name	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment	Comments
Donato *et al*. (2002), Brescia, Italy, 1995–2000	464 (380 men, 84 women) patients with first diagnosis of HCC admitted between 1995–2000; aged <76 years; Italian, lived in province of Brescia	Hospital-based; 824 (686 men, 138 women), aged <76 years; no liver disease or cancer; frequency-matched with cases on age (±5 years), sex, date or hospital admission; from Brescia, Italia	Questionnaire; blood sample	*Men*			Age, residence, HBV, HCV markers	For women, categories of alcohol consumption above 80 g/day were omitted; higher levels of alcohol consumption (>81 g/day) associated with HCC in men.
				Non-drinkers	8	1.0 (reference)		
				1–20 g/day	24	2.3 (0.7–7.2)		
				21–40 g/day	27	0.9 (0.3–2.7)		
				41–60 g/day	44	1.6 (0.5–4.6)		
				61–80 g/day	33	2.4 (0.8–7.1)		
				81–100 g/day	62	4.2 (1.5–11.7)		
				101–120 g/day	47	7.7 (2.7–22.7)		
				121–140 g/day	48	9.8 (3.3–29.1)		
				>140 g/day	87	11.0 (3.9–31.0)		
				Women				
				Non-drinkers	24	1.0 (reference)		
				1-20 g/day	22	0.6 (0.2–1.7)		
				21-40 g/day	15	1.4 (0.4–5.4)		
				41-60 g/day	11	1.9 (0.4–8.1)		
				61-80 g/day	4	3.1 (0.3–29.7)		
				>80 g/day	8	16.5 (3.0–90.1)		

CI, confidence interval; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus

examination. Significantly higher relative risks were reported among heavy drinkers compared with non-, light or moderate drinkers in nine studies (Vall Mayans *et al*., 1990; Mohamed *et al*., 1992; Tanaka *et al*., 1992; La Vecchia *et al*., 1998; Donato *et al*., 2002; Yuan *et al*., 2004; Gelatti *et al*., 2005; Marrero *et al*., 2005; Franceschi *et al*., 2006). In these studies, the magnitude of the association ranged from 2.6 for intake of more than 100 g/day compared with 60 g/day or less (Gelatti *et al*., 2005); to 24.9 for those who consumed more than four drinks per day compared to those who consumed no drinks per day (La Vecchia *et al*., 1998). Tanaka *et al*. (1992) found a significant 1.7-fold increase in risk among men whose cumulative alcohol consumption was greater than 76.6 drink–years. No significant associations were observed among women. However, despite the number of studies that have demonstrated evidence of an association between heavy alcoholic beverage consumption and liver cancer, a clear, consistent dose–response relationship between light or moderate drinking and HCC risk has not yet been established.

2.5.3 *Meta-analyses (Table 2.26)*

Two meta-analyses have examined the association between alcoholic beverage consumption and liver cancer. A meta-analysis of 229 studies that evaluated the association between alcohol drinking and risk for cancer included data from 17 case–control and three cohort studies and 2294 cases of HCC. These 20 studies reported a direct trend in risk for HCC with increasing alcoholic beverage consumption. The reported relative risks were 1.17 (95% CI, 1.11–1.23) for consumption of 25 g alcohol per day, 1.36 (95% CI, 1.23–1.51) for 50 g per day and 1.86 (95% CI, 1.53–2.27) for 100 g per day (Bagnardi *et al*., 2001). An additional review of the Chinese literature included a meta-analysis of 55 case–control studies that investigated the risk factors for primary liver cancer in China. Twenty-two of these 55 studies assessed the effect of exposure to alcohol. A total of 3207 cases of primary liver cancer and 3983 controls were identified (Luo *et al*., 2005). The combined odds ratio reported from these 22 studies was 1.88 (95% CI, 1.53–2.32) for alcoholic beverage drinkers versus non-drinkers. No information regarding the dose–risk relationship was given. [The Working Group could not determine whether there was possible overlap between the individual cohort and case–control studies listed and the studies included in the meta-analyses conducted by Bagnardi *et al*. (2001) and Luo *et al*. (2005), because the individual studies included in the meta-analyses were not identified.]

2.5.4 *Interaction with hepatitis viral infection (Table 2.27)*

The impact of alcohol on primary liver cancer is difficult to measure because of the existence of other factors, in particular chronic infection with HBV and HCV—which have already been shown to be important determinants for HCC worldwide, and may modify the relationship between alcoholic beverage consumption and liver cancer.

Table 2.26 Meta-analyses of liver cancer and alcoholic beverage consumption

Reference, description, study	Cohort description	Exposure assessment	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment	Comments
Luo *et al*. (2005); meta-analysis of 55 case–control studies from China	Database search of Chinese biomedical literature database (1979–2003), China Hospital Knowledge Database (1999–2003) and Medline (1966–2003); inclusion criteria were: case–control studies investigating risk factors for PLC in Chinese population.	22 studies assessed exposure to alcohol	Non-drinkers Drinkers	Not reported 3207	1.0 1.88 (1.53–2.32) $p<0.001$	Not reported	Studies of alcohol showed significant heterogeneity
Bagnardi *et al*. (2001); meta-analysis of 229 cohort and case–control studies	3 cohort and 16 case–control studies on liver cancer; total of 1961 cases	Exposure to alcohol	25 g/day 50 g/day 100 g/day		1.20 (1.13–1.27) 1.41 (1.26–1.56) 1.83 (1.53–2.19) p-trend <0.01	Gender	A gender effect was also observed (p-trend<0.05)

CI, confidence interval; PLC, primary liver cancer

Table 2.27 Selected cohort and case–control studies of liver cancer by alcoholic beverage consumption and infection with hepatitis B virus (HBV) and hepatitic C virus (HCV)

Study design	Odds ratio (95% CI) of risk for liver cancer by alcoholic beverage intake			
Cohort study				
Wang *et al*. (2003b)	*None*	*Light/moderate*		
HBV-negative	1	1.64 (0.74–3.64)		
HBV-positive	13.12 (7.82–22.01)	17.93 (9.58–33.68)		
Case–control studies				
Kuper *et al*. (2000a)	*None*	*<20 drinks/week*	*20–39 drinks/week*	*≥40 drinks/week*
HBV/HCV	1	1.0 (0.2–4.1)	1.4 (0.3–7.9)	5.4 (0.6–50.3)
No infection	1	0.7 (0.3–1.3)	0.6 (0.2–1.4)	1.6 (0.8–3.4)
Donato *et al*. (2002)		*<60 g/day*	*>60 g/day*	
No infection		1	7.0 (4.5–11.1)	
HCV		55.0 (29.9–101)	109 (50.9–233)	
HBV		22.8 (12.1–42.8)	48.6 (24.1–98.0)	
Yuan *et al*. (2004)		*<4 drinks/day*	*>4 drinks/day*	
No infection		1	2.6 (1.3–5.1)	
HBV/HCV		8.1 (4.6–14.4)	48.3 (11.0–212.1)	
Franceschi *et al*. (2006)		*<14 drinks/week*	*14–34 drinks/week*	*≥35 drinks/week*
No infection		1	0.68 (0.26–1.76)	4.96 (2.19–11.24)
HBV/HCV		28.82 (12.84–64.69)	47.6 (20.76–109)	74.36 (22.89–242)

CI, confidence interval

Chronic infections with HBV and HCV have been shown to increase the risk for HCC by approximately 20-fold (Parkin, 2006). Five studies examined the association between alcoholic beverage consumption and the risk for liver cancer among patients with chronic infection with HBV and HCV; one cohort study (Wang *et al*., 2003b) and four case–control studies (Kuper *et al*., 2000a; Donato *et al*., 2002; Yuan *et al*., 2004; Franceschi *et al*., 2006). The cohort study reported a relative risk of 13.12 among non-drinkers with chronic HBV infection. Light to moderate drinking and heavy drinking further increased the relative risk to 17.93. All four case–control studies showed an increased risk for HCC with increased alcoholic beverage consumption among subjects infected with HBV or HCV. Three of these studies showed a significant increase in risk. However, the study by Kuper *et al*. (2000a), based on 333 cases of HCC and 360 controls, did not indicate the same significant trend in increased risk for HCC.

2.5.5 *Interaction with tobacco smoking*

The interaction between alcoholic beverage consumption and tobacco smoking—another recognized risk factor for HCC (IARC, 2004)—was considered in case–control studies in Greece (Kuper *et al*., 2000a) and the USA (Yuan *et al*., 2004; Marrero *et al*., 2005). In the Greek study (Kuper *et al*., 2000a), the relative risk was 5.6 (95% CI, 1.70–19.0) for heavy drinkers and heavy smokers compared with never smokers and non- and light drinkers. In a US dataset (Marrero *et al*., 2005), the relative risk was 7.2 (95% CI, 2.2–14.1) for combined exposure to alcoholic beverages and tobacco compared with cirrhotic subjects. In another US dataset (Yuan *et al*., 2004), the corresponding relative risk for exposure to both factors was 5.9 (95% CI, 3.3–10.4).