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ABSENCE OF EXCESS BODY FATNESS

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2.2.4 Cancer of the liver (hepatocellular carcinoma)

Hepatocellular carcinoma (HCC) is the most frequent primary malignancy of the liver (> 80% of primary liver cancers) and occurs predominantly in patients with underlying chronic liver disease or cirrhosis. Worldwide, liver cancer is among the most common causes of cancer death; the highest rates of liver cancer incidence and mortality occur in some areas in Asia and sub-Saharan Africa, as a result of chronic hepatitis infection (Jemal et al., 2014).

In 2001, the Working Group of the *IARC Handbook* on weight control and physical activity (IARC, 2002) concluded that the evidence of an association between avoidance of weight gain and liver cancer was *inadequate*. Since then, numerous individual cohort studies with at least 100 cases (Table 2.2.4a), case–control studies (Table 2.2.4b), and pooled and meta-analyses of cohort studies and case–control studies (Table 2.2.4c) have been published examining the association of anthropometric factors with liver cancer incidence and/or mortality. Notably, because chronic liver disease is among the most common risk factors for cancer of the liver, results from cohort studies of anthropometric factors in relation to liver cancer incidence and/or mortality in patients with liver disease have also been included.

(a) Cohort studies

(i) Body weight and body mass index

Six cohort studies of BMI or weight in relation to risk of HCC specifically (Samanic et al., 2006; Joshi et al., 2008; Ohishi et al., 2008; Borena et al., 2012; Loomba et al., 2013; Schlesinger et al., 2013) have been published (Table 2.2.4a). Of these studies, four showed statistically significant positive associations and/or trends (Samanic et al., 2006; Ohishi et al., 2008; Borena et al., 2012; Schlesinger et al., 2013). In a large cohort of men in Sweden, a relative risk for BMI ≥ 30 kg/m^2 versus BMI < 25 kg/m^2 of 3.13 (95% CI, 2.04–4.79) was reported (Samanic et al., 2006).

At least eight other studies have examined the association between BMI and liver cancer (hepatocellular and intrahepatic bile duct combined, or NOS) incidence and/or mortality (Table 2.2.4a). One study of Japanese men and women showed no evidence of association with increased incidence (Kuriyama et al., 2005) [the number of liver cancer cases in the highest categories of BMI was small or zero in both sexes, and therefore power was limited to detect an association]. Conversely, in the large Korea National Health Insurance Corporation Study, risk of liver cancer increased significantly for BMI ≥ 30 kg/m^2 in men (relative risk [RR], 1.63; 95% CI, 1.27–2.10) and in women (RR, 1.39; 95% CI, 1.00–1.94), compared with the reference category of BMI of 23.0–24.9 kg/m^2. Significant P_{trend} values were found in both men and women (Jee et al., 2008). Strong positive associations were also observed in another prospective cohort study of BMI in relation to liver cancer incidence, a data linkage study in the United Kingdom where a 5 kg/m^2 increase in BMI was associated with a 19% increase in risk (95% CI, 1.12–1.27) (Bhaskaran et al., 2014).

In general, studies of BMI in relation to liver cancer mortality (Calle et al., 2003) or liver cancer incidence and mortality combined (Borena et al., 2012) showed strong positive associations. For example, in the Cancer Prevention Study II in the USA, there was a strong positive association between liver cancer mortality in men (RR, 4.52; 95% CI, 2.94–6.94 for BMI ≥ 35 kg/m^2 vs 18.5–24.9 kg/m^2; P_{trend} < 0.001), and to a lesser extent in women (RR, 1.68; 95% CI, 0.93–3.05 for BMI ≥ 35 kg/m^2 vs 18.5–24.9 kg/m^2; P_{trend} < 0.04) (Calle et al., 2003). In the Japan Collaborative Cohort Study, there was evidence of an association between higher BMI and liver cancer mortality when men with liver disease were excluded (Li et al., 2013).

Associations of measures of body weight and liver cancer have been examined in at least six cohort studies of patients with cirrhosis, hepatitis infections, or other liver conditions. Of these studies, four showed statistically significant positive associations or trends between BMI and risk of HCC (N'Kontchou et al., 2006; Ioannou et al., 2007; Yu et al., 2008; Ohki et al., 2008). In the study with the largest number of HCC cases, the relative risk for BMI ≥ 30 kg/m² versus BMI < 18.5 kg/m² was 3.10 (95% CI, 1.41–6.81) in Japanese men and women who were patients at a liver clinic (Ohki et al., 2008). Two studies of cirrhosis patients also showed statistically significant 2.5–2.8-fold higher risks of HCC for obese versus normal-weight patients (N'Kontchou et al., 2006; Ioannou et al., 2007). The association was approximately of the same magnitude in a prospective study in Taiwan, China, of carriers of hepatitis B virus (HBV) (RR, 1.96; 95% CI, 0.72–5.38 for BMI ≥ 30 kg/m² vs 18.5–24.9 kg/m²; P_{trend} = 0.048) [only 4 obese men developed HCC during follow-up] (Yu et al., 2008). A Japanese study of patients with hepatitis C virus (HCV) infection also found evidence of a borderline positive association when BMI was modelled as a continuous measure in women (RR per 1 kg/m² increase in BMI, 1.09; 95% CI, 0.99–1.19) but not in men (RR per 1 kg/m² increase in BMI, 1.01; 95% CI, 0.93–1.09) (Arano et al., 2011).

There have been numerous meta-analyses (Larsson & Wolk, 2007; Renehan et al., 2008; Chen et al., 2012; Rui et al., 2012; Tanaka et al., 2012; Wang et al., 2012; WCRF/AICR, 2015; Table 2.2.4c) and a large pooled analysis of 57 cohorts (Whitlock et al., 2009) on BMI and (primary) liver cancer incidence or mortality. Overall, these meta-analyses showed an increased risk of liver cancer in individuals with higher BMI independently of sex, geographical region, duration of follow-up, and potential confounders such as alcohol consumption, cigarette smoking, or diabetes history. The largest meta-analysis, by Chen et al. (2012), which included 26 prospective cohorts from Asia, Europe, and the USA, found a stronger risk of primary liver cancer in relation to higher BMI in patients with liver cirrhosis or HBV or HCV infection (n = 9 cohorts, summary RR, 1.73; 95% CI, 1.28–2.35) compared with the BMI-associated risk observed in the general population (n = 17 cohorts, summary RR, 1.36; 95% CI, 1.20–1.53) [the P value for difference was 0.15]. In the recent meta-analysis of the WCRF Continuous Update Project, a 5 kg/m² increase in BMI was associated with a 43% (95% CI, 1.19–1.70) increase in liver cancer incidence and a 13% (95% CI, 1.00–1.28) increase in liver cancer mortality based on 8 and 4 cohort studies, respectively, and the association was stronger in studies in Europe (summary RR, 1.59; 95% CI, 1.35–1.87) than in studies in Asia (summary RR, 1.18; 95% CI, 1.04–1.34) (WCRF/AICR, 2015).

(ii) Weight at different ages and weight change

Only a few cohort studies examined associations of BMI and/or weight at earlier ages or change in BMI or weight with risk of liver cancer. In the EPIC study, BMI at age 20 years was overall not associated with liver cancer mortality (Schlesinger et al., 2013). However, in that study there was a positive dose–response relationship between the average annual weight change from age 20 years to age at reporting and increased risk; the relative risk for each kilogram per year increase in weight of HCC was 3.51 (95% CI, 1.93–6.41), after adjustment for weight at age 20 years and other confounding factors. In a large Swedish occupational cohort, 6-year BMI change during adulthood in relation to liver cancer incidence was examined (Samanic et al., 2006). Although the results were somewhat suggestive of an increasing risk with increasing BMI gain, there were only 55 cases in total [and therefore statistical power was limited to detect associations]. Similarly, in the Japan Collaborative Cohort Study, change in weight between age 20 years and baseline was not associated with liver cancer mortality in men or women, although some evidence for a trend could be observed in women (Li et al., 2013).

(iii) Waist circumference

A positive association between waist circumference and incidence of HCC was shown in the EPIC study, which was the only study to examine this association (Schlesinger et al., 2013). In that study, each increase of 5 cm in waist circumference was associated on average with a 25% (95% CI, 1.17–1.33) increase in risk in men and women combined.

(b) Case–control studies

A total of five case–control studies have been published since 2001 on the association of BMI with HCC in Canada, China, France, Italy, and the USA (Table 2.2.4b).

In the USA, a study of 622 cases and 660 population control subjects showed an increased risk of HCC for men and women with early adulthood (mid-20s to mid-40s) obesity (BMI > 30 kg/m^2) compared with normal-weight individuals (men: OR, 2.3; 95% CI, 1.2–4.4; women: OR, 3.6; 95% CI, 1.5–8.9) (Hassan et al., 2015), but no association was found for recalled BMI in the mid-50s. A hospital-based case–control study in Italy also showed an increased risk for subjects with elevated recalled BMI at about age 30 years, but not for BMI 1 year before cancer diagnosis (or equivalent time frame for the controls) (Polesel et al., 2009), and a study in France also showed a direct association of HCC risk with recalled past obesity in patients with non-viral liver cirrhosis (Archambeaud et al., 2015). In contrast, a population-based case–control study in Canada showed no association between risk of liver cancer and self-reported BMI 1 year before diagnosis (Pan et al., 2004).

Finally, using waist circumference as a measure of adiposity, a large population-based case–control study with 3649 cases all aged 68 years or older identified through the Surveillance, Epidemiology, and End Results (SEER) Program of the United States National Cancer Institute, and with 195 953 population control subjects, showed a significantly increased risk of HCC in men with waist circumference greater than 40 inches (101 cm) and in women with waist circumference greater than 35 inches (89 cm), compared with men or women with a smaller waist circumference (OR, 1.93; 95% CI, 1.71–2.18) (Welzel et al., 2011).

Several of the above-mentioned studies considered HBV or HCV infection as a confounder or effect modifier for the association between BMI and risk of liver cancer. In the study in Italy (Polesel et al., 2009), HCC risk was significantly increased in obese subjects without HBV and HCV infection (OR, 3.5; 95% CI, 1.3–9.2; compared with BMI < 30 kg/m^2) but not in subjects with HBV or HCV infection. The study by Hassan et al. (2015) in the USA showed a synergistic interaction between obesity and hepatitis virus infection, with highly increased risk in obese subjects with HBV or HCV infection.

Table 2.2.4a Cohort studies of measures of body fatness and cancer of the liver

Reference Cohort Location Follow-up period	Total no. of subjects Sex Incidence/mortality	Organ site or cancer type (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Hepatocellular carcinoma							
N'Kontchou et al. (2006) Cohort of patients with cirrhosis France 1994–2004	771 Men and women Incidence	HCC	BMI < 25 25–30 ≥ 30	220 total	 1.0 2.0 (1.4–2.7) 2.8 (2.0–4.0)		Patients with alcohol- or hepatitis C-related cirrhosis
Samanic et al. (2006) Swedish Construction Worker Cohort Sweden 1958–1999	362 552 Men Incidence	HCC	BMI 18.5–24.9 25–29.9 ≥ 30 [P_{trend}]	 73 90 31	 1.00 1.45 (1.06–1.98) 3.13 (2.04–4.79) [< 0.001]	Attained age, calendar year, smoking	Based on fewer than 30 incident cases, no significant associations for cholangiocarcinoma or adenocarcinoma of the liver were found. No associations between BMI change and liver cancer overall observed (n = 469)
Ioannou et al. (2007) Cohort of cirrhosis patients in the Veterans Affairs facility USA 1994–2005	2126 Men and women Incidence	HCC ICD-9: 155.0	BMI 18.5–24.9 25–29 ≥ 30	 15 45 40	 1.00 2.8 (1.4–5.4) 2.5 (1.3–4.9)	Age, HCV infection, HBsAg, HBV core antibody, type 2 diabetes mellitus, platelet count	

Table 2.2.4a (continued)

Reference Cohort Location Follow-up period	Total no. of subjects Sex Incidence/ mortality	Organ site or cancer type (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Joshi et al. (2008) Korean male civil service workers cohort Republic of Korea 1999–2004	548 530 Men Mortality	HCC ICD-10: C22.0	BMI < 18.5 18.5–24.9 25–29.9 ≥ 30	989 total	 1.00 1.38 (0.90–2.11) 0.98 (0.85–1.12) 1.08 (0.67–1.72)	Age, serum glucose, alcohol consumption, tobacco use, HBsAg	
Ohishi et al. (2008) Nested case–control in the Adult Health Study (atomic bomb survivors) Japan 1970–2002	868 Men and women Incidence	HCC	BMI 10 yr before diagnosis < 19.6 19.6–21.2 21.3–22.9 23–25 > 25 per 1 kg/m² [P_{trend}]	 38 33 36 49 54	 1.31 (0.51–3.34) 1.24 (0.43–3.54) 1.00 2.51 (0.99–6.37) 4.57 (1.85–11.3) 1.12 (1.03–1.22) [0.01]	Hepatitis infection, alcohol consumption, smoking, coffee consumption, diabetes, radiation dose to liver	
Ohki et al. (2008) Hospital-based cohort of patients with chronic hepatitis C Tokyo, Japan 1994–2006	1431 Men and women Incidence	HCC	BMI < 18.5 18.5–24.9 25–29.9 ≥ 30	340 total	 1.00 1.52 (0.93–2.47) 1.86 (1.09–3.16) 3.10 (1.41–6.81)	Age, sex, heavy alcohol consumption, diabetes mellitus, serum albumin concentration, total bilirubin concentration, ALT levels, prothrombin time activity, platelet counts, AFP concentration	
Yu et al. (2008) Cohort of male government employees (HBV carriers) Taiwan, China 1989–2005	2903 Men Incidence	HCC	BMI < 18.5 18.5–24.9 25–29.9 ≥ 30 [P_{trend}]	 3 77 50 4	 1.55 (0.49–4.93) 1.00 1.48 (1.04–2.12) 1.96 (0.72–5.38) [0.048]	Age, number of clinic visits, smoking, alcohol consumption, diabetes	

Table 2.2.4a (continued)

Reference Cohort Location Follow-up period	Total no. of subjects Sex Incidence/mortality	Organ site or cancer type (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Loomba et al. (2010) HBV-positive men part of the REVEAL-HBV cohort Taiwan, China 1991–2004	2260 Men Incidence	HCC	BMI per 1 kg/m^2 increase	136	1.00 (0.93–1.06)	Age, serum HBV DNA level, smoking, serum ALT level, HBeAg status, cirrhosis at baseline visit	Alcohol consumption–BMI interaction
Arano et al. (2011) Hospital-based cohort of patients with hepatitis C Japan 1994–2009	146 Men Incidence	HCC	BMI per 1 kg/m^2 increase	67	1.01 (0.93–1.09)	Age, alcohol consumption, serum biomarkers, platelet count, diabetes	
	179 Women Incidence	HCC	BMI per 1 kg/m^2 increase	55	1.09 (0.99–1.19)	Age, alcohol consumption, serum biomarkers, platelet count, diabetes	
Borena et al. (2012) Me-Can cohorts Austria, Norway, and Sweden 1972–2006, follow-up varied by cohort	578 700 Men and women Incidence and mortality	HCC	BMI, per unit SD	155 total	1.51 (1.29–1.77)	Age, cohort, year of birth, sex, smoking status	
Loomba et al. (2013) Population-based cohort of residents (7 townships) Taiwan, China 1991–2004	23 712 Men and women Incidence	HCC	BMI < 30 ≥ 30	 284 21	 1.00 1.47 (0.85–2.30)	Only univariate model available	A significant interaction was reported between alcohol drinkers (4 days per week for at least 1 yr) and BMI ≥ 30 kg/m^2, with a 7-fold increased risk of HCC

Table 2.2.4a (continued)

Reference Cohort Location Follow-up period	Total no. of subjects Sex Incidence/mortality	Organ site or cancer type (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Schlesinger et al. (2013) EPIC cohort 10 European countries 1992–2010	Men and women Incidence	HCC ICD-10: C22.0	BMI, tertiles (sex-specific)			Age, sex, study centre, education level, smoking, alcohol consumption, height Analysis of weight change also adjusted for weight at age 20 yr	Associations were lost when BMI analyses were further adjusted for WC
			Men: Women:				
			< 24.93 < 23.04	33	1.00		
			24.93–27.8 23.04–26.64	49	1.31 (0.84–2.05)		
			≥ 27.81 ≥ 26.65	95	2.28 (1.50–3.45)		
			[P_{trend}]		[< 0.0001]		
			per 5 kg/m²		1.55 (1.31–1.83)		
			Weight, tertiles				No significant associations were observed with weight at age 20 yr, when comparing extreme tertiles (P_{trend} = 0.95)
			T1	46	1.00		
			T2	50	1.19 (0.78–1.80)		
			T3	81	2.04 (1.36–3.06)		
			[P_{trend}]		[< 0.001]		
			per 5 kg		1.18 (1.11–1.25)		
			Weight change from age 20 yr to age at reporting, tertiles				
			T1	30	1.00		
			T2	32	1.30 (0.77–2.19)		
			T3	46	2.48 (1.49–4.13)		
			[P_{trend}]		[< 0.001]		
			per kg/yr		3.51 (1.93–6.41)		
			WC, tertiles				
			T1	27	1.00		
			T2	50	1.45 (0.90–2.34)		
			T3	100	2.60 (1.66–4.07)		
			[P_{trend}]		[< 0.0001]		
			per 5 cm		1.25 (1.17–1.33)		
Liver NOS							
Calle et al. (2003) Cancer Prevention Study II (CPS II) USA 1982–1998	404 576 Men Mortality	Liver	BMI			Age, education level, smoking, physical activity, alcohol consumption, marital status, race, aspirin use, consumption of fat and vegetables	
			18.5–24.9	222	1.00		
			25–29.9	296	1.13 (0.94–1.34)		
			30–34.9	78	1.90 (1.46–2.47)		
			≥ 35	24	4.52 (2.94–6.94)		
			[P_{trend}]		[< 0.001]		

Table 2.2.4a (continued)

Reference Cohort Location Follow-up period	Total no. of subjects Sex Incidence/mortality	Organ site or cancer type (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Calle et al. (2003) (cont.)	495 477 Women Mortality	Liver	BMI			For women, also adjusted for HRT use	
			18.5–24.9	200	1.00		
			25–29.9	96	1.02 (0.80–1.31)		
			30–34.9	37	1.40 (0.97–2.00)		
			≥ 35	12	1.68 (0.93–3.05)		
			[P_{trend}]		[0.04]		
Samanic et al. (2004) United States Veterans cohort USA 1969–1996	4 500 700 Men Incidence	Liver ICD-9: 155	Obesity			Age, calendar year	Obesity defined as discharge diagnosis of obesity: ICD-8: 277; ICD-9: 278.0 Significantly different risk in White men and Black men ($P < 0.001$)
				White men:			
			Non-obese	3612	1.00		
			Obese	322	1.44 (1.28–1.61)		
				Black men:			
			Non-obese	1168	1.00		
			Obese	38	0.68 (0.49–0.94)		
Kuriyama et al. (2005) Population-based cohort in Miyagi Prefecture Japan 1984–1992	12 485 Men Incidence	Liver ICD-9: 155.0–155.2	BMI			Age, smoking, alcohol consumption, consumption of red meat, fruits and vegetables, and bean paste, type of health insurance; for women, also adjusted for menopausal status, parity, age at menarche, age at first pregnancy	
			18.5–24.9	55	1.00		
			25.0–27.4	9	0.80 (0.40–1.63)		
			27.5–29.9	5	1.14 (0.46–2.87)		
			≥ 30	–	–		
			[P_{trend}]		[0.92]		
	15 054 Women Incidence	Liver ICD-9: 155.0–155.2	BMI				
			18.5–24.9	220	1.00		
			25.0–27.4	7	1.30 (0.54–3.16)		
			27.5–29.9	4	0.91 (0.30–2.80)		
			≥ 30	–	–		
			[P_{trend}]		[0.94]		
Jee et al. (2008) Cohort from National Health Insurance Corporation Republic of Korea 1992–2006	770 556 Men Incidence	Liver	BMI			Age, smoking	
			< 20.0	862	0.90 (0.81–1.00)		
			20.0–22.9	3260	0.97 (0.90–1.04)		
			23.0–24.9	2463	1.00		
			25.0–29.9	2062	1.04 (0.96–1.13)		
			≥ 30.0	112	1.63 (1.27–2.10)		
			[P_{trend}]		[0.0002]		

Table 2.2.4a (continued)

Reference Cohort Location Follow-up period	Total no. of subjects Sex Incidence/ mortality	Organ site or cancer type (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Jee et al. (2008) (cont.)	423 273 Women Incidence	Liver	BMI			Age, smoking	
			< 20.0	195	0.85 (0.67–1.06)		
			20.0–22.9	505	0.76 (0.64–0.91)		
			23.0–24.9	411	1.00		
			25.0–29.9	587	1.14 (1.97–1.35)		
			≥ 30.0	63	1.39 (1.00–1.94)		
			[P_{trend}]		[< 0.0001]		
Whitlock et al. (2009) Pooled analysis of 57 cohort studies Europe, Japan, and USA Follow-up varied by cohort	894 576 Men and women Mortality	Liver ICD-9: 155	BMI			Study, sex, age, smoking	
			For BMI 15–25	201	1.37 (0.87–2.15)		
			For BMI 25–50	221	1.61 (1.26–2.05)		
			For BMI 15–50	422	1.47 (1.26–1.71)		
Parr et al. (2010) Pooled analysis of 39 cohort studies Asia, Australia, and New Zealand 1961–1999, median follow-up 4 yr	326 387 Men and women Mortality	Liver ICD-9: 155 ICD-10: C22	BMI	774		Age, sex, smoking status	
			12.0–18.4		1.13 (0.78–1.64)		
			18.5–24.9		1.00 (0.89–1.13)		
			25–29.99		1.06 (0.83–1.36)		
			≥ 30		1.10 (0.63–1.91)		
			per 5 kg/m^2		1.11 (0.94–1.31)		
			[P_{trend}]		[0.58]		
Borena et al. (2012) Me-Can cohorts Austria, Norway, and Sweden 1972–2006, follow-up varied by cohort	578 700 Incidence and mortality	Liver, primary cancer ICD-7: 155.0	BMI, quintiles (mean)			Age, smoking status, cohort, year of birth, sex	
			Q1 (20.7)	36	1.00		
			Q2 (23.0)	38	0.91 (0.55–1.51)		
			Q3 (24.7)	45	0.97 (0.59–1.57)		
			Q4 (26.8)	53	1.02 (0.63–1.64)		
			Q5 (31.3)	94	1.92 (1.23–2.96)		
			[P_{trend}]		[0.001]		

Table 2.2.4a (continued)

Reference Cohort Location Follow-up period	Total no. of subjects Sex Incidence/ mortality	Organ site or cancer type (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Li et al. (2013) JACC cohort Japan 1988–2009	31 018 Men Mortality	Liver ICD-10: C22.0–22.9	BMI at baseline			Age, smoking status, alcohol consumption, physical activity, intake of coffee and fish, education level, area of residence, diabetes, gall bladder disease, blood transfusions, history of liver disease	In stratified analyses, significant associations were observed in men without liver disease (P_{trend} = 0.03)
			< 18.5	32	1.42 (0.93–2.15)		
			18.5–20.9	82	1.09 (0.81–1.48)		
			21–22.9	88	1.00		
			23–24.9	73	1.04 (0.76–1.42)		
			≥ 25	63	1.15 (0.83–1.60)		
			[P_{trend}]		[0.37]		
			BMI at age 20 yr				
			< 18.5	14	0.74 (0.42–1.29)		
			18.5–20.9	91	0.89 (0.68–1.18)		
			21–22.9	115	1.00		
			23–24.9	75	0.92 (0.69–1.24)		
			≥ 25	43	0.91 (0.64–1.31)		
			[P_{trend}]		[0.54]		
			Weight change (kg), age 20 yr to baseline				
			≤−10.0	27	0.68 (0.43–1.08)		
			−9.9 to −5.0	76	1.08 (0.80–1.46)		
			−4.9 to 4.9	124	1.00		
			5.0 to 9.9	55	1.06 (0.77–1.47)		
			≥ 10.0	56	0.98 (0.70–1.37)		
			[P_{trend}]		[0.88]		

Table 2.2.4a (continued)

Reference Cohort Location Follow-up period	Total no. of subjects Sex Incidence/mortality	Organ site or cancer type (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Li et al. (2013) (cont.)	41 455 Women Mortality	Liver ICD-10: C22.0–22.9	BMI at baseline			Age, smoking status, alcohol consumption, physical activity, intake of coffee and fish, education level, area of residence, diabetes, gall bladder disease, blood transfusions, history of liver disease	
			< 18.5	8	0.74 (0.35–1.60)		
			18.5–20.9	36	1.08 (0.69–1.68)		
			21–22.9	42	1.00		
			23–24.9	41	1.16 (0.75–1.79)		
			≥ 25	62	1.42 (0.95–2.13)		
			[P_{trend}]		[0.10]		
			BMI at age 20 yr				
			< 18.5	11	0.98 (0.58–1.64)		
			18.5–20.9	17	0.85 (0.58–1.25)		
			21–22.9	28	1.00		
			23–24.9	13	0.91 (0.60–1.38)		
			≥ 25	14	0.73 (0.45–1.18)		
			[P_{trend}]		[0.18]		
			Weight change (kg), age 20 yr to baseline				
			≤−10.0	10	0.68 (0.34–1.40)		
			−9.9 to −5.0	24	0.83 (0.51–1.35)		
			−4.9 to 4.9	62	1.00		
			5.0 to 9.9	46	1.31 (0.89–1.94)		
			≥ 10.0	47	1.41 (0.94–2.11)		
			[P_{trend}]		[0.08]		
Bhaskaran et al. (2014) Clinical Practice Research Datalink United Kingdom 1987–2012	5 243 978 Men and women Incidence	Liver ICD-10: C22	BMI	1859 total		Age, sex, diabetes, smoking, alcohol consumption, socioeconomic status, calendar year	Similar association in never-smokers only
			per 5 kg/m^2		1.19 (1.12–1.27)		
			[P_{trend}]		[< 0.0001]		

AFP, α-fetoprotein; ALT, alanine aminotransferase; BMI, body mass index (in kg/m^2); CI, confidence interval; EPIC, European Prospective Investigation into Cancer and Nutrition; HBeAg, hepatitis B envelope antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; ICD, International Classification of Diseases; JACC, Japan Collaborative Cohort Study for Evaluation of Cancer Risk; Me-Can, Metabolic Syndrome and Cancer Project; NOS, not otherwise specified; SD, standard deviation; WC, waist circumference; yr, year or years

Table 2.2.4b Case–control studies of measures of body fatness and hepatocellular carcinoma

Reference Study location Period	Total number of cases Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment for confounding	Comments
Pan et al. (2004) Canada 1994–1997	Men: 225 Women: 84 Population	BMI 1 yr before diagnosis			Age, geographical region, education level, smoking, physical activity, total calorie intake, total vegetable consumption, dietary fibre intake, multivitamin intake; for women, also adjusted for menopausal status, parity, age at menarche, age at end of first pregnancy	Self-reported BMI
		Men:	225 total			
		< 25		1.00		
		25– < 30		0.99 (0.72–1.38)		
		≥ 30		1.30 (0.85–1.97)		
		[P_{trend}]		[0.31]		
		Women:	85 total			
		< 25		1.00		
		25– < 30		0.61 (0.35–1.07)		
		≥ 30		0.94 (0.48–1.84)		
		[P_{trend}]		[0.40]		
Polesel et al. (2009) Italy 1999–2003	185 Hospital	BMI 1 yr before interview			Centre, sex, age, education, drinking status, lifetime maximal alcohol consumption, smoking status, cigarettes smoked per day, HBsAg and/or anti-HCV positivity	BMI calculated from self-reported weights and heights
		< 25	71	1.00		
		25– < 30	76	1.0 (0.5–1.9)		
		≥ 30	38	1.9 (0.9–3.9)		
		5 kg/m² increase		1.1 (0.8–1.5)		
		BMI at age 30 yr				
		< 25	109	1.00		
		≥ 25	69	1.0 (0.6–1.7)		
		5 kg/m² increase		0.8 (0.6–1.2)		
		BMI increase from age 30 yr				
		< 1	73	1.00		
		1– < 4	53	1.2 (0.6–2.4)		
		≥ 4	52	1.6 (0.8–3.2)		
Welzel et al. (2011) USA 1993–2005	3649 Population	WC (≥ 40 inches [101 cm] in men, ≥ 35 inches [89 cm] in women)	308 total	1.93 (1.71–2.18)	Age, sex, race, geographical location, Medicare/Medicaid dual enrolment	
Archambeaud et al. (2015) France 2007–2010	200 Hospital	Maximum BMI	125 total		Sex, age, diabetes, smoking (past or present)	
		< 30		1.00		
		≥ 30		1.56 (1.02–2.37)		

Table 2.2.4b (continued)

Reference Study location Period	Total number of cases Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment for confounding	Comments
Hassan et al. (2015) USA 2004–2013	Men: 473 Women: 149 Population	Normal weight (reference)			Sex, age, ethnicity, education level, HCV, HBV, alcohol consumption, cigarette smoking, history of diabetes, physical activity, family history of cancer	BMI calculated from self-reported weights and heights at different ages; overweight and obesity defined as BMI 24–29.9 and BMI ≥ 30, respectively
		Overweight at different ages				
			Men:			
		Mid-20s	124	1.5 (0.9–2.3)		
		Mid-30s	172	1.3 (0.9–2.1)		
		Mid-40s	174	0.9 (0.6–1.4)		
		Mid-50s	170	0.5 (0.3–0.9)		
			Women:			
		Mid-20s	11	2.4 (0.9–3.0)		
		Mid-30s	19	1.2 (0.5–2.6)		
		Mid-40s	29	0.8 (0.4–1.6)		
		Mid-50s	35	0.9 (0.5–1.7)		
		Obesity at different ages				
			Men:			
		Mid-20s	33	1.8 (0.8–4.1)		
		Mid-30s	58	3.1 (1.6–6)		
		Mid-40s	101	2.2 (1.2–4)		
		Mid-50s	104	0.8 (0.4–1.4)		
			Women:			
		Mid-20s	13	5.2 (1.6–7.2)		
		Mid-30s	15	3.3 (1.3–8.6)		
		Mid-40s	26	2.1 (1.1–4.5)		
		Mid-50s	30	1.2 (0.5–2.5)		
		Obesity in early adulthood (mid-20s to mid-40s)	Men: 192	2.3 (1.2–4.4)		
			Women: 54	3.6 (1.5–8.9)		

BMI, body mass index (in kg/m^2); CI, confidence interval; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; WC, waist circumference

Table 2.2.4c Meta-analyses of measures of body fatness and cancer of the liver

Reference	Total number of studies Total number of cases	Organ site	Exposure categories	Relative risk (95% CI)	Adjustment for confounding	Comments
Larsson & Wolk (2007)	11 cohort studies (7 on overweight with 5037 cases, and 10 on obesity with 6042 cases)	Liver	BMI Overweight vs normal Obese vs normal	 1.17 (1.02–1.34) 1.89 (1.51–2.36)	Age and other covariates depending on study (calendar year, sex, race, diabetes, education, marital status, smoking, physical activity, diet, family history of cancer, alcohol consumption, occupational group, aspirin use, estrogen replacement therapy in women)	The relative risk for obesity compared with normal BMI was stronger in men than in women
Renehan et al. (2008)	4 cohort studies in men and 1 in women 2070	Liver	BMI per 5 kg/m^2 increase	Men: 1.24 (0.95–1.62) Women: 1.07 (0.55–2.08)	NR	Results are from random-effects models. Substantial heterogeneity was observed (I^2 = 83.1% in men)
Chen et al. (2012)	26 prospective cohort studies 25 337	Liver (primary cancer)	BMI < 25 25–29.9 ≥ 30 BMI < 25 25–29.9 ≥ 30 BMI < 25 25–29.9 ≥ 30	All: 1.00 1.48 (1.31–1.67) 1.83 (1.59–2.11) Men: 1.00 1.42 (1.22–1.65) 1.91 (1.51–2.41) Women: 1.00 1.18 (1.08–1.30) 1.55 (1.30–1.85)	Age (all studies), and most of the studies included alcohol consumption, HBV and/or HCV infection, diabetes mellitus	Significant heterogeneity in the overall analyses, and in analyses in men; effects significantly different in men vs women; associations independent of geographical location, alcohol consumption, diabetes, or HBV/HCV infections
Rui et al. (2012)	8 cohort studies in men and women 11 616	Liver	BMI 18.5–24.9 25–30 ≥ 30	 1.00 1.13 (1.05–1.21) 2.09 (1.72–2.45)	NR	Associations remained significant after excluding 3 studies on cirrhosis cohorts

Table 2.2.4c (continued)

Reference	Total number of studies Total number of cases	Organ site	Exposure categories	Relative risk (95% CI)	Adjustment for confounding	Comments
Tanaka et al. (2012)	9 cohort studies and 3 case–control studies NR	Liver	BMI per 1 kg/m² increase	1.13 (1.07–1.20)	Different adjustment factors depending on study (hepatitis, alcohol consumption, diabetes, smoking)	Study restricted to Japanese populations Overweight/obese individuals showed a 74% increased risk compared with those with normal weight
Wang et al. (2012)	21 prospective cohort studies (11 in men and 5 in women) 17 624	Liver (primary cancer)	BMI per 5 kg/m² increase	All: 1.39 (1.25–1.55) Men: 1.26 (1.11–1.44) Women: 1.18 (1.08–1.29)	Age (all studies). Other covariates, depending on study	Significant heterogeneity among studies was observed. Non-linear association was reported, with a steeper increase in risk from BMI > 32 kg/m²
WCRF/AICR (2015)	12 studies Men and women Incidence and mortality 14 311	Liver	BMI per 5 kg/m²	1.30 (1.16–1.46)		Heterogeneity between studies; non-linear associations; similar risks in men and women; associations stronger for incidence than for mortality, and for European vs Asian studies
	8 studies Men and women Incidence 11 530	Liver	BMI per 5 kg/m²	1.43 (1.19–1.70)		
	4 studies Men and women Mortality 2543	Liver	BMI per 5 kg/m²	1.13 (1.00–1.28)		
	8 studies Men Incidence and mortality 11 180	Liver	BMI per 5 kg/m²	1.21 (1.02–1.44)		

Table 2.2.4c (continued)

Reference	Total number of studies Total number of cases	Organ site	Exposure categories	Relative risk (95% CI)	Adjustment for confounding	Comments
WCRF/AICR (2015) (cont.)	4 studies Women Incidence and mortality 2337	Liver	BMI per 5 kg/m^2	1.21 (1.10–1.33)		
	Meta-analysis of European studies: 4 studies Men and women Incidence and mortality 588	Liver	BMI per 5 kg/m^2	1.59 (1.35–1.87)		
	Meta-analysis of Asian studies: 7 studies Men and women Incidence and mortality 12 520	Liver	BMI per 5 kg/m^2	1.18 (1.04–1.34)		

BMI, body mass index (in kg/m^2); CI, confidence interval; HBV, hepatitis B virus; HCV, hepatitis C virus; NR, not reported; WCRF/AICR, World Cancer Research Fund/American Institute for Cancer Research

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