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ABSENCE OF EXCESS BODY FATNESS

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2.2.5 Cancer of the gall bladder

Cancer of the gall bladder cancer is uncommon, and almost all gall bladder cancers are adenocarcinomas. 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 gall bladder cancer was *inadequate*. Since then, numberous individual studies and meta-analyses of anthropometric measures of body fatness and risk of gall bladder cancer have been published. Results are presented here for cohort studies with at least 50 cases (Table 2.2.5a) and for case–control studies (Table 2.2.5b) and meta-analyses (Table 2.2.5c).

(a) Cohort studies

There are at least 11 individual informative prospective studies of the associations of BMI or weight with gall bladder cancer incidence or mortality (Table 2.2.5a). No association was observed in three of these studies (Samanic et al., 2006; Ishiguro et al., 2008; Hemminki et al., 2011). Findings from the other eight prospective studies showed statistically significant positive association between BMI or weight and risk of gall bladder cancer (Calle et al., 2003; Samanic et al., 2004; Engeland et al., 2005; Kuriyama et al., 2005; Jee et al., 2008; Schlesinger et al., 2013; Bhaskaran et al., 2014; Borena et al., 2014), and in several of those studies there was a dose–response relationship. In a large study of nearly 1.2 million public servants in the Republic of Korea (Jee et al., 2008), the relative risk of gall bladder cancer incidence for BMI ≥ 30 kg/m^2 versus 23.0–24.9 kg/m^2 was 1.44 (95% CI, 0.98–2.12) in women (P_{trend} = 0.0007) and 1.65 (95% CI, 1.11–2.44) in men (P_{trend} = 0.0003). A large cohort study in the United Kingdom that included more than 5.2 million men and women also showed a statistically significant positive association between BMI and risk of gall bladder cancer (RR per 5 kg/m^2 increase, 1.31; 95% CI, 1.12–1.52; P_{trend} < 0.0001) (Bhaskaran et al., 2014). In a nationwide prospective study in the USA, there was evidence of a strong positive association between being obese (BMI ≥ 30 kg/m^2) and risk of gall bladder cancer mortality in both women (RR, 2.13; 95% CI, 1.56–2.90; P_{trend} < 0.001) and men (RR, 1.76; 95% CI, 1.06–2.95; P_{trend} = 0.02) (Calle et al., 2003).

In one study that assessed waist circumference in relation to risk of gall bladder cancer, each increase of 5 cm in waist circumference was associated with a 17% (95% CI, 1.06–1.30) higher risk in men and women combined (Schlesinger et al., 2013). [These results should be interpreted with caution because only 76 cases of gall bladder cancer were identified during follow-up in 359 156 men and women included in the analysis.]

The association between weight change and risk of gall bladder cancer was also examined in the EPIC cohort. Average annual weight change from age 20 years to the age at cohort enrolment was not associated with risk of gall bladder cancer (Schlesinger et al., 2013).

(b) Case–control studies

Of the case–control studies that examined the association between BMI and risk of gall bladder cancer (Table 2.2.5b), seven showed no association (Strom et al., 1995; Serra et al., 2002; Máchová et al., 2007; Grainge et al., 2009; Nakadaira et al., 2009; Alvi et al., 2011; Cha, 2015), whereas in three studies there was a statistically significant positive association between adult BMI and risk of gall bladder cancer, which appeared to be dose-related (Zatonski et al., 1997; Ahrens et al., 2007; Hsing et al., 2008).

(c) Pooled analyses and meta-analyses

There have been one pooled analysis (Whitlock et al., 2009; Table 2.2.5a) and several meta-analyses of cohort and case–control studies (Larsson & Wolk, 2007; Renehan et al., 2008; Tan et al., 2015; WCRF/AICR, 2015; Table 2.2.5c) that

examined the relationship between BMI and gall bladder cancer incidence or mortality.

All meta-results were significantly positive. In the largest and most recent meta-analysis (Tan et al., 2015), which included 12 prospective studies in Asia, Europe, and the USA, both overweight (RR, 1.15; 95% CI, 1.02–1.29) and obesity (RR, 1.62; 95% CI, 1.45–1.81) were statistically significantly positively associated with risk of gall bladder cancer. Similarly, results from the 2015 WCRF Continuous Update Project on BMI and risk of gall bladder cancer showed a statistically significant 25% (95% CI, 1.15–1.37) higher risk per 5 kg/m^2 increase reported in a dose–response analysis based on eight prospective studies (WCRF/AICR, 2015). In the WCRF analysis, associations were similar between cancer incidence and mortality, between men and women, and between studies in Asia and in Europe. In a meta-analysis of eight case–control studies, both overweight (RR, 1.16) and obesity (RR, 1.37) were associated with statistically significant higher risks of gall bladder cancer (Tan et al., 2015).

Table 2.2.5a Cohort studies of measures of body fatness and cancer of the gall bladder

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Calle et al. (2003) Cancer Prevention Study II (CPS II) USA 1982–1998	495 477 Women Mortality	Gall bladder and extrahepatic bile ducts ICD-9: 156.0–156.9	BMI 18.5–24.9 25–29.9 30–34 [P_{trend}]	 159 86 59	 1.00 1.12 (0.86–1.47) 2.13 (1.56–2.90) [< 0.001]	Age, education level, smoking, physical activity, alcohol consumption, marital status, race, aspirin use, fat consumption, vegetable consumption; for women, also adjusted for HRT use	
	404 576 Men Mortality		BMI 18.5–24.9 25–29.9 30–34 [P_{trend}]	 66 94 20	 1.00 1.34 (0.97–1.84) 1.76 (1.06–2.94) [0.02]		
Samanic et al. (2004) United States Veterans cohort USA 1969–1996	4 500 700 Men Incidence	Gall bladder and extrahepatic bile ducts ICD-9: 156	Obesity Non-obese Obese Non-obese Obese	 White men: 265 26 Black men: 45 2	 1.00 1.70 (1.13–2.57) 1.00 0.93 (0.23–3.86)	Age, calendar year	Obesity defined as discharge diagnosis of obesity: ICD-8: 277; ICD-9: 278.0
Engeland et al. (2005) Norwegian men and women Norway 1963–2002	1 037 892 Women Incidence	Gall bladder ICD-7: 155.1	BMI < 18.5 18.5–24.9 25.0–29.9 ≥ 30 [P_{trend}]	1087 total	 1.02 (0.54–1.91) 1.00 1.27 (1.10–1.47) 1.88 (1.60–2.21) [< 0.001]	Age, birth cohort, height	
	963 619 Men Incidence		BMI < 18.5 18.5–24.9 25.0–29.9 ≥ 30 [P_{trend}]	628 total	 0.31 (0.04–2.24) 1.00 1.00 (0.84–1.17) 1.38 (1.01–1.89) [0.2]		

Table 2.2.5a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Kuriyama et al. (2005) Japanese men and women Japan 1984–1992	15 054 Women Incidence	Gall bladder and extrahepatic bile ducts ICD-9: 156.0–156.9	BMI 18.5–24.9 25.0–27.4 27.5–29.9 ≥ 30 [P_{trend}]	 12 3 5 4	 1.00 0.83 (0.23–2.98) 3.43 (1.19–9.94) 4.45 (1.39–14.23) [0.004]	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	
	12 485 Men Incidence		BMI 18.5–24.9 25.0–27.4 27.5–29.9 ≥ 30 [P_{trend}]	 8 1 – – 	 1.00 0.46 (0.05–3.93) – – [0.48]		
Samanic et al. (2006) Swedish Construction Worker Cohort Sweden 1958–1999	362 552 Men Incidence	Gall bladder ICD-7: 155.1	BMI 18.5–24.9 25–29.9 ≥ 30 [P_{trend}]	 53 45 11 	 1.00 0.93 (0.62–1.39) 1.40 (0.73–2.70) [> 0.5]	Attained age, calendar year, smoking	
Ishiguro et al. (2008) Japan Public Health Center Japan 1990–2004	53 187 Women Incidence	Gall bladder ICD-O-3: C23.9, C24.0	BMI < 23 23.0–24.9 25.0–26.9 ≥ 27.0 [P_{trend}]	 35 9 8 11 	 1.00 0.47 (0.22–0.98) 0.62 (0.29–1.34) 0.94 (0.48–1.88) [0.50]	Age, study area, cholelithiasis, diabetes, smoking, alcohol consumption	
	48 681 Men Incidence		BMI < 23 23.0–24.9 25.0–26.9 ≥ 27.0 [P_{trend}]	 14 6 6 4 	 1.00 0.74 (0.28–1.92) 1.26 (0.48–3.33) 1.39 (0.45–4.34) [0.52]		

Table 2.2.5a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Ishiguro et al. (2008) (cont.)	101 868 Men and women Incidence		BMI < 23 23.0–24.9 25.0–26.9 ≥ 27.0 [P_{trend}]	 49 15 14 15	 1.00 0.55 (0.31–0.98) 0.80 (0.44–1.46) 1.06 (0.59–1.90) [0.82]		
Jee et al. (2008) Cohort from the National Health Insurance Corporation Republic of Korea 1992–2006	443 273 Women Incidence	Gall bladder (NOS)	BMI < 20.0 20.0–22.9 23.0–24.9 25.0–29.9 ≥ 30.0 [P_{trend}]	 121 302 262 341 36	 0.97 (0.78–1.21) 1.12 (0.90–1.41) 1.00 1.27 (1.02–2.12) 1.44 (0.98–2.12) [0.0007]	Age, smoking	Excluded first 2 yr of follow-up Update of study by Oh et al. (2005)
	770 556 Men Incidence		BMI < 20.0 20.0–22.9 23.0–24.9 25.0–29.9 ≥ 30.0 [P_{trend}]	 246 787 670 542 31	 0.80 (0.68–0.94) 0.86 (0.77–0.96) 1.00 0.97 (0.86–1.10) 1.65 (1.11–2.44) [0.0003]		
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	Gall bladder and extrahepatic bile ducts ICD-9: 156	BMI, per 5 kg/m^2	120	1.29 (0.90–1.85)	Age, sex, smoking status, study	
Hemminki et al. (2011) Swedish hospital patients Sweden 1964–2006	30 020 Men and women Incidence	Gall bladder ICD-7: 155.1	Obesity Observed vs expected rates	19	SIR 1.55 (0.93–2.43)	Age, sex, time period, region, SES	Overlap with study by Wolk et al. (2001) is unclear Obesity defined as hospital discharge diagnosis

Table 2.2.5a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Schlesinger et al. (2013) EPIC cohort 10 European countries 1992–2010	359 156 (191 856 for weight change) Men and women Incidence	Gall bladder ICD-10: C23.9	BMI, per 5 kg/m²	76 total	1.28 (0.99–1.65) 0.70 (0.43–1.15)*	Age, sex, study centre, education level, smoking, alcohol consumption, height *additional adjustment for WC **additional adjustment for BMI	
			Baseline weight, per 5 kg	76 total	1.11 (1.00–1.22)		
			Weight change (kg/year)	37 total	1.76 (0.59–5.29)		
			WC, per 5 cm	76 total	1.17 (1.06–1.30) 1.33 (1.10–1.62)**		
Bhaskaran et al. (2014) Clinical Practice Research Datalink United Kingdom 1987–2012	5 243 978 Men and women Incidence	Gall bladder ICD-10: C23	BMI per 5 kg/m² [P_{trend}]	303 total	HR (99% CI) 1.31 (1.12–1.52) [< 0.0001]	Age, sex, diabetes, smoking, alcohol consumption, SES, calendar year	
Borena et al. (2014) Metabolic Syndrome and Cancer Project (Me-Can) cohort Austria, Norway, and Sweden 1972–2006	578 700 Men and women Incidence	Gall bladder ICD-7: 155.1	BMI, quintiles (mean)			Smoking status, baseline age, cohort, sex, year of birth	
			Q1 (20.7)	20	1.00		
			Q2 (23.0)	26	1.12 (0.58–2.19)		
			Q3 (24.7)	38	1.49 (0.80–2.76)		
			Q4 (26.8)	47	1.70 (0.93–3.09)		
			Q5 (31.3)	53	1.94 (1.08–3.51)		
			[P_{trend}]		[0.08]		
			BMI				
			< 25	77	1.00		
			≥ 25	107	1.52 (1.12–2.10)		

BMI, body mass index (in kg/m²); CI, confidence interval; EPIC, European Prospective Investigation into Cancer and Nutrition; HR, hazard ratio; HRT, hormone replacement therapy; SES, socioeconomic status; SIR, standardized incidence ratio; WC, waist circumference

Table 2.2.5b Case–control studies of measures of body fatness and cancer of the gall bladder

Reference Study location Period	Total number of cases Total number of controls Source of controls	Organ site	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment for confounding
Strom et al. (1995) Bolivia and Mexico 1984–1988	84 126 Men and women Hospital		BMI, most of adult life < 24 24–25.9 26–28 > 28 BMI, maximum ever < 24 24–25.9 26–28 > 28	 33 17 12 3 12 15 22 19	 1.0 1.5 (0.5–4.6) 2.2 (0.7–8.4) 1.6 (0.4–6.1) 1.0 1.6 (0.4–7.6) 1.3 (0.3–5.6) 2.6 (0.5–18.6)	Age, sex, country
Zatonski et al. (1997) Australia, Canada, The Netherlands, and Poland 1983–1988	Men: 44 815 Population Women: 152 700 Population		BMI, quartiles Q1 Q2 Q3 Q4 [P_{trend}] BMI, quatiles Q1 Q2 Q3 Q4 [P_{trend}]	Men: 9 11 13 11 Women: 30 37 22 56	 1.0 1.0 (0.3–3.0) 0.7 (0.3–2.0) 1.0 (0.3–2.8) [0.74] 1.0 1.7 (0.9–3.1) 1.5 (0.3–3.0) 2.1 (1.2–3.8) [0.02]	
Serra et al. (2002) Chile 1992–1995	114 114 Hospital		BMI < 25 25–29.9 ≥ 30	 53 42 19	 1.0 0.8 (0.4–1.4) 0.9 (0.4–1.8)	Age, sex
Ahrens et al. (2007) Europe 1995–1997	104 1401 (men only) Population	Gall bladder ICD-O: C23.9	BMI ≤ 25 25– < 27 27– < 30 ≥ 30	62 total	 1.0 1.8 (0.4–7.2) 11.0 (2.9–41.9) 13.3 (1.4–123)	Age, country, history of gallstones

Table 2.2.5b (continued)

Reference Study location Period	Total number of cases Total number of controls Source of controls	Organ site	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment for confounding
Máchová et al. (2007) Czech Republic 1987–2002	93 37 772 Population		BMI Men: 18.5–24.9 25–30 ≥ 30 Women: 18.5–24.9 25–30 ≥ 30	 14 total 79 total 	 1.00 1.01 (0.24–4.32) 0.76 (0.08–7.41) 1.00 1.07 (0.58–1.95) 0.73 (0.36–1.50)	Age, smoking, height, hypertension
Hsing et al. (2008) China 1997–2001	627 959 Population	Gall bladder, excluding extrahepatic bile ducts and ampulla of Vater	Usual adult BMI < 18.5 18.5–22.9 23.0–24.9 ≥ 25 [P_{trend}] Maximum adult BMI < 18.5 18.5–22.9 23.0–24.9 ≥ 25 [P_{trend}] BMI change in adulthood ≤ 0.74 0.75–2.77 2.78–5.21 > 5.21 [P_{trend}]	 17 30 73 145 6 74 83 185 74 62 86 93 	 0.62 (0.35–1.09) 1.0 1.20 (0.85–1.68) 1.56 (1.17–2.10) [< 0.001] 1.24 (0.47–3.29) 1.00 1.35 (0.94–1.95) 1.48 (1.08–2.03) [0.02] 1.00 0.93 (0.62–1.39) 1.45 (0.98–2.14) 1.47 (1.00–2.16) [0.01]	Age (continuous), sex (male, female), and education level (none/ primary, junior middle, senior, some college)
Grainge et al. (2009) United Kingdom 1987–2002	184 3007 Population	Gall bladder, excluding cholangiocarcinomas and unspecified biliary tract cancers	BMI < 25 25–29.9 ≥ 30	 36 31 19	 1.00 1.03 (0.62–1.72) 1.51 (0.83–2.75)	Smoking, alcohol consumption, NSAID use

Table 2.2.5b (continued)

Reference Study location Period	Total number of cases Total number of controls Source of controls	Organ site	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment for confounding
Nakadaira et al. (2009) Hungary 2003–2006	41 30 Hospital		BMI ≤ 24.9 25–29.9 ≥ 30	 13 9 19	 1.0 1.5 (0.4–5.0) 0.8 (0.3–1.8)	Age
Alvi et al. (2011) Pakistan 1988–2007	60 120 (70% of cases were women) Hospital		BMI < 23 > 23	 14 46	 1.00 1.98 (0.62–6.28)	Sex, hypertension, diabetes, smoking
Shebl et al. (2011) China 1997–2001	627 959 Population	Gall bladder, excluding extrahepatic bile ducts and ampulla of Vater	WC (cm) Low High (men: ≥ 90; women: ≥ 80)	 83 111	 1.00 0.98 (0.65–1.47)	Age, sex, BMI
Cha (2015) Republic of Korea 2008–2013	78 78 Population		BMI < 23 ≥ 23	 18 23	 1.00 0.74 (0.28–1.97)	Age, sex, hypertension, diabetes mellitus, vascular occlusive disease, alcohol consumption, smoking, polypoid lesions of gall bladder, gallstone disease

BMI, body mass index (in kg/m^2); CI, confidence interval; NSAID, non-steroidal anti-inflammatory drug; WC, waist circumference

Table 2.2.5c Meta-analyses of measures of body fatness and cancer of the gall bladder

Reference Period	Number and type of studies	Population Incidence/mortality	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates, comments
Larsson & Wolk (2007) 1966–2007	8 cohort studies	Men and women Incidence and mortality	Obese vs normal (definition varies by study)		1.69 (1.48–1.92)	See also Table 2.2.5b
	8 cohort studies, 4 case–control studies	Men and women Incidence and mortality	Obese vs normal (definition varies by study)	-	1.66 (1.47–1.88)	
Renehan et al. (2008) 1966–2007	2 cohort studies	Women Incidence	BMI, per 5 kg/m²	1111 total	1.59 (1.02–2.47)	Also split up by geographical region
	4 cohort studies	Men Incidence	BMI, per 5 kg/m²	928 total	1.09 (0.99–1.21)	
Tan et al. (2015) Cohort studies: 1964–2006	12 cohort studies	Men and women Incidence and mortality	Overweight Obese	5101 total	1.15 (1.02–1.29) 1.62 (1.45–1.81)	Normal BMI used as reference
Case–control studies: 1984–2007	8 case–control studies		Overweight Obese		1.16 (0.96–1.41) 1.37 (1.10–1.71)	
	12 cohort studies, 8 case–control studies		BMI Overall: 25–30 > 30 Men: 25–30 > 30 Women: 25–30 > 30		 1.14 (1.04–1.25) 1.56 (1.41–1.73) 1.06 (0.94–1.20) 1.42 (1.21–1.66) 1.26 (1.13–1.40) 1.67 (1.38–2.02)	
WCRF/AICR (2015) NR	8 cohort studies	Men and women Incidence and mortality	BMI, per 5 kg/m²	6004 total	1.25 (1.15–1.37)	

BMI, body mass index (in kg/m²); CI, confidence interval; ICD, International Classification of Diseases; NR, not reported; WCRF/AICR, World Cancer Research Fund/American Institute for Cancer Research

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