2.4 Cancer of the oesophagus

The evidence for the carcinogenic effects of alcoholic beverage consumption on the risk for oesophageal cancer was considered to be sufficient by a previous Working Group (IARC, 1988). Several epidemiological studies have been published since that time, and this section evaluates the risk for oesophageal cancer based on the relevant cohort and case–control studies after 1988.

The 18 cohort and 38 case–control studies conducted in Argentina, China, Denmark, Europe, India, Italy, Japan, Norway, Sweden, the United Kingdom, Uruguay and the

USA summarized in this section are described in Tables 2.15, 2.16 (literature originally in the Chinese language) and 2.17.

2.4.1 *Cohort studies (Table 2.15)*

(a) Special populations

Five cohort studies were based on either individuals who had high exposure to alcoholic beverages, such as alcoholics or workers in the brewery industry, or who had lower alcoholic beverage consumption, such as teetotalers (Carstensen *et al*., 1990; Adami *et al*., 1992b; Kjaerheim *et al*., 1993; Tønnesen *et al*., 1994; Boffetta *et al*., 2001). This type of study does not usually consider individual exposure levels. The point estimates were either the SIRs or SMRs with no adjustment for tobacco smoking. The four studies of alcoholics or brewery workers reported a statistically significant association, and the point estimates of the SIR ranged from 2.5 to 5.5 (Carstensen *et al*., 1990; Adami *et al*., 1992b; Tønnesen *et al*., 1994; Boffetta *et al*., 2001); the point estimate was 0.26 for teetotalers (Kjaerheim *et al*., 1993).

(b) General population

Thirteen cohort studies of the general population have been published, including two in the Chinese literature (Table 2.16), most of which adjusted for tobacco smoking. Ten cohort studies reported a statistically significant association between alcoholic beverage consumption and the risk for oesophageal cancer after controlling for tobacco smoking. In addition, these studies were carried out in different geographical regions of the world. The adjusted relative risks ranged from 2.8 in the USA (Thun *et al*., 1997) to 14.5 in Japan (Kono *et al*., 1987) for two or more drinks per day after adjusting for tobacco smoking. One study (Lindblad *et al*., 2005) reported a positive association for adenocarcinoma of the oesophagus with a relative risk of 1.76 (95% CI, 1.16–2.66) for heavy drinkers.

The two cohort studies in Linxian County, China, based on the same population reported a null association (Guo *et al*., 1994; Tran *et al*., 2005). The null association between alcoholic beverage consumption and oesophageal cancer in rural high-risk areas of China is probably due to the relatively low consumption of alcoholic beverages in these areas or other strong risk factor(s) which may mask or highly confound the association between alcoholic beverage consumption and oesophageal cancer. Another study from the Chinese literature (Wang *et al*., 2005a; Table 2.16) reported that an increased risk for oesophageal cancer was associated with elevated alcoholic beverage consumption (relative risk, 5.08 for >70 g/day or 5 or more drinks/day) after adjusting for tobacco smoking; however, no 95% CI was provided.

In summary, the results of the majority of the prospective cohort studies support that alcoholic beverage consumption can cause cancer of oesophagus.

Table 2.15 Cohort studies of oesophageal cancer and consumption of alcoholic beverages

Reference, location, name of study	Cohort description	Exposure assessment	Cancer site (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors	Comments
Special populations								
Kono *et al.* (1987), Japan, Japanese Physicians' Study	5130 male Japanese physicians, aged 27–89 years; followed up for 19 years, 1965–83; response rate, 51%	Self-administered questionnaire;	Oesophagus	Never and occasional Daily <2 go Daily ≥2 go		1.00 1.53 (0.14–16.83) 14.46 (3.00–69.71)	Age, smoking	No significant interaction with smoking (p>0.05); 1 go of sake ≃ 27 mL alcohol
Carstensen *et al*. (1990), Sweden	6230 men employed in the Swedish brewery industry in 1960, aged 20–69 years; followed–up 1961–79	Population census	Oesophagus	Not reported	20	2.46 (1.51–3.81)	Not reported	All Swedish men used as a reference group.
Adami *et al.* (1992b), Sweden, Uppsala Alcoholics Study	9353 (8340 men, 1013 women) with a discharge diagnosis of alcoholism in 1965–83; 94% confirmed microscopically; followed up for 19 years (mean, 7.7 years)	Record-linkage to the nationwide Registry of Causes of Death;	Oesophagus	*Years of follow-up* 1–4 5–9 10–19		**SIR** 11.7 (6.9–18.4) 3.7 (1.2–8.7) 4.6 (1.5–10.7)	Expected rates were derived from the study population.	

Table 2.15 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Cancer site (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors	Comments
Kjaerheim *et al*. (1993), Norway	5332 members of International Organization of Good Templars, Norwegian teetotalers; followed–up 1980–89	Cancer registry	Oesophagus	Not reported	1	0.26 (1–145)	Compared with that of the total Norwegian population	
Tønnesen *et al*. (1994), Denmark, Alcohol Abusers Study	18 368 non-hospitalized alcohol abusers during 1954–87; 15 214 men were observed for 12.9 years and 3093 women for 9.4 years.	Central population registry	Oesophagus	Not reported	57 2 59	Men 5.3 (4.0–6.9) $p \leq 0.01$ Women 4.9 (0.6–17.7) Total 5.3 (4.0–6.8) $p \leq 0.01$	Compared with that of Danish population	

Table 2.15 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Cancer site (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors	Comments
Boffetta *et al*. (2001), Sweden, Uppsala Alcoholics Study	173 665 patients (138 195 men, 35 470 women) with a hospital discharge diagnosis of alcoholism during1965–94, aged >20 years; followed up for 10.2 years	Linkage between the Swedish In–patient Register and the National Cancer Register	Oesophagus	Diagnosed alcoholics	 521 465 56	**SIR** *Both genders* 5.54 (5.07–6.04) *Men* 5.26 (4.79–5.76) *Women* 10.0 (7.57–13.0)		Compared with incidence in the national population
General populations								
Boffetta & Garfinkel (1990), USA, American Cancer Society Cancer Prevention Study I	276 802 white men, aged 40–59 years, volunteers for the American Cancer Society in 25 states; enrolled in 1959 and followed for 12 years	A detailed four-page questionnaire; vital status checked yearly; death certificates of deceased participants obtained from state health departments	Oesophagus	Non-drinkers Occasional 1 drink/day 2 drinks/day 3 drinks/day 4 drinks/day 5 drinks/day ≥6 drinks/day Irregular	59 9 20 18 19 19 6 22 13	1.0 1.12 (0.55–2.28) 1.37 (0.81–2.30) 1.61 (0.94–2.77) 3.52 (2.05–6.02) 5.35 (3.08–9.27) 3.53 (1.47–8.48) 5.79 (3.44–9.74) 1.64 (0.89–3.01)	Age, smoking	

Table 2.15 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Cancer site (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors	Comments
Kato *et al*. (1992c), USA, Hawaii, American Men of Japanese Ancestry Study	6701 American men of Japanese ancestry, born in 1900–19, and residing on the Hawaiian island of Oahu; 19 year follow-up survey, 1965–90	Structured interview	Oral cavity, pharynx, oesophagus, larynx	0 mL/day <30 mL/day ≥30 ml/day	13 21 36	1.0 1.2 (0.6–2.3) 5.4 (2.8–10.4)	Age, smoking	
Guo *et al*. (1994), China, Lin Xian Nutrition Intervention Trial	Nested case–control study; a cohort of 29 584 adults in a randomized intervention trial, aged 40–69 years; follow-up 1986–91; 640 cases; 3200 controls; 5 controls per case matched by age and sex	Structured interview	Oesophagus	Lifetime use of alcoholic beverages	640	Not reported	Not reported	Drinking alcoholic beverages was relatively uncommon in Lin Xian residents, but was reported by 22% of the cancer patients; no significant association between oesophageal and alcohol drinking found.

Table 2.15 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Cancer site (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors	Comments
Thun *et al.* (1997), USA, American Cancer Society Cancer Prevention Study II	490 000 (251 420 women, 238 206 men), mean age, 56 years (range, 30–104); study subjects were recruited by American Cancer Society volunteers; followed up from 1982– 91	Self-reported alcoholic beverage and tobacco use	Alcohol-related (mouth, oesophagus, pharynx, larynx, liver)		*Men*		Age, race, education, body mass index, smoking	Study subjects were recruited by American Cancer Society volunteers; they were also more likely than the general US population to be college educated, married, middle class and white; number of case or risk related to oesophageal cancer can not be determined.
				None	69	1.0		
				Less than daily	106	1.4 (1.0–1.9)		
				1 drink/day	58	1.4 (1.0–2.0)		
				2–3 drinks/ day	101	1.5 (1.1–2.1)		
				4 drinks/day	144	2.8 (2.1–3.8) $p<0.001$		
					Women			
				None	43	1.0		
				Less than daily	30	1.1 (0.7–1.8)		
				1 drink/day	10	0.8 (0.4–1.6)		
				2–3 drinks/ day	26	1.5 (0.9–2.5)		
				4 drinks/day	21	3.0 (1.7–5.3) $p<0.002$		

Table 2.15 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Cancer site (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors	Comments
Grønbaek *et al*. (1998), Denmark, The Copenhagen Centre for Prospective Population Studies	15 117 men, 13 063 women, aged 20–98 years; follow-up of 13.5 years, –1994; mean participation rate, 80%	Self–administered questionnaire; health examination	Oropharynx, oesophagus	See Tables 2.19a, b		See Tables 2.19a, b	Age, sex, smoking habits, educational level	There was a strong dose-dependent increase in risk for upper digestive tract cancer with increased alcoholic beverage intake.
Kinjo *et al*. (1998), Japan, Six-Prefecture Study	220 272 residents (100 840 men, 119 432 women), aged 40–69 years at the baseline of 1965, from 29 public health districts in six Prefectures of Japan; followed up 1966–81	Structured questionnaire	Oesophagus	None 1–3 times/ month 1–3 times/ week 4 times/week or more	149 31 76 184	1.0 0.7 (0.5–1.1) 1.1 (0.8–1.5) 2.4 (1.8–3.1) $p<0.001$	Age, Prefecture, occupation, sex	Joint effect of alcohol and tobacco, 3.9 (2.7–5.4); dose–response relationship, p for trend <0.001

Table 2.15 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Cancer site (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors	Comments
Kjaerheim *et al*. (1998), Norway, Norwegian Cohort Study	10 960 Norwegian men, born in 1893–1929, who had answered questionnaires, were alive and living in Norway on 1 January 1968 and had no diagnosis of upper aerogastric tract cancer prior to this date; mean age at start of follow-up, 59 years; followed up 1968–92; histological verification, 95.8%	Structured questionnaire; cancer registry	Oral cavity, pharynx, larynx, oesophagus	*Times/week* Never or <1 Previously 1–3 4–7	*Upper aerogastric tract cancer* 22 3 17 18	 1.0 0.8 (0.2–2.7) 1.1 (0.6–2.1) 3.2 (1.6–6.1) p=0.01	Age, smoking	

Table 2.15 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Cancer site (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors	Comments
Lindblad *et al*. (2005), United Kingdom, General Practitioner Research Database	Nested case–control study; 287 oesophageal adenocarcinomas and 10 000 controls, aged 40–84 years; controls randomly selected, frequency-matched by sex, age, same calendar year from the pool; 5 controls per case; 1994–2001	Patients reviewed by one investigator kept blinded to exposure information during the review process	Oesophagus	*Units/day* 0–2 3–15 16–34 >34 Unknown use	 294 156 54 30 375	 1.0 1.06 (0.86–1.30) 1.04 (0.76–1.43) 1.76 (1.16–2.66) 1.04 (0.82–1.32)	Sex, age, smoking, body mass index, reflux, calendar year	One unit of an alcoholic beverage = 10 mL (7.9 g) pure ethanol.

Table 2.15 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Cancer site (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors	Comments
Sakata *et al*. (2005), Japan, Japan Collaborative Cohort Study	110 792 (46 465 men, 64 327 women), aged 40–79 years; followed-up 1988– 99; a baseline survey conducted in 45 areas throughout Japan	Self-administered questionnaire; death and cause of death confirmed annually or biannually	Oesophagus	Non-drinkers	9	1.0	Age, centre	42 578 men for analysis; one unit of alcohol contains about 22 g alcohol
				<1.0 units/day	2	1.47 (0.28–7.68)		
				1.0–1.9 units/ day	16	1.58 (0.65–3.86)		
				2.0–2.9 units/ day	31	3.74 (1.62–8.66)		
				≥3.0 units/day	18	6.39 (2.54–16.12) *p*=0.028		
				Years of drinking				
				Non-drinkers	9	1.00		
				≤25.0	14	1.71 (0.64–4.60)		
				25.1–35.0	19	3.23 (1.32–7.92)		
				35.1–45.0	18	3.23 (1.33–7.81)		
				≥45.1	7	2.77 (0.85–9.03) *p*=0.100		
				Cumulative intake				
				Non-drinkers	9	1.0		
				1–29.9 unit–years	4	0.68 (0.19–2.42)		
				31.0–39.9 unit–years	6	2.31 (0.75–7.06)		
				≥40.0 unit–years	46	3.80 (1.70–8.46) *p*=0.089		

Table 2.15 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Cancer site (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors	Comments
Tran *et al.* (2005), China, Linxian Intervention Trial Study	Population-based prospective study of 29 584 adults in the Linxian General Population Trial, 40–69 years of age at baseline; follow–up, 15 years; case ascertainment considered complete and loss to follow-up minimal (*n*=176 or 1%)	Structured interviewed;	Oesophagus	Alcoholic in previous 12 months	450	0.92 (0.82–1.03)	Sex, age	No association

CI, confidence interval; ICD, International Classification of Diseases; SIR, standardized incidence

Table 2.16 Analytical studies of oesophageal cancer and alcoholic beverage consumption published in the Chinese literature

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment factors	Comments
Cohort studies	*Characteristics of the cohort*						
Zhang *et al.* (1998), Shandong, 1982–94	15 803 residents from 29 villages, aged 20 years; followed 1982-94	-	Questionnaire	*Alcoholic beverage intake (g)*		Not specified	
				0–49	1.00		
				50–149	2.05 (1.37–3.06)		
				150–249	1.20 (0.65–2.21)		
				≥250	1.03 (0.53–1.99)		
				Duration (years)			
				15–24	1.00		
				25–34	0.75 (0.27–2.10)		
				35–44	1.18 (0.44–3.20)		
				45–54	2.59 (0.99–6.73)		
				55–64	4.10 (1.52–11.08)		
				≥65	2.02 (0.51–8.06)		

Table 2.16 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment factors	Comments
Wang *et al.* (2005a), Shanghai, 1986–2002	18 244 cancer-free men; followed 1986–2000	-	Interview	*Alcoholic beverage intake (g/day)* 0 <30 30–70 >70	 1.00 1.33 2.47 5.08	Age, smoking, education	Significant result, but with no CI
Case–control studies							
Chen *et al.* (2000), Jiangsu, 1997–98	100 new cases from 11 hospitals	100 healthy controls matched on village of residence, gender, age	Questionnaire	*Alcoholic beverage consumption* <25 g/day >25 g/day	 1.00 2.09 (1.21–4.29)	Crude analysis	
Liu *et al.* (2000), TianJing, 1999	86 randomly sampled men	158 from the general population	Questionnaire	*Duration of drinking (years)* 0 1–10 10–20 >20 *Volume consumed (mL)* 0–50 50–99 100–249 ≥250	 1.00 1.85 (0.70–4.85) 2.15 (1.23–4.79) 3.10 (1.55–6.97) 1.00 1.23 (0.56–2.69) 4.31 (1.89–10.07) 18.66 (5.23–27.56)	Age, occupation, education, smoking	

Table 2.16 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment factors	Comments
Lu *et al.* (2000b), LinZhou, 1995–96	352 from cancer registry	352; matched on age, sex, neighborhood	Questionnaire	*Alcoholic beverage consumption* No Yes	 1.00 2.67 (1.04–6.81) $p<0.05$	Crude analysis	
Zhang *et al.* (2000), Ci, HeBei, 1973–97	350 hospital patients; categorized by geographical area	350 cancer-free; matched on village of residence, gender, occupation, age	Interviewer-administered questionnaire	*Alcoholic beverage consumption* No Yes	 1.0 0.62 (0.41–0.93)	Crude analysis	Alcoholic beverage consumption appears to be a protective factor for oesophageal cancer in this study.
Cui *et al.* (2001a), JiangYan, Jiangsu, 1995–99	156 living	156 healthy residents from the same community as cases, matched on age	Interviewer-administered questionnaire	*Alcoholic beverage consumption* No Yes	 1.0 3.58 (0.68–5.08)	Hot food, spicy food, smoking	
Ding *et al.* (2001a,b), TaiXing, Jiangsu, 1998–99	591 cases	591 from the same community; matched on gender, age	Interviewer-administered questionnaire	*Consumption of distilled spirits* No Yes	 1.00 2.71 (1.09–7.64)	Crude analysis	

Table 2.16 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment factors	Comments
Gao *et al.* (2001), HuaiAn, 1997–2000	141 hospital patients	223 cancer-free from the general population; matched on age	Interview	*Alcoholic beverage consumption* <1 per week ≥1 per week	 1.00 1.65 (0.90–3.03)	Gender, age, smoking	
Li *et al.* (2001), ChaoShan, Guangdong, 1997–2000	1248 from four hospitals within 3 months of diagnosis; residents of ChaoShan for over 10 years	1248 hospital patients; matched on age	Questionnaire	*Alcohol beverage consumption* No Yes	Result insignificant; number not reported		The study was primarily on smoking. A possible effect modification between smoking and alcohol beverage was detected (not significant).
Chen *et al.* (2003a), Lin Xian, 1984–97	3 periods: 1244 in 1985 640 in 1991 702 in 1997	3 periods: 1314 in 1985 3200 in 1991 702 in 1997	Interview		Result insignificant;. number not reported		Cases and controls from 3 time periods were analysed separately in this study.
Ding *et al.* (2003), Shanghai, 2000	204 hospital patients	397 healthy controls from general population	Interview	*Alcoholic beverage consumption* No Yes	 1.00 16.31 (5.57–47.77)	Education, gastritis, eating speed, smoking, drinking tea, personality	

Table 2.16 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment factors	Comments
Mu *et al*. (2003), TaiXing, Jiangsu, 2000	218	415 from the general population	Questionnaire	**Alcoholic beverage consumption stratified by green tea consumption**		Age, gender, education	
				Green tea drinker			
				Alcoholic beverages			
				No	1.00		
				Yes	1.21 (0.65–2.28)		
				Green tea non-drinker			
				Alcoholic beverages			
				No	1.00		
				Yes	1.98 (1.00–3.91)		
Wang *et al*. (2003a), XiAn	Meta-analysis; 530 cases	Meta-analysis; 4005 controls		*Alcoholic beverage consumption*			This study is a meta-analysis.
				No	1.00		
				Yes	1.72 (1.27–2.33)		

Table 2.16 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment factors	Comments
Zhao *et al.* (2003), FeiCheng	185	204 cancer-free from the general population	Interviewer-administered questionnaire	*Alcohol consumed each month (kg*years)*		Age, gender, education, smoking	
				0	1.00		
				1–280	1.00 (0.58–1.74)		
				>280	1.74 (0.88–3.42)		
Wang *et al.* (2004)	78 hospital patients	118 cancer-free from general population; matched on age	Interview	*Alcoholic beverage consumption*		Not specified	
				No	1.00		
				Yes	6.41 (2.81–14.62)		
Yan *et al.* (2004), ZhangYe, 1999–2000	125 hospital patients, residents of ZhangYe for over 20 years	145 cancer-free hospital patients	In-hospital interview with questionnaires	*Alcoholic beverage consumption*		Not specified	
				No	1.00		
				Yes	2.55 (1.47–4.43)		
Huang *et al.* (2005), Shandong	92 hospital patients	115 healthy controls from general population	Questionnaire	*Alcohol consumed each month (kg*years)*		Age, gender, smoking	
				0	1.00		
				<100	2.73 (1.04–7.20)		
				100–300	6.61 (2.34–18.67)		
				>300	23.40 (5.62–97.49)		

Table 2.16 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment factors	Comments
Wang *et al.* (2005b), Inner Mongolia, 2004	50 hospital-based	100 (1:2); matched on sex, neighbourhood, race/ethnicity, age ±5 years, time of visit	Questionnaire interview	Univariate history of alcoholic beverage consumption	4.43 (2.64–8.90)	Multivariate with years of alcoholic beverage drinking, years of smoking, difficulty in swallowing, history of psychological event, worsening of financial state, stool with blood	
				Multivariate years of alcoholic beverage consumption	5.41 (3.89–6.79)		
Zhao *et al.* (2005), Jiangsu, 2002	95 hospital patients	95; matched on gender, age	Interviewer-administered questionnaire	*Alcoholic beverage consumption*		Hot food, eating garlic, eating nuts	
				No	1.00		
				Yes	3.94 (1.81–8.59)		

CI, confidence interval

2.4.2 *Case–control studies (Table 2.17)*

Among the 38 case–control studies, 20 studies were published in the English literature and 18 in the Chinese literature. Of the 20 studies published in the English literature, 18 adjusted for tobacco smoking, 8 were population-based and 12 were hospital-based. Sixteen of the 20 studies in the English literature on alcoholic beverage consumption and the risk for oesophageal cancer reported a statistically significant association. The adjusted odds ratios ranged from 1.7 to 3.5 for ever drinkers and from 5.4 to 37.3 for heavy drinkers. Among the case–control studies identified in the Chinese literature (Table 2.16), the majority were hospital-based and 10 studies did not adjust for tobacco smoking (Chen *et al*., 2000; Lu *et al*., 2000b; Zhang *et al*., 2000; Ding *et al*., 2001a,b; Li *et al*., 2001; Mu *et al*., 2003; Wang B *et al*., 2003a; Wang *et al*., 2004; Yan *et al*., 2004; Zhao *et al*., 2005). Eight of these reported a positive association with alcoholic beverage consumption; the odds ratios ranged from 1.72 to 6.41 for ever drinkers of alcoholic beverages and from 3.1 to 23.4 for heavy drinkers. The evidence for alcoholic beverage consumption and the risk for oesophageal cancer in the Chinese literature are consistent with that in the English literature. In addition, the results from case–control studies are also consistent with those from prospective cohort studies.

2.4.3 *Histological types (Tables 2.17 and 2.18)*

Consumption of alcoholic beverages is an established cause of oesophageal cancer and is strongly associated with the risk for squamous-cell carcinoma of the oesophagus and, to a lesser degree, with the risk for oesophageal adenocarcinoma (Brown *et al*., 1994; Gammon *et al*., 1997; Lagergren *et al*., 2000; Wu *et al*., 2001; Lindblad *et al*., 2005; Hashibe *et al*., 2007a).

One prospective study of alcoholics (Boffetta *et al*., 2001), one nested case–control study (Lindblad *et al*., 2005) and eight case–control studies of adenocarcinoma of the oesophagus (Table 2.18) in relation to alcoholic beverage consumption have been published. A cohort study of alcoholics in Sweden (Boffetta *et al*., 2001) reported an SIR of 1.45 (95% CI, 0.96–2.11) for oesophageal adenocarcinoma and 6.76 (95% CI, 6.15–7.41) for oesophageal squamous-cell carcinoma. The nested case–control study on adenocarcinoma of the oesophagus observed a null association (Lindblad *et al*., 2005). Among the eight case–control studies, two reported a significant association between alcoholic beverage consumption and oesophageal adenocarcinoma. The increased risk for adenocarcinoma of oesophagus was associated with a higher level of alcoholic beverage consumption in two studies (Kabat *et al*., 1993; Vaughan *et al*., 1995), but not in the other six. Thus, the evidence for alcoholic beverage consumption and the risk for adenocarcinoma of the oesophagus was considered to be insufficient.

Table 2.17 Case–control studies of oesophageal cancer and alcoholic beverage consumption

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No.of cases	Odds ratio (95% CI)	Adjustment factors	Comments
DeStefani *et al*. (1990), Uruguay, 1985–88	261 squamous-cell carcinomas (199 men, 62 women); clinical and/ or radiological diagnosis; in four main hospitals in Montevideo; response rate, 92%	522 hospital patients (398 men, 124 women), without diagnosis of tobacco- and/ or alcohol-related diseases; 1:2 matched by sex, age, hospital	Interviewer-administered standardized questionnaire	*Alcohol (mL per day)*			Sex, age, residence, smoking	Joint effect of alcoholic beverage and tobacco consumption; odds ratio for those who smoked and drank heavily compared with that of light smokers and drinkers, 22.6
					Men			
				0	26	1.00		
				1–24	16	0.85 (0.4–1.8)		
				25–49	12	0.71 (0.3–1.6)		
				50–149	50	1.37 (0.8–2.4)		
				150–249	46	3.57 (1.9–6.7)		
				≥250	49	5.27 (2.7–10.2)		
					Women			
				0	38	1.00		
				1–24	12	1.04 (0.4–2.4)		
				25–49	–			
				50–149	–			
				150–249	12	1.89 (0.7–4.9)		
				≥250	–			

Table 2.17 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No.of cases	Odds ratio (95% CI)	Adjustment factors	Comments
Franceschi *et al*. (1990), northern Italy, 1986–89	288 men, aged <75 years; histologically confirmed; interviews generally (90%) conducted within 2 months from diagnosis; no next-of-kin respondents; refusal rate, 2%	1272 hospital-based men; 26% non-traumatic orthopaedic conditions, 25% trauma, 17% eye disorders, 13% other illness; matched by area of residence, hospital, age; no next-of-kin respondents; refusal rate, 3%;	Interviewer-administered standardized questionnaire	≤19 drinks/week 20–34 drinks/week 35–59 drinks/week ≥60 drinks/week *Years of alcohol use* <30 30–39 ≥40	45 41 115 87 60 93 116	1.0 1.0 (0.6–1.7) 3.1 (2.0–4.7) 6.0 (3.7–10.0) p<0.01 1.0 1.1 (0.7–1.7) 0.9 (0.6–1.5) p=0.24	Age, residence, education, occupation, smoking	High level of combined alcoholic beverage and cigarette consumption increased the risk to 18 times that of the lowest levels of consumption; the effect of drinking 60 or more alcoholic drinks per week in nonsmokers was slightly stronger than that of heavy smoking in light drinkers (odds ratio, 7.9 versus 6.4).

Table 2.17 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No.of cases	Odds ratio (95% CI)	Adjustment factors	Comments
Castelletto *et al*. (1992), Argentina, 1985–86	170 (99 men, 71 women), >15 years old; patients from 1 hospital and 9 private clinics; patients had various gastrointestinal symptoms	226 (109 men, 117 women) with histologically normal oesophagus	Of 406 study subjects, 396 completed information on the variable under study using a simple questionnaire	**Men** *Drinking status* Non-drinkers Drinkers *Amount* 0–39 mL/day 40–79 mL/day ≥80 mL/day	 41 58 41 15 43	 1.0 2.4 (1.3–4.3) 1.0 1.9 (0.8–4.7) 2.5 (1.2–5.1)	Age, smoking	All subjects had various gastrointestinal symptoms; patients with oesophageal cancer or with severe erosions, ulcerations and stenosis associated with gastric reflux were not included.

Table 2.17 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No.of cases	Odds ratio (95% CI)	Adjustment factors	Comments
Cheng *et al*. (1992), Hong Kong, China, 1989–90	400 (345 men , 55 women); histologically confirmed; 85% squamous-cell carcinomas; participation rate, 86.8%	1598 (800 hospital and 798 general practice; 1378 men, 220 women); 1:4 matched by age, sex; 2 controls admitted to the same surgical departments; patients with tobacco- or alcohol-related cancers were excluded; 2 controls selected from private or general practice clinics in the area where case was originally referred to the physician; response rate, 95%	Interviewer-administered standardized questionnaire	Never drinker <50 g/week 50–99 g/week 100–199 g/week 200–299 g/week 400–599 g/week 600–799 g/week 800–999 g/week ≥1000 g/week	53 57 16 30 48 44 39 25 66	1.00 1.07 (0.66–1.75) 1.36 (0.67–2.74) 1.82 (0.99–3.35) 3.40 (1.92–6.01) 5.05 (2.72–9.39) 11.11 (5.4.–22.85) 18.07 (7.40–44.13) 9.93 (5.27–18.74)	Age, education, birthplace, smoking	Cases or controls with diabetes mellitus were excluded.

Table 2.17 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No.of cases	Odds ratio (95% CI)	Adjustment factors	Comments
Negri *et al*. (1992), northen Italy, 1984–90	300 (244 men, 56 women), aged 29–74 years; histologically confirmed newly diagnosed cancer of the oesophagus, admitted to the National Cancer Institute	1203 (901 men, 302 women) hospital patients, aged 25–74 years; 34% traumas, 26% non-traumatic orthopaedic conditions, 28% acute surgical disease, 12% various other diseases; diseases related to alcohol or tobacco consumption excluded	Interviewer-administered standardized questionnaire	<4 drinks/day 4–6 drinks/day >6 drinks/day	111 58 131	1.0 1.6 (1.1–2.4) 3.5 (2.5–5.1) $p<0.001$	Age, sex, education, smoking, β-carotene intake	Compared with the lowest risk category (nonsmokers, moderate alcohol drinkers and high β-carotene consumers), relative risk rose to 45.9 for men and to 36.4 for women who were heavy drinkers, heavy smokers and had a diet poor in β-carotene.

Table 2.17 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No.of cases	Odds ratio (95% CI)	Adjustment factors	Comments
Kabat *et al*. (1993), USA, 1981–90	Adenocarcinoma of oesophagus/ cardia (160 men, 21 women), squamous-cell carcinoma of oesophagus (122 men, 78 women) and adenocarcinoma of distal stomach (113 men, 30 women); newly diagnosed, histologically confirmed	Hospitalized patients with disease not related to smoking and of organ systems other than the gastrointestinal tract (4162 men, 2222 women); matched by age, sex, race, hospital	Interviewer-administered structured questionnaire; all subjects interviewed in 28 hospitals in 8 cities in the USA between 1981 and 1990	*Squamous-cell carcinoma* **Men** Non-drinker Occasional 1–3.9 oz WE/ day ≥4 WE/day **Women** Non-drinker Occasional 1–3.9 oz WE/ day ≥4 WE/day		 1.0 1.4 (0.6–3.5) 2.3 (1.0–5.4) 10.9 (4.9–24.4) 1.0 1.4 (0.7–2.9) 4.4 (2.2–8.7) 13.2 (6.1–28.8)	Age, education, smoking, hospital, time period (1981–84, 1985–90)	Non-drinker, <1 drink/week; occasional, ≥1 drink/week but <1 drink/day; WE = whiskey–equivalent per day; the analysis was limited to whites; joint effect of smoking and drinking (analysis limited to men), 7.6 (3.1–18.6) for squamous-cell carcinoma of oesophagus and 2.4 (1.3–4.2) for adenocarcinoma of oesophagus/ cardia

Table 2.17 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No.of cases	Odds ratio (95% CI)	Adjustment factors	Comments
Brown *et al*. (1994), USA, 1986–89	174 white men with adenocarcinoma of oesophagus (median age, 63 years); residents of geographical areas covered by the population-based cancer registries; response rate, 74%	750 (median age, 61 years) living in three areas of the USA selected by random-digit dialling for those aged 30–64 years (response rate, 72%) and random sampling from computerized listings of Medicare recipients (response rate, 76%)	Structured questionnaire administered by trained interviewers	*Adenocarcinoma of oesophagus and oesophagogastric junction*			Age, area, smoking, income	
				Never drank	32	1.0		
				Drank	142	0.9 (0.6–1.4)		
				<8 drinks/week	38	0.7 (0.4–1.3)		
				8–21 drinks/week	42	0.8 (0.4–1.3)		
				22–56 drinks/week	43	1.1 (0.6–1.9)		
				>56 drinks/week	18	1.5 (0.7–3.1)		

Table 2.17 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No.of cases	Odds ratio (95% CI)	Adjustment factors	Comments
Cheng *et al.* (1995), Hong Kong, China 1989–90	400 consecutive patients during a 21-month period in 1989–90; histologically confirmed; response rate, 87%	1598 patients from the same surgical departments as the cases and from general practices from which the cases were originally referred; matched by age, sex; response rate, 95%	Interviewer-administered structured questionnaire	Never drinkers	53	1.0	Age, sex, education, smoking	
				1–199 g/week	103	1.1 (0.7–1.8)		
				200–599 g/week	92	3.3 (2.0–5.4)		
				≥600 g/week	130	9.2 (5.4–15.7)		
				Duration				
				Never drinkers	53	1.0		
				1–19 years	24	2.0 (1.0–3.8)		
				20–39 years	175	2.1 (1.4–3.2)		
				≥40 years	131	2.4 (1.6–3.8)		
				Years since stopped drinking				
				Current drinkers	207	1.0		
				0–1 year	47	2.5 (1.4–4.4)		
				1–4 years	36	1.5 (0.9–2.6)		
				5–9 years	22	0.5 (0.3–0.9)		
				10–14 years	22	0.8 (0.4–1.5)		
				≥15 years	11	0.2 (0.1–0.6)		
				Never drinkers	33	0.6 (0.4–1.0)		

Table 2.17 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No.of cases	Odds ratio (95% CI)	Adjustment factors	Comments
Vaughan *et al*. (1995), western Washington, USA, 1983–90	298 adenocarcinomas (267 men, 31 women), 106 squamous-cell carcinomas (64 men, 42 women), aged 20–74 years; histologically confirmed; identified through the Cancer Surveillance System; proportion of the closest next of kin interviewed, 33%; response rate, 82.9%	724 (506 men, 218 women) population-based identified by random-digit dialling; frequency-matched on age, gender; response rate, 76.6%	Interviewer-administered standardized questionnaire	*Drinks/week* 0–6 7–13 14–20 ≥21 0–6 7–13 14–20 ≥21	 27 20 11 20 147 39 18 44	*Squamous-cell carcinoma* 1.0 6.0 (2.7–13.5) 6.3 (2.2–17.9) 9.5 (4.0–22.3) *Adenocarcinoma* 1.0 1.1 (0.7–1.8) 1.2 (0.6–2.3) 1.8 (1.1–3.1)	Cigarette use, body mass index, age, gender, race, education	Significant association between usual intake of undiluted hard liquor and adenocarcinoma (2.6; 1.4–4.6) and a weaker (not significant) association with squamous-cell carcinoma (1.7; 0.6–4.7)

Table 2.17 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No.of cases	Odds ratio (95% CI)	Adjustment factors	Comments
Gammon *et al*. (1997), USA, 1993–95	Oesophageal adenocarcinoma (245 men, 48 women), gastric cardia adenocarcinoma (223 men, 38 women), oesophageal squamous-cell carcinoma (176 men, 45 women), other gastric adenocarcinoma (254 men, 114 women); histologically confirmed; newly diagnosed; all cases identified by use of established rapid reporting systems	695 population-based (555 men, 140 women), aged 30–64 years; frequency-matched by age (±5years), sex; identified by use of Waksberg's random-digit dialling method; overall response rate, 70.2%	Structured questionnaire administered by trained interviewers	*Oesophageal squamous-cell carcinoma*			Age, sex, geographical centre, race, body mass index, income, cigarette smoking, all other types of alcohol use	Interviews were administered directly to subjects rather than to closest next of kin (usually the spouse) for 70.4% of target cases, 67.8% of comparison cases and 96.6% of controls.
				Never	19	1.0		
				Ever	195	3.5 (1.9–6.2)		
				<5 drinks/week	16	0.8 (0.4–1.6)		
				5–11 drinks/ week	25	1.8 (0.9–3.5)		
				12–30 drinks/ week	48	2.9 (1.5–5.4)		
				>30 drinks/week	106	7.4 (4.0–13.7)		

Table 2.17 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No.of cases	Odds ratio (95% CI)	Adjustment factors	Comments
Lagergren *et al*. (2000), Sweden, 1995–97	618 (81% of all eligible) patients (189 oesophageal adenocarcinoma, 262 cardia adenocarcinoma, 167 oesophageal squamous-cell carcinoma) (median ages at diagnosis, 69, 66 and 67 years, respectively); men constituted 87%, 85% and 72%, respectively	820 randomly selected population (median age, 68 years); frequency-matched on age, sex; men constituted 83%; participation rate, 73%	Structured questionnaire administered by trained interviewers	*Oesophageal squamous–cell carcinoma*			Age, sex, tobacco smoking, educational level, body mass index, reflux symptoms, intake of fruit and vegetables, energy intake, physical activity	
				Never	16	1.0		
				Ever	151	1.1 (0.6–2.1)		
				Ethanol (g) per week				
				1–15	34	0.9 (0.4–1.8)		
				16–70	39	0.8 (0.4–1.8)		
				>70	78	3.1 (1.4–6.7)		
				None		1	Age, sex, smoking	Increase in the risk of 1.95-fold (p<0.01) with habit of daily bidi smoking
				Occasional		1.36 (0.68–2.70)		
				Daily		7.81 (2.38–25.6)		

Table 2.17 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No.of cases	Odds ratio (95% CI)	Adjustment factors	Comments
Gallus *et al.* (2001), Italy, Switzerland	114 women aged <79 years (median age, 63 years); newly diagnosed; histologically confirmed squamous-cell oesophageal cancer; admitted to the major hospitals in the areas under study	425 women (median age, 62 years) admitted for acute, non-neoplastic conditions to the same hospitals: 40% trauma, 21% non-traumatic orthopaedic conditions, 24% acute surgical disorders, 15% miscellaneous other illnesses (including skin, eye or ear disorders); frequency-matched to cases by age, study centre; control: case ratio, 4	Interviewer-administered standardized questionnaire	<1 drink/day 1–2 drinks/day ≥3 drinks/day		1.0 1.99 (1.15–3.44) 5.40 (2.70–10.80)	Age, education, body mass index, smoking	Data from three case–control studies of squamous-cell oesophageal cancer: first conducted in 1984–93 in the provinces of Milan and Pordenone (Fioretti *et al*, 1999); second in 1992–97 in the provinces of Padua and Pordenone, and the greater Milan area, northern Italy (Franceschi *et al.*, 2000); third in 1992–99 in the Swiss Canton of Vaud (Levi *et al*., 2000).

Table 2.17 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No.of cases	Odds ratio (95% CI)	Adjustment factors	Comments
Wu *et al*. (2001), Los Angeles, USA, 1992–97	222 incident oesophageal adenocarcinoma (202 men, 20 women), 277 gastric cardia and 443 distal gastric adenocarcinoma, aged 30–74 years; histologically confirmed; identified by Cancer Surveillance Program	1356 multiethnic population-based (999 men, 357 women); matched by sex, race, date of birth; diagnosis of oesophageal or stomach cancer excluded; neighbourhood control sought by use of a systematic algorithm based on the address of the case patient	Interviewer-administered structured questionnaire; interviews completed by 55% of those identified and 77% of those approached	*Adenocarcinoma of oesophagus* 1–7 drinks/week 8–21 drinks/week 22–35 drinks/week ≥36 drinks/week *Alcoholic beverage* Never Former Current		 0.72 (0.5–1.2) 0.57 (0.3–0.9) 0.77 (0.4–1.4) 0.93 (0.5–1.6) *p*-trend=0.79 1.0 0.74 (0.5–1.2) 0.70 (0.5–1.1)	Age, sex, race, birthplace, education, smoking	
Znaor *et al*. (2003), Chennai and Trivandrum, South India, 1993–99	566 men; histologically confirmed	3638 men (1711 non-tobacco-related cancer controls, 1927 healthy hospital visitors); histologically confirmed	Interviewer-administered structured questionnaire	Never Ever <20 mL/day 20–50 mL/day >50 mL/day *Duration (years)* <20 20–29 30–39 ≥40	304 262 70 80 110 69 82 91 20	1.0 1.70 (1.36–2.13) 1.13 (0.83–1.55) 1.83 (1.31–2.55) 2.53 (1.85–3.46) 1.21 (0.88–1.67) 1.69 (1.23–2.34) 2.80 (1.95–4.01) 1.88 (0.98–3.59)	Age, centre, education, smoking, chewing habit	Joint effect between smoking and alcoholic beverage drinking: odds ratio, 7.33 (5.06–10.62); joint effect of smoking, chewing with tobacco and alcoholic beverage drinking: odds ratio, 8.65 (5.50–13.62) (ICD-9 150)

Table 2.17 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No.of cases	Odds ratio (95% CI)	Adjustment factors	Comments
Yang *et al*. (2005), Japan, 2001–04	165 (148 men, 17 women; 159 squamous-cell carcinoma, 6 adenocarcinoma), aged 18–80 years; histologically diagnosed	495 hospital-based (444 men, 51 women) randomly selected; matched 1:3 for age, sex	Interviewer-administered structured questionnaire; 7-mL of blood; 95% of eligible subjects completed the questionnaire and about 60% provided blood samples	Non-drinker Moderate drinker Heavy drinker Never Former Current	8 63 94 8 12 145	1.00 5.16 (2.33–11.4) 27.8 (12.2–63.5) 1.0 6.20 (2.34–16.4) 9.44 (4.36–20.4)	Age, sex	Significant gene–environment interaction between alcoholic beverage drinking and *ALDH2* polymorphism
Lagergren *et al*. (2006), Sweden, 1995–97	189 oesophageal adenocarcinoma (88% of all eligible), 262 adenocarcinoma (84%); all histologically classified	Controls randomly selected from the total population register; frequency-matched by age, sex; 820 (73%) interviewed in person	A computer-aided face-to-face interview	*Carbonated low-alcohol beer (times/week)* See Table 2.18		See Table 2.18	Age, sex, smoking status, socioeconomic status, dietary intake of fruits and vegetables (in quartiles), body mass index	No association between consumption of carbonated soft drinks and risk for oesophageal adenocarcinoma

Table 2.17 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No.of cases	Odds ratio (95% CI)	Adjustment factors	Comments
Wu *et al*. (2006a), Taiwan, China [dates not reported]	165 men (oesophageal squamous-cell carcinoma), aged 35–92 years; pathologically proven	255 hospitalized men, aged 40–92 years; none had malignant tumours or any condition known to be associated with betel chewing, cigarette smoking or alcoholic beverage consumption; refusal rate, 11.8%	Interviewer-administered structured questionnaire	*Daily quantity*			Cigarette smoking, betel chewing, age, years of education	Dose–response effects found in daily quantity of drinking and smoking; synergistic effect between alcoholic beverage intake and cigarette use (odds ratio, 108.0; 35.1–478.0)
				Non-drinker	17	1.0		
				750 mL/day	113	15.8 (8.3–31.7)		
				>750 mL/day	30	65.1 (20.0–264.8)		
						p-trend<0.001		
				Drinking status				
				Non-drinker	17	1.0		
				Former drinker	13	5.4 (1.9–15.4)		
				Current drinker	135	23.3 (12.0–47.7)		
				Starting age				
				Non-drinker	17	1.0		
				≥25 years old	103	15.7 (8.1–32.0)		
				<25 years old	43	30.8 (12.5–82.1)		
				Duration (years)				
				Non-drinker	17	1.0		
				30	75	14.9 (7.2–32.4)		
				>30	68	23.0 (10.6–52.9)		
						p-trend=0.001		
				Cumulative exposure (mL /year)				
				Non-drinker	17	1.0		
				<7500	22	6.8 (3.0–15.9)		
				7500–15 000	24	13.7 (5.3–37.8)		
				>15 000	45	37.3 (14.8–105.1)		
						p-trend<0.001		

Table 2.17 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No.of cases	Odds ratio (95% CI)	Adjustment factors	Comments
Wu *et al*. (2006b), Jiangsu, China, 2003–04	531 (381 men, 150 women); 45% and 72% of all newly registered cases recruited and interviewed in Dafeng (high risk area) and Ganyu (low risk area), respectively	531 population-based (381 men, 150 women); randomly selected by a computer from the demographic database of the general population; response rate, 70%	Interviewer-administered structured questionnaire; a 5-mL blood sample	*Dafeng (high-risk area)* 1–249 mL/week 250–499 mL/week 500–749 mL/week ≥750 mL/week *p*-trend=0.74 *Alcohol drinking* Never Ever *p*-trend=0.964 *Age of first drink (years)* <20 20–34 ≥35 *p*-trend=0.815 *Duration of drinking (years)* 1–24 25–34 35–44 ≥45 *p*-trend=0.834	 175 116 	 0.87 (0.49–1.54) 1.06 (0.60–1.89) 0.97 (0.52–1.79) 1.10 (0.63–1.93) 1.0 1.01 (0.70–1.46) 0.83 (0.44–1.58) 1.23 (0.79–1.91) 0.81 (0.48–1.35) 0.96 (0.56–1.59) 0.89 (0.48–1.64) 1.57 (0.92–2.70) 0.77 (0.43–1.40)	Age, gender, education, economic status, tobacco smoking	In Ganyu (low-risk area), odds ratio for oesophageal cancer versus non-drinker category was 1.71 (1.02–2.88).

Table 2.17 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No.of cases	Odds ratio (95% CI)	Adjustment factors	Comments
Yokoyama *et al*. (2006), Japan, 2000–04	52 women with primary oesophageal squamous-cell carcinoma at the National Cancer Center Hospital, aged 40–79 years; histological diagnosis; none of the patients refused to participate.	412 cancer-free women, aged 40–79 years; most of the controls were ordinary residents or workers living in Tokyo or neighbouring areas; 82% of the eligible subjects who were contacted were enrolled in the study.	Self-administered structured questionnaire	Never/rare Light Moderate Heavy Former drinker *Strong alcoholic beverages* Never Sometimes Frequently	24 11 6 7 4 46 4 2	1.0 1.81 (0.81–4.05) 3.97 (1.40–11.26) 15.35 (4.85–48.62) 4.58 (1.25–16.79) *p*-trend<0.0001 1.0 2.58 (0.80–8.33) 12.47 (0.97–160.06) *p*-trend=0.012	Age	Never/rare, <1 unit/week; light, 1–8.9 units/week; moderate, 9–17.9 units/week; heavy, ≥18 units/week; 1 unit=22 g ethanol

Table 2.17 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No.of cases	Odds ratio (95% CI)	Adjustment factors	Comments
Hashibe *et al*. (2007c), central and eastern Europe, 2000–02	192 squamous-cell carcinoma (170 men, 22 women), 35 adenocarcinoma (31 men, 4 women) of the oesophagus diagnosed at 5 centres in the Czech Republic, Poland,Romania, Russia, confirmed histologically or cytologically; recruited into the study within 3 months of diagnosis; response rate, 96%	1114 (846 men, 268 women); frequency-matched from same hospital as the cases with a recent diagnosis of disease unrelated to tobacco and alcohol; in Moscow, frequency-matched to cases by age, sex, centre, referral or residence area; in other centres, overlapped with those in study of lung cancer; interviewed more than 6 months before the beginning of recruitment of cases; response rate, 97%	Face-to-face interviews using a structured questionnaire	*Squamous-cell carcinoma* No drinking Ever drinking *Intake of ethanol (g/week)* No drinking 1–139 140–279 280–419 ≥420 *Years of drinking* No drinking 1–19 20–39 ≥40 *Cumulative consumption (grams)* No drinking 1–1399 1400–2799 2800–4199 4200–5599 ≥ 5600	 5 181 5 69 34 20 55 5 12 131 35 5 23 33 16 16 93	 1.00 2.86 (1.06–7.74) 1.00 3.08 (1.11–8.60) 4.51 (1.46–13.94) 8.14 (2.45–27.04) 9.78 (3.08–31.04) *p*-trend<0.01 1.00 2.25 (0.63–8.04) 4.80 (1.68–13.72) 2.39 (0.83–6.90) *p*-trend=0.08 1.00 1.70 (0.59–4.87) 4.91 (1.62–14.84) 3.29 (1.01–10.72) 6.62 (1.99–22.08) 7.21 (2.37–21.98) *p*-trend<0.01	Centre, age, sex, education, body mass index, fruit intake, vegetable intake, pack–years of tobacco	A synergistic interaction between tobacco and alcohol was observed for the risk for oesophageal squamous-cell carcinoma. (ICD-0-2 C 15)

ALDH, acetaldehyde dehydrogenase; CI, confidence interval; WE, whiskey equivalent

2.4.4 *Type of alcoholic beverage (Table 2.19a and Table 2.19b)*

The types of alcoholic beverage consumed were examined in several studies. Consumption of beer or hard liquor led to a higher relative risk than consumption of wine (Kato *et al*., 1992c; Brown *et al*., 1994; Gammon *et al*., 1997; Grønbaek *et al*., 1998; Kjaerheim *et al*., 1998; Lagergren *et al*., 2000), whereas two studies (Barra *et al*., 1990; Sakata *et al*., 2005) also found an excess risk for wine drinkers. Most of the studies that investigated types of alcoholic beverage showed no substantial difference in risk.

2.4.5 *Evidence of a dose–response*

The risk for oesophageal cancer was shown to increase with increasing number of drinks per day or the number of days per week on which alcoholic beverages were consumed in 10 cohort and 21 case–control studies. Some studies found a relationship between the duration of alcoholic beverage consumption in years and the risk for oesophageal cancer (Cheng *et al*., 1995; Zhang *et al*., 1998; Liu *et al*., 2000; Znaor *et al*., 2003; Sakata *et al*., 2005; Wu *et al*., 2006a; Hashibe *et al*., 2007a). Using non-drinkers as the baseline, the influence of the cumulative amount of alcoholic beverage consumed was apparent (Lagergren *et al*., 2000; Sakata *et al*., 2005; Wu *et al*., 2006a; Hashibe *et al*., 2007a). A dose–response relationship was found between the frequency of alcoholic beverage intake and the risk for oesophageal cancer (Grønbaek *et al*., 1998; Kinjo *et al*., 1998; Wu *et al*., 2006a; Hashibe *et al*., 2007a). In two studies (Yang *et al*., 2005; Wu *et al*., 2006a), the relative risks were lower in former drinkers than in current drinkers but remained significantly elevated.

2.4.6 *Effect of cessation of alcoholic beverage consumption (Table 2.20)*

Studies on the cessation of alcoholic beverage consumption may be confounded by the fact that the precursors and early malignancies of the oesophagus may lead to such cessation. Nevertheless, this type of confounding may result in an underestimation of the effect. For recent quitters, the risk for oesophageal cancer increased above that of current drinkers; as the number of years of having quit increased, however, the risk gradually decreased to below that of current drinkers or even to close to the levels of non-drinkers in some studies.

Cheng *et al*. (1995) observed that risk could decrease to nearly the levels of non-drinkers after more than 10 years of quitting. Castellsagué *et al*. (2000) showed that risk can be reduced to 50% of that of current drinkers after more than 10 years of cessation. Bosetti *et al*. (2000) observed an odds ratio of 0.37 (95% CI, 0.14–0.99) after 10 or more years of cessation. All three case–control studies suggested a reduction in risk after cessation of alcoholic beverate consumption for more than 10 years.

Table 2.18 Selected cohort and case–control studies of oesophageal cancer by histological type and alcoholic beverage intake

Reference	Exposure categories	Histological type and risks			
Cohort studies					
Boffetta *et al*. (2001)		Adenocarcinoma		Squamous-cell carcinoma	
		Cases	*SIR (95% CI)*	*Cases*	*SIR (95% CI)*
		27	1.45 (0.96–2.11)	449	6.76 (6.15–7.41)
Lindblad *et al*. (2005) (nested case–control)		Adenocarcinoma		Squamous-cell carcinoma	
	Units/day	*Cases*	*Relative Risk (95% CI)*	*Cases*	*Relative Risk (95% CI)*
	0–2	95	1.00	49	1.00
	3–15	59	1.06 (0.76–1.49)	20	1.01 (0.59–1.72)
	16–34	15	0.69 (0.39–1.20)	13	2.44 (1.26–4.71)
	>34	9	1.25 (0.61–2.55)	5	3.39 (1.28–8.99)
	Unknown use	109	1.21 (0.81–1.79)	53	0.79 (0.42–1.49)
Case–control studies					
Kabat *et al*. (1993)		Distal oesophagus/cardia		Squamous-cell carcinoma	
	Men	*Cases*	*Odds ratio (95% CI)*	*Cases*	*Odds ratio (95% CI)*
	Non-drinker	16	1.0	7	1.0
	Occasional	55	2.0 (1.1–3.5)	15	1.4 (0.6–3.5)
	1–3.9 oz WE/day	61	2.1 (1.2–3.6)	27	2.3 (1.0–5.4)
	≥4 oz WE/day	41	2.3 (1.3–4.3)	86	10.9 (4.9–24.4)
	Women				
	Non-drinker	10	1.0	16	1.0
	Occasional	5	0.6 (0.2–1.9)	17	1.4 (0.7–2.9)
	1–3.9 oz WE/day	3	0.9 (0.2–3.5)	25	4.4 (2.2–8.7)
	≥4 oz WE/day	3	3.8 (0.9–16.6)	20	13.2 (6.1–28.8)

Table 2.18 (continued)

Reference	Exposure categories	Histological type and risks			
Brown *et al.* (1994)		Adenocarcinoma of oesophagus and oesophagogastric junction			
		Cases	*Odds ratio (95% CI)*		
	Never drinker	32	1.0		
	Drinker	142	0.9 (0.6–1.4)		
	<8 drinks/week	38	0.7 (0.4–1.3)		
	8–21 drinks/week	42	08 (0.4–1.3)		
	22–56 drinks/week	43	1.1 (0.6–1.9)		
	>56 drinks/week	18	1.5 (0.7–3.1)		
Vaughan *et al.* (1995)		Adenocarcinoma		Squamous-cell carcinoma	
		Cases	*Odds ratio (95% CI)*	*Cases*	*Odds ratio (95% CI)*
	0–6 drinks/week	147	1.0	27	1.0
	7–13 drinks/week	39	1.1 (0.7–1.8)	20	6.0 (2.7–13.5)
	14–20 drinks/week	18	1.2 (0.6–2.3)	11	6.3 (2.2–17.9)
	≥21 drinks/week	44	1.8 (1.1–3.1)	30	9.5 (4.0–22.3)
Gammon *et al.* (1997)		Adenocarcinoma		Squamous-cell carcinoma	
		Cases	*Odds ratio (95% CI)*	*Cases*	*Odds ratio (95% CI)*
	Never	79	1.0	19	1.0
	Ever	210	0.7 (0.5–1.0)	195	3.5 (1.9–6.2)
	<5 drinks/week	56	0.7 (0.4–1.0)	16	0.8 (0.4–1.6)
	5–11 drinks/week	45	0.6 (0.4–0.9)	25	1.8 (0.9–3.5)
	12–30 drinks/week	57	0.7 (0.4–1.1)	48	2.9 (1.5–5.4)
	>30 drinks/week	52	0.9 (0.5–1.4)	106	7.4 (4.0–13.7)
Lagergren *et al.* (2000)		Adenocarcinoma		Squamous-cell carcinoma	
		Cases	*Odds ratio (95% CI)*	*Cases*	*Odds ratio (95% CI)*
	Never	41	1.0	16	1.0
	Ever	148	0.5 (0.3–0.9)	151	1.1 (0.6–2.1)
	1–15 g/week	54	0.6 (0.4–1.1)	34	0.9 (0.4–1.8)
	16–70 g/week	51	0.4 (0.2–0.7)	39	0.8 (0.4–1.8)
	>70 g/week	43	0.6 (0.3–1.1)	78	3.1 (1.4–6.7)

Table 2.18 (continued)

Reference	Exposure categories	Histological type and risks	
Wu *et al*. (2001)		Adenocarcinoma of oesophagus	
		Cases	*Odds ratio (95% CI)*
	1–7 drinks/week	Not	0.72 (0.5–1.2)
	8–21 drinks/week	reported	0.57 (0.3–0.9)
	22–35 drinks/week		0.77 (0.4–1.4)
	≥36 drinks/week		0.93 (0.5–1.6)
			p=0.79
	Alcohol use		
	Never		1.0
	Former		0.74 (0.5–1.2)
	Current		0.70 (0.5–1.1)
Lagergren *et al*. (2006)	*Carbonated low-alcohol beer (times/week)*	Adenocarcinoma of oesophagus	
		Cases	*Odds ratio (95% CI)*
	Unexposed (0)	40	1.00
	Low (≤1)	44	1.05 (0.60–1.83)
	Medium (>1–4)	46	1.16 (0.65–2.07)
	High (>4)	50	1.33 (0.74–2.40)
			p=0.78

Table 2.18 (continued)

Reference	Exposure categories	Histological type and risks			
Hashibe *et al*. (2007c)		Adenocarcinoma		Squamous-cell carcinoma	
		Cases	*Odds ratio (95% CI)*	*Cases*	*Odds ratio (95% CI)*
	No drinking	3	1.00	5	1.00
	Ever drinking	32	1.21 (0.31–4.77)	181	2.86 (1.06–7.74)
	1–139 g/week	13	1.06 (0.25–4.58)	69	3.08 (1.11–8.60)
	140–279 g/week	6	2.22 (0.40–12.39)	34	4.51 (1.46–13.94)
	280–419 g/week	4	5.39 (0.73–39.93)	20	8.14 (2.45–27.04)
	≥420 g/week	6	2.31 (0.30–17.58)	55	9.78 (3.08–31.04)
			p=0.20		p<0.01
	Years of drinking				
	No drinking	3	1.00	5	1.00
	1–19	1	0.38 (0.02–6.09)	12	2.25 (0.63–8.04)
	20–39	17	1.08 (0.24–4.94)	131	4.80 (1.68–13.72)
	≥40	11	1.44 (0.31–6.66)	35	2.39 (0.83–6.90)
			p=0.55		p=0.08
	Cumulative consumption (grams)				
	No drinking	3	1.00	5	1.00
	1–1399	7	1.08 (0.24–4.82)	23	1.70 (0.59–4.87)
	1400–2799	6	1.48 (0.29–7.41)	33	4.91 (1.62–14.84)
	2800–4199	4	1.16 (0.21–6.51)	16	3.29 (1.01–10.72)
	4200–5599	0	–	16	6.62 (1.99–22.08)
	≥5600	15	1.96 (0.39–9.88)	93	7.21 (2.37–21.98)
			p=0.54		p<0.01

CI, confidence interval; SIR, standardized incidence ratio; WE, whiskey equivalent

Table 2.19a. Selected cohort studies of oesophageal cancer and consumption of different types of alcoholic beverages

Reference, location, name of study	Exposure categories	Beer		Wine		Hard liquors	
		No. of exposed cases	Relative risk (95% CI)	No. of exposed cases	Relative risk (95% CI)	No. of exposed cases	Relative risk (95% CI)
Cohort studies							
Kato *et al.* (1992c), USA, Hawaii, American Men of Japanese Ancestry Study	*Alcohol intake* 0 mL/day <500 mL/day ≥500 mL/day	 24 16 30	 1.0 0.7 (0.4–1.4) 2.6 (1.5–4.6) *p* 0.01		Not reported		Not reported
Grønbaek *et al.* (1998), Denmark, The Copenhagen Centre for Prospective Population Studies	*Frequency of drinking* 0 drinks/week 1–6 drinks/week ≥7 drinks/week	 Not reported	 1.0 1.5 (0.9–2.5) 2.9 (1.8–4.8)	 Not reported	 1.0 0.8 (0.5–1.1) 0.4 (0.2 –0.8)	 Not reported	 1.0 0.7 (0.5–1.1) 1.5 (1.2–1.9)
Kjaerheim *et al.* (1998), Norway, Norwegian Cohort Study	*Frequency of drinking (times/week)* Never or <1 Previously 1–3 4–7	 37 11 8 14	*Upper aerogastric tract cancer* 1.0 1.0 (0.5–1.9) 1.4 (0.7–3.1) 4.4 (2.4–8.3) *p* 0.001	 Not reported	 Not reported	 42 15 5 5	 1.0 1.3 (0.7–2.3) 1.4 (0.6–7.0) 2.7 (1.1–7.0) *p*=0.06
Sakata *et al.* (2005), Japan, Japanese Collaborative Cohort Study		17	1.42 (0.58–3.52)	6	6.24 (1.53–25.37)	48 15 9	Sake 2.72 (1.22–6.08) Shochu 3.40 (1.33–8.68) Whisky 2.60 (0.91–7.41)

Table 2.19b Selected case–control studies of oesophageal cancer and consumption of different types of alcoholic beverages

Reference, location, name of study	Beer			Wine			Hard liquors		
	Exposure categories	No. of exposed cases	Odds ratio (95% CI)	Exposure categories	No. of exposed cases	Odds ratio (95% CI)	Exposure categories	No. of exposed cases	Odds ratio (95% CI)
Case–control studies									
Barra *et al*. (1990), northern Italy, 1986–90	≤55 drinks/ week	6	1.8 (0.7–4.5)		61	1.7 (1.1–2.7)		27	1.8 (1.0–3.1)
	56–83 drinks/ week	8	4.3 (1.6–11.3)		39	5.4 (3.1–9.3)		31	3.6 (2.0–6.4)
	≥84 drinks/ week	6	4.3 (1.5–12.4)		7	15.0 (4.6–49.1)			10.0 (4.1–24.5)
Brown *et al*. (1994), USA, 1986–89	Never	60	1.0			1.0		64	1.0
	Drank	114	6 (0.4–0.9)			0.9 (0.6-1.4)		110	1.6 (1.1–2.4)
	<8 drinks/ week	46	0.6 (0.4–1.0)	<3 drinks/ week		0.9 (0.5–1.5)	<8 drinks/ week	50	1.3 (1.0–3.2)
	8–15 drinks/ week	26	0.7 (04–1.2)	3–13 drinks/ week		0.8 (04–1.5)	8–15 drinks/ week	24	0.8 (04–1.3)
	15–28 drinks/ week	21	0.6 (0.3–1.1)	≥14 drinks/ week		1.6 (0.7–3.8)	15–28 drinks/ week	21	2.1 (1.1–4.0)
	≥29 drinks/ week	50	0.6 (0.3–1.3)				≥29 drinks/ week	13	2.8 (1.2–6.3)
Gammon *et al*. (1997), USA, 1993–95	Never	57	1.0		149	1.0		48	1.0
	Ever	164	2.2 (1.4–3.3)		72	0.6 (0.4–0.9)		173	3.1 (2.0–4.8)

Table 2.19b (continued)

Reference, location, name of study	Beer			Wine			Hard liquors		
	Exposure categories	No. of exposed cases	Odds ratio (95% CI)	Exposure categories	No. of exposed cases	Odds ratio (95% CI)	Exposure categories	No. of exposed cases	Odds ratio (95% CI)
Lagergren *et al*. (2000), Sweden, 1995–97			Strong beer						
	Never	103	1.0		68	1.0		26	1.0
	Ever	64	1.3 (0.9–2.0)		99	0.9 (0.6–1.4)		141	1.0 (0.6–1.8)
	Grams of ethanol/week								
	1–5	21	1.3 (0.7–2.3)	1–5	26	0.8 (0.5–1.5)	1–7	26	0.6 (0.3–1.2)
	6–25	21	1.0 (0.6–1.9)	6–25	29	0.9 (0.5–1.7)	8–30	39	1.1 (0.5–2.2)
	>25	22	1.2 (0.6–2.3)	>25	44	1.2 (0.7–2.1)	>30	76	2.3 (1.1–4.7)
Wu *et al*. (2001), Los Angeles, USA, 1992–97	None	Not reported	1.0		Not reported	1.0			1.0
	<7/week		0.44 (0.3–0.7)			0.86 (0.6–1.3)			0.93 (0.6–1.4)
	7–14/week		0.30 (0.2–0.5)			0.72 (0.4–1.3)			1.35 (0.8–2.3)
	≥15/week		0.57 (0.3–1.0)			1.27 (0.6–2.8)			1.34 (0.8–2.3)
Hashibe *et al*. (2007c), central and eastern Europe, 2000–02		12	0.87 (0.38–1.98)		4	0.50 (0.15–1.72)		19	Spirits 0.71 (0.39–1.29)

CI, confidence interval

Table 2.20 Case–control studies of oesophageal cancer and cessation of alcoholic beverage consumption

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No. of cases	Odds ratio (95% CI)	Adjustment factors	Comments
Cheng *et al*. (1995), Hong Kong, China, 1989–90	400 consecutive patients during a 21-month period in 1989–90; histologically confirmed; response rate, 87%	1598 patients from the same surgical departments as the cases and from general practices from which the cases were originally referred; matched by age, sex; response rate, 95%	Interviewer-administered structured questionnaire	Never drinkers	53	1.0	Age, sex, education, smoking	
				1–199 g/week	103	1.1 (0.7–1.8)		
				200–599 g/week	92	3.3 (2.0–5.4)		
				≥600 g/week	130	9.2 (5.4–15.7)		
				Duration				
				Never drinkers	53	1.0		
				1–19 years	24	2.0 (1.0–3.8)		
				20–39 years	175	2.1 (1.4–3.2)		
				≥ 40 years	131	2.4 (1.6–3.8)		
				Years since stopped drinking				
				Current drinkers	207	1.0		
				0–1	47	2.5 (1.4–4.4)		
				1–4	36	1.5 (0.9–2.6)		
				5–9	22	0.5 (0.3–0.9)		
				10–14	20	0.8 (0.4–1.5)		
				≥ 15	11	0.2 (0.1–0.6)		
				Never drinkers	53	0.6 (0.4–1.0)		

Table 2.20 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No. of cases	Odds ratio (95% CI)	Adjustment factors	Comments
Bosetti *et al*. (2000), multicentre, 1992–99	404 squamous-cell cancer (356 men, 48 women), median age, 60 years (range, 34–77 years); newly diagnosed; histologically confirmed	1070 (878 men, 192 women), median age, 60 years (range, 32–77 years); patients admitted to the same hospitals for nonsmoking- or alcohol consumption-related non-neoplastic conditions	Interviewer-administered structured questionnaire	*Time since drinking cessation (years)* Current 1–9 ≥ 10		 1 1.28 (0.67–2.43) 0.37 (0.14–0.99)	Age, sex, study centre, education, alcoholic beverage and tobacco consumption	Odds ratio represents the combined effect of time since smoking and drinking cessation on risk of oesophageal cancer.
Castellsagué *et al*. (2000), 1986–92	655 men with incident squamous-cell carcinoma	1408 men; individually matched to the cases on admitting hospital, age (±5 years)	Interviewer-administered structured questionnaire	*Years of drinking cessation* Current > 1–9 > 10 *p* for trend (two-sided)	 348 176 34	 1.0 0.9 0.5 0.02	Age group, hospital, years of schooling, average amount of pure ethanol consumed	Joint effect of years of smoking and drinking cessation on oesophageal cancer; reported odds ratios adjusted for years since quitting smoking.

CI, confidence interval

2.4.7 *Effect modification*

The combined effects of smoking and alcoholic beverage consumption on the development of cancer of the oesophagus have been examined in several studies (Tables 2.17 and 2.21), which varied in the methods and approaches used to assess effect modification, and ranged from being descriptive to giving a formal estimation of interaction terms in multivariate models. Eight case–control studies (Franceschi *et al*., 1990; Negri *et al*., 1992; Kabat *et al*., 1993; Lagergren *et al*., 2000; Gallus *et al*., 2001; Znaor *et al*., 2003; Wu *et al*., 2006a; Hashibe *et al*., 2007c) and two cohort studies (Kato *et al*., 1992c; Sakata *et al*., 2005) reported the joint effect of alcoholic beverage consumption and tobacco smoking on the risk for oesophageal cancer. Overall, the studies showed that the joint effects were multiplicative rather than additive, but, since multiple logistic regression models were used in the analyses in most of these studies, some also showed them to be additive rather than multiplicative.

Some studies investigated sex-specific effects (Table 2.22), and reported similar risks for both men and women (Negri *et al*., 1992; Kabat *et al*., 1993; Kinjo *et al*., 1998). Most studies found non-significantly increased relative risks among women with oesophageal cancer, but a significant risk among men who were classified as heavy drinkers, after controlling for tobacco smoking (DeStefani *et al*., 1990; Adami *et al*., 1992b; Kinjo *et al*., 1998). The studies from Japan and Italy found a significantly increased risk for oesophageal cancer among women (Gallus *et al*., 2001; Yokoyama *et al*., 2006).