2.3 Cancer of the larynx

The consumption of alcoholic beverages and tobacco smoking are the two major risk factors for laryngeal cancer (Austin & Reynolds, 1996; Doll *et al*., 1999). A relationship between the consumption of alcoholic beverages and cancer of the larynx was first suggested in the early 1900s by mortality statistics and clinical reports, and was subsequently supported by ecological studies that compared per-capita alcoholic beverage consumption and trends in the incidence of and mortality from laryngeal cancer (Wynder, 1952; Tuyns, 1982). However, the definition of alcoholic beverages as an independent etiological factor for laryngeal cancer and its quantification was not obtained until the late 1950s and early 1960s following ad-hoc epidemiological investigations (Schwartz *et al*., 1962; Wynder *et al*., 1976; Jensen, 1979).

Several case–control studies found an independent dose–risk relationship between alcoholic beverage consumption and the risk for laryngeal cancer, as well as a synergistic effect with tobacco smoking. Studies published up to 1988 were reviewed in a previous monograph (IARC, 1988). These included six prospective studies (Sundby, 1967;

Hakulinen *et al*., 1974; Monson & Lyon, 1975; Robinette *et al*., 1979; Jensen, 1980; Schmidt & Popham, 1981) and 14 case–control studies conducted in North America and Europe (Wynder *et al*., 1956; Schwartz *et al*., 1962; Vincent & Marchetta, 1963; Wynder *et al*., 1976; Spalajkovic, 1976; Williams & Horm, 1977; Burch *et al*., 1981; Herity *et al*., 1982; Elwood *et al*., 1984; Olsen *et al*., 1985; Zagraniski *et al*., 1986; Brugère *et al*., 1986; Tuyns *et al*., 1988). Four of the six prospective studies showed significant increases in risk. Furthermore, all of the case–control studies showed an association with alcoholic beverage consumption, and a trend in risk for the amount consumed, but no indication of a difference in risk for various types of alcoholic beverage. The previous IARC Working Group concluded that the occurrence of malignant cancer of the larynx was causally related to the consumption of alcoholic beverages (IARC, 1988).

However, several important aspects of the relationship between alcoholic beverage consumption and the risk for laryngeal cancer remained unsolved. These included the role of time-related variables, such as duration of the habit, age at starting, time since cessation of consumption for former drinkers and the effect of different types of alcoholic beverage. Further, the risk may differ by anatomical subsite, such as the supraglottis and the glottis/subglottis.

The epidemiological evidence for an association between alcoholic beverage consumption and the risk for laryngeal cancer includes at least four cohort and 18 case–control studies that have been published since 1988.

2.3.1 *Cohort studies (Table 2.10)*

Since 1988, six prospective studies have examined the relationship between alcohol beverage consumption and laryngeal cancer.

A study from Sweden (Adami *et al*., 1992b) of 9353 individuals discharged from care facilities with a diagnosis of alcoholism, including 11 cases of laryngeal cancer, showed an SIR of 3.3 for this cancer type. No information on individual consumption of alcoholic beverages was available, although the level of consumption of these subjects was presumably much higher and of longer duration than that of the general population. Moreover, no adjustment was available for tobacco consumption or for other potentially confounding factors such as socioeconomic status or diet, although an unfavourable risk pattern in alcoholics is probable. In the largest study of subjects who had a hospital discharge diagnosis of alcoholism in Sweden (Boffetta *et al*., 2001), the relative risk for laryngeal cancer was 4.21 (95% CI, 3.78–4.68; based on 347 cases).

The Honolulu Heart Program study (Chyou *et al*., 1995) was based on 7995 American men of Japanese ancestry who lived in Hawaii, and included 93 cases of cancers of the oral cavity and pharynx, oesophagus and larynx. A strong dose–risk relationship with alcoholic beverage consumption was found with a relative risk of 4.7 for ≥25 oz/month of total alcoholic beverage intake, compared with non-drinkers. In a prospective study of 10 960 Norwegian men followed from 1962 through to 1992 (Kjaerheim

Table 2.10 Selected prospective studies of laryngeal cancer and alcoholic beverage consumption

Reference, location	Study subjects	Exposure categories	No. of cases	Relative risk (95% CI)	Adjustment factors	Comments
Adami *et al*. (1992b), Uppsala, Sweden	9353 patients, 8340 men, 1013 women diagnosed with alcoholism from the Uppsala In-patient Register	Not reported	*Men* 10 *Women* 1 *Total* 11	 3.1 (1.5–5.7) 23.2 (0.3–129.1) 3.3 (1.7–6.0)	Age, sex	SIR reported
Chyou *et al*. (1995), Japan	7995 men of Japanese-American descent; interviewed and examined from 1965–1968; aged 45–68 years; identified through continuous surveillance of Oahu hospitals and linkage with the Hawaiian Tumor Registry	Non-drinkers <4 oz/month 4–24.9 oz/month ≥25 oz/month	16 5 18 52	1.00 0.57 (0.21–1.57) 1.74 (0.88–3.41) 4.67 (2.62–8.32) $p<0.0001$	Age, number of cigarettes/day, number of years smoked	
Kjaerheim *et al*. (1998), Oslo, Norway	10 960 Norwegian men born between 1893 and 1929; no prior diagnosis of upper aerogastric tract disease	*Total alcohol* Never or <1 time/week Previously 1–3 times/week 4–7 times/week Unknown	 26 4 18 19 4	 1.00 0.9 (0.3–2.7) 1.1 (0.6–1.9) 3.9 (2.1–7.1) 0.6 (0.2–1.8) $p=0.003$	Age, smoking level	

Table 2.10 (continued)

Reference, location	Study subjects	Exposure categories	No. of cases	Relative risk (95% CI)	Adjustment factors	Comments
Boffetta *et al*. (2001), Sweden	182 667 patients with a diagnosis of alcoholism aged 20 years or over and hospitalized during 1965–1994; identified in the In-patient Register and the National Cancer Register	Not reported	347	4.21 (3.78–4.68)	Not reported	SIR reported

CI, confidence interval; SIR, standardized incidence ratio

et al., 1998) that included 71 incident cases of upper digestive tract and respiratory neoplasms, the relative risk for the highest level of alcoholic beverage consumption (4–7 times/week) was 3.9 compared with never or occasional drinkers. These results were not confounded by marital status, occupational group or body-mass index. In the two latter prospective studies, no separate risk estimates were given for laryngeal cancer.

2.3.2 *Case–control studies (Table 2.11)*

Twenty case–control studies published since 1988 have included information on alcoholic beverage consumption and laryngeal cancer. All of these included overall allowance for tobacco use. Two additional case–control studies from China of 99 and 116 patients also found an excess risk in heavy alcoholic beverage drinkers, but did not allow for tobacco smoking.

The dose–risk relationship between alcoholic beverage consumption and major digestive and respiratory tract neoplasms was estimated from the data of a series of Italian case–control studies using regression spline models, and showed substantial increases in risk for laryngeal cancer with regular consumption of more than 50 g ethanol per day (Polesel *et al*., 2005).

A meta-analysis of 20 case–control studies (Bagnardi *et al*., 2001) included over 3500 cases of laryngeal cancer and reported a strong direct trend in risk, with multivariate relative risks of 1.38 (95% CI, 1.32–1.45) for 25 g alcohol per day, 1.94 (95% CI, 1.78–2.11) for 50 g per day and 3.95 (95% CI, 3.43–4.57) for 100 g per day, based on a dose–risk regression model. Corrao *et al*. (2004) found significantly increased risks for laryngeal cancer when comparing point-based and model-based relative risks to that of meta-pooled relative risks from studies that provided information on low doses (i.e., $\leq$ 25g of alcohol per day), thus confirming the evidence of an association for modest doses as well.

2.3.3 *Subsites of the larynx (Table 2.12)*

The larynx can be divided into the supraglottis (also called extrinsic larynx) and epilarynx, which border on the hypopharynx, and the glottis (also called intrinsic larynx) and subglottis, which lie wholly within the respiratory system (Spleissl *et al*., 1990). These various subsites of the larynx are exposed to potential carcinogens at different levels: the glottis and subglottis are more highly exposed to inhaled agents and the supraglottis to ingested agents, while the junctional area between the larynx and the pharynx is exposed to both inhaled and ingested agents. Thus, each site could react differently to different etiological factors.

At least seven case–control studies (Brugère *et al*., 1986; Guénel *et al*., 1988; Falk *et al*., 1989; Maier *et al*., 1992b; Muscat & Wynder, 1992; Talamini *et al*., 2002; Menvielle *et al*., 2004) and one meta-analysis (Bagnardi *et al*., 2001) suggested that the risk from alcoholic beverage consumption was stronger for cancer of the supraglottis than for

Table 2.11 Case–control studies of laryngeal cancer and alcoholic beverage consumption

Reference, study location, period	Characteristics of cases	Characteristics of controls	Organ site (ICD code)	Exposure categories	No. of cases	Relative risk (95% CI)	Adjustment factors	Comments
Burch *et al*. (1981), Canada, 1977–79	204 newly diagnosed cases of laryngeal cancer; 100% histologically confirmed	204 individually matched neighbourhood controls, matched on age (±5 years), sex		*Ounces of ethanol in lifetime* 0 <10 000 10 000–25 000 ≥26 000		 1.0 2.0 3.9 7.7	Smoking	Presented results were limited to men
Elwood *et al*. (1984), Canada 1977–1980	374 patients diagnosed primary epithelial cancers of the oral cavity, oro- and hypopharynx and larynx	374 patients diagnosed with another cancer within 3 months of the date of diagnosis of the study patient; diagnoses were not related to smoking, alcohol or occupational exposure; 1:1 matched for age (±2 years), sex; interview time of patient (within 3 years)	Larynx (ICD0 161)	See Table 2.12	See Table 2.12	See Table 2.12	Socioeconomic status, marital status, dental care, history of tuberculosis, smoking	Including age and sex in the multivariate model did not substantially change the estimates.
Olsen *et al*. (1985), Denmark 1980–82	326 newly diagnosed cases of laryngeal cancer	1134 matched for sex and closest date of birth	ICD161.1, 161.2, 161.0	See Table 2.12	See Table 2.12	See Table 2.12		

Table 2.11 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Organ site (ICD code)	Exposure categories	No. of cases	Relative risk (95% CI)	Adjustment factors	Comments
Brugère *et al.* (1986), France 1975–82	2540 male patients with cancer of larynx, pharynx and mouth, selected from male and female patients treated in the Neck and Head Department of the Institut Curie in Paris	National Institute of Statistics and Economic Studies data; more than 4000 men; stratified by age and cancer location for analysis		See Table 2.12	See Table 2.12	See Table 2.12	Smoking	Data collected by different methods between patients and controls
Guénel *et al.* (1988), France, 1975–85	197 glottis, 214 supraglottis; males >25 years old; cases with squamous-cell carcinoma	4135 controls from the population	ICD-8 161.5, 161.4	See Table 2.12	See Table 2.12	See Table 2.12	Age, tobacco	Relative risk for combined heavy tobacco and alcoholic beverage consumption, 289.4 (83.0–705.8) for glottis and 1094 (185.8–2970.7) for supraglottis
Tuyns *et al.* (1988), France, Italy, Spain, Switzerland	727 endolarynx, 188 epilarynx	3057 men from the population		0–20 g/day 21–40 g/day 41–80 g/day 81–120 g/day ≥121 g/day		1 (reference) 0.9 (0.7–1.3) 1.1 (0.8–1.5) 1.7 (1.2–2.4) 2.6 (1.8–3.6)	Age, residence, smoking	Relative risk for >120 g/day: 2.6 for endolarynx, 10.6 for epilarynx

Table 2.11 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Organ site (ICD code)	Exposure categories	No. of cases	Relative risk (95% CI)	Adjustment factors	Comments
Falk *et al*. (1989), Texas, USA, 1975–80	151 men from 56 hospitals in Texas and identified through hospital records	235 identified from Texas Department of Public Safety drivers license files or HCFA medicare recipients roster; frequency-matched by residence, age, ethnicity	ICD-9 161.X, 231.0	Non-drinkers	13	1 (reference)	Age, residence, employment, smoking, fruit and vegetable consumption	No consistent linear trend in risk, but relatively low consumption
				<2 drinks/week	8	0.8 (0.3–2.6)		
				2–3 drinks/week	6	0.5 (0.2–1.6)		
				4–6 drinks/week	17	2.1 (0.8–5.3)		
				7–10 drinks/week	19	2.3 (0.9–5.8)		
				11–15 drinks/week	17	1.5 (0.6–3.8)		
				16–21 drinks/week	22	1.8 (0.7–4.6)		
				22–29 drinks/week	14	1.3 (0.5–3.4)		
				≥30 drinks/week	35	2.1 (0.9–5.0)		
Franceschi *et al*. (1990), Italy, 1986–89	162 men with laryngeal cancer from hospitals in northern Italy	1272 men admitted with acute illnesses not related to alcohol or tobacco consumption	ICD-9 161	*Total number of drinks per week*			Age, smoking, residence, education, occupation	Combined effect with tobacco compatible with a multiplicative effect
				≤19	39	1 (reference)		
				20–34	27	0.8 (0.5–1.4)		
				35–59	51	1.3 (0.8–2.1)		
				≥60	45	2.1 (1.2–3.8)		
Sankaranarayanan *et al*. (1990), India, 1983–84	191 men with squamous cell cancer	549 hospital patients attending the Regional Cancer Centre	ICD-0 161	Never	98	1 (reference)		No data on dose
				≥20 years	13	2.7 (0.9–4.5)		
				>21 years	47	4.2 (1.5–4.3)		
						p-trend<0.001		

Table 2.11 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Organ site (ICD code)	Exposure categories	No. of cases	Relative risk (95% CI)	Adjustment factors	Comments
Ahrens *et al.* (1991), Germany, 1986–87	100 prevalent male cases of laryngeal cancer; cases recruited from Ear, Nose and Throat Clinic; 100% histologically confirmed	100 hospital controls with diseases not related to alcohol, smoking or occupational exposures; same age distribution as cases; admission diagnosis with an expected length of stay in hospital comparable with that of laryngeal cancer		Non-drinkers Occasional drinkers Daily drinkers	 28 	1 (reference) 3.2 (1.4–7.5) 1.1 (0.5–2.3)	Age, smoking, occupation	Number of cases among non-drinkers or daily drinkers not given
Choi & Kahyo (1991a), Seoul, Republic of Korea, 1986–89	94 male cases of laryngeal cancer; 100% histologically confirmed	282 hospital controls from Korea Cancer Center Hospital; non-cancer, non-alcohol or tobacco-related diseases	161	Non-drinkers Light Moderate Medium–heavy Heavy	17 5 28 29 15	1 (reference) 0.3 (0.1–0.7) 1.2 (0.6–2.5) 2.4 (1.2–4.9) 11.1 (3.8–32.4)	Age (matched), smoking	Data related to alcohol consumption among women were limited.

Table 2.11 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Organ site (ICD code)	Exposure categories	No. of cases	Relative risk (95% CI)	Adjustment factors	Comments
Zatonski *et al*. (1991), Warsaw, Poland, 1986–87	249 men with cancer of the larynx; 70% supraglottis, 30% glottis; response rate, 88%	965 men from the general population aged 25–65 years; response rate, 94%		Irregular 1–15 years 16–30 years >30 years	142 18 65 24	1 (reference) 3.4 (1.6–7.0) 9.5 (5.2–17.2) 10.4 (4.0–27.2)	Age, residence, education, smoking	Vodka main type of alcoholic beverage; higher risk for regular than for irregular drinkers
Freudenheim *et al*. (1992), New York, USA, 1975–85	250 pathologically confirmed cases of laryngeal cancer; white men	250 age- and neighbourhood-matched controls		0–339 drinks/year 340–1243 drinks/year 1244–2925 drinks/year ≥2926 drinks/year	32 33 48 137	1 (reference) 1.5 (0.7–3.2) 1.1 (0.6–2.1) 3.5 (1.8–6.9) *p*-trend<0.001	Education, smoking	Race and gender differences
Maier *et al*. (1992b), Germany, 1988–89	164 men with histologically proven squamous-cell carcinoma	656 matched male controls with no known tumorous disease selected from outpatient clinics		<25 g/day 25–75 g/day ≥75 g/day		1 (reference) 2.6 (1.6–4.0) 9.0 (5.2–15.53)	Age, residence, smoking	Number of cases not reported

Table 2.11 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Organ site (ICD code)	Exposure categories	No. of cases	Relative risk (95% CI)	Adjustment factors	Comments
Muscat & Wynder (1992), USA, 1985–90	194 men with histologically confirmed laryngeal cancer; Memorial Sloan-Ketterling and 7 other hospitals	184 hospital controls admitted for unrelated tobacco-induced disease; age matched (±5 years)		Never/ <29.6 mL/ day	40	1 (reference)	Age (matched), education, smoking, quetelet index	Relative risk 14.8 for binge drinkers
				29.7–88.9 mL/day	19	1.1 (0.6–2.3)		
				89–206 mL/ day	41	2.8 (1.5–5.2)		
				≥207 mL/ day	55	4.8 (2.5–9.4)		
				Binge drinkers	31	14.8 (1.6–46.3)		
Zheng *et al.* (1992), China, 1988–90	201 male residents of urban Shanghai; aged 20–75 years diagnosed with laryngeal cancer	414 hospital controls; age and sex matched; Shanghai Resident Registry		Never drinkers	80	1 (reference)	Age, education, smoking	Absence of association attributed to alcoholic beverage consumption during meals; data for female alcohol consumption not presented
				<144 g/week	16	0.8 (0.4–1.7)		
				144–284 g/ week	22	1.0 (0.5–2.0)		
				285–479 g/ week	27	0.9 (0.5–1.9)		
				≥480 g/week	32	0.8 (0.4–1.6)		
Hedberg *et al.* (1994), western Washington, USA, 1983–87	235 patients with laryngeal cancer aged 20–74 years; from 3 counties in western Washington state; response rate, 81%	547 controls identified through random-digit dialing; response rate, 75%	ICD-9 161.0–161.9	<7 drinks/ week	89	1 (reference)	Age, sex, smoking, MAST score	
				7–13 drinks/ week	42	1.9 (1.1–3.2)		
				14–20 drinks/week	27	2.1 (1.0–4.4)		
				21–41 drinks/week	37	2.8 (1.4–5.7)		
				>42 drinks/ week	24	3.1 (1.2–7.9)		

Table 2.11 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Organ site (ICD code)	Exposure categories	No. of cases	Relative risk (95% CI)	Adjustment factors	Comments
Dosemeci *et al*. (1997), Istanbul, Turkey, 1979–84	832 men with laryngeal cancer; selected from oncology treatment centre	829 hospital patients with selected cancers not related to alcohol or tobacco use	ICD-0 161.0–161.3; 161.9	Never drinkers	625	1 (reference)	Age, smoking	Possible underestimation of alcohol drinking due to low social acceptance; females excluded due to low prevalence of smoking and alcohol use among women in Turkey
				1–35 cL/ week	46	1.7 (1.0–3.2)		
				36–140 cL/ week	85	1.8 (1.1–2.9)		
				>141 cL/ week	41	1.5 (0.8–2.9)		
Rao *et al*. (1999), India, 1980–84	427 men diagnosed with cancer of vocal cords, supraglottis and larynx	635 male hospital patients free from cancer, infectious disease and benign lesions	ICD-9 161.0, 161.1, 161.9	Non-drinkers	308	1 (reference)		Multivariate relative risk for drinkers versus non-drinkers, adjusted for tobacco smoking and chewing and education, 1.64 (1.16–2.31; p=0.005)
				Once per day	85	1.5 (1.0–2.2)		
				Twice per day	17	2.8 (1.4–7.5)		

Table 2.11 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Organ site (ICD code)	Exposure categories	No. of cases	Relative risk (95% CI)	Adjustment factors	Comments
Schlecht *et al.* (2001), Brazil, 1986–89	784 newly diagnosed cases of carcinoma of the oral cavity, pharynx and larynx; selected from hospitals in 3 metropolitan areas in Brazil	1578 controls 2:1 matched by age (±5 years), gender, trimester of admission	ICD-9 140–145, 146–149, 161	*>100 kg of lifetime condumption versus non-drinker*			Age, study location, admission period, tobacco smoking, remaining alcohol consumption, income, education, race, beverage temperature, religion, wood stove use, consumption of spicy food	
				Beer	39	1.8 (0.6–5.7)		
				Wine	60	1.5 (0.6–4.0)		
				Hard liquor	61	1.3 (0.6–5.4)		
Bosetti *et al.* (2002), Italy, Switzerland, 1986–92; 1992–2000	40 non smoking cases and 68 non-drinking cases of laryngeal cancer; aged 30–74 years	160 nonsmoking and 161 non-drinking controls matched on study, sex, age, study centre; aged 31–79 years; admitted for acute, non-neoplastic conditions		*Drinks per day*			Smoking	
				<8	31	1		
				≥8	9	2.46 (0.98–6.20)		

Table 2.11 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Organ site (ICD code)	Exposure categories	No. of cases	Relative risk (95% CI)	Adjustment factors	Comments
Talamini *et al* (2002), Italy, Switzerland, 1992–2000	527 cases of squamous-cell carcinoma of the larynx; <79 years old; response rate, 97%	1297 hospital subjects admitted for non-alcohol-or tobacco-related illnesses	ICD-9 161.0–161.3, 161.8, 161.9	Abstainers >0–13 drinks/week 14–27 drinks/week 28–55 drinks/week ≥56 drinks/week	19 37 68 159 184	1 (reference) 0.9 (0.5–1.8) 1.2 (0.6–2.2) 2.6 (1.4–4.7) 5.9 (3.1–11.3) *p*-trend<0.0001	Age, sex, centre, education, smoking	No clear risk for duration; association in women too
Corrao *et al*., (2004) 1966–1998	Meta analyses of 99 case-control and 57 cohort studies published between 1966–88; for larynx, 20 case-control studies were the basis of the analysis			25 g/day 50 g/day 100 g/day		1.43 (1.38–1.48) 2.02 (1.89–2.16) 3.86 (3.42–4.35)		

Table 2.11 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Organ site (ICD code)	Exposure categories	No. of cases	Relative risk (95% CI)	Adjustment factors	Comments
Menvielle *et al*. (2004), France, 1989–91	504 men (125 glottis, 80 supraglottis, 97 epilarynx, 201 hypopharynx)	242 men with non-respiratory cancers; frequency-matched by age		Occasional drinkers	22	1 (reference)	Age, tobacco	Relative risk higher for hypopharynx compared with the glottis, supraglottis and epipharynx
				1–2 drinks/day	56	1.4 (1.2–1.6)		
				3–4 drinks/day	80	2.0 (1.5–2.7)		
				5–8 drinks/day	156	2.9 (1.9–4.4)		
				9–12 drinks/day	109	4.1 (2.4–7.2)		
				≥13 drinks/day	81	5.9 (2.9–11.8)		
Lee *et al*. (2005), Taiwan, China, 2000–03	128 male laryngeal cancer patients	255 hospital controls non-frequency matched; 40 years of age and older	ICD-10 C32	Non-drinkers	56	1 (reference)	Age, tobacco, use of betel quid	
				≤750 mL	52	3.1 (1.7–5.8)		
				>750 mL	15	10.3 (3.0–42.5)		
						p-trend<0.0001		

Table 2.11 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Organ site (ICD code)	Exposure categories	No. of cases	Relative risk (95% CI)	Adjustment factors	Comments
Polesel *et al*. (2005), Italy, Switzerland, 1982–99	588 histologically confirmed cases of laryngeal cancer	1663 patients <80 years of age, admitted to the same network of hospitals as cases, any acute non-neoplastic condition frequency matched by area of residence, age and year of interview						Spline models showed an increased risk with increasing alcohol consumption. See Polesel *et al*. (2005) for details regarding the estimation of spline model fit.
Garavello *et al*. (2006), Italy, 1986–2000	672 cases of laryngeal cancer (613 men and 59 women) aged 30–80 years; histologically confirmed; admitted to major teaching and general hospitals	3454 hospital-based controls (2646 men, 808 women); admitted to same network of hospitals as cases for non-neoplastic conditions not associated with smoking or alcohol		*Total alcohol* 0 1–2 drinks/day 3–4 drinks/day 5–7 drinks/day 8–11 drinks/day ≥12 drinks/day	 46 96 111 149 180 84	 1.00 * 1.12 (0.83–1.50) 2.43 (1.79–3.28) 3.65 (2.68–4.98) 4.83 (3.18–7.33) $p<0.0001$	Study centre, sex, age, education, body mass index, smoking	Pattern of increasing risk with increasing number of drinks was similar for drinkers of wine only and of wine plus beer and spirits; *for multivariate models, abstainers (0 drinks/day) or light drinkers (1–2 drinks/day) were compared with other levels of drinking.

Table 2.11 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Organ site (ICD code)	Exposure categories	No. of cases	Relative risk (95% CI)	Adjustment factors	Comments
Hashibe *et al.* (2007a), central and eastern Europe, 2000–02	384 incident (254 glottis, 108 supraglottis)	918 hospital	ICD-10 C32.0, C32.1, C32.2, C32.8, C32.9	Non-drinker	6	0.6 (0.22–1.65)	Age, sex, education, body mass index, fruit intake, study centre, pack–years of tobacco use	Significant trend in risk with dose; direct relation of borderline significance with duration of drinking
				1–139.9 g/week	161	1 (reference)		
				140–279 g/week	94	1.57 (1.05–2.33)		
				280–419 g/week	29	1.13 (0.62–1.99)		
				≥420 g/week	80	1.45 (0.92–2.26) *p*-trend=0.08		

CI, confidence interval; HCFA, Health Care Financing Administration; ICD, International Classification of Diseases; MAST, Michigan alcoholism-screening test

Table 2.12 Selected case–control studies of alcoholic beverage consumption and cancer of the larynx by anatomical subsite

Reference	Amount of alcohol consumption	Relative risk (95% CI)					
		No. of cases	Epilarynx	No. of cases	Supraglottis	No. of cases	Glottis/ subglottis
Elwood *et al*. (1984)	≥20 oz/week vs <1			46	6.4	108	2.2
Olsen *et al*. (1985)	≥301 g/week vs 0–100			191	3.0	103	5.0
Brugère *et al*. (1986)	≥160 g/day vs 0–40	217	101.4 (44–233.9)	224	42.1 (20.5–86.4)	242	6.1 (3.4–10.9)
Guénel *et al*. (1988)	≥160 g/day vs ≤39 g/day			81	35.7 (19.2–66.5)	61	14.9 (8.7–25.4)
Tuyns *et al*. (1988)	≥121 g/day vs 0–20	118	10.6 (4.4–25.8)	426	2.0 (1.3–3.0)	270	3.4 (2.1–5.6)
Falk *et al*. (1989)	20 drinks/week vs non-drinkers			9	4.6 (0.6–39.1)	40	1.8 (0.8–4.0)
Maier *et al*. (1992b)	>75 g/day versus <25				11.8 (4.5–29.6)		7.9 (3.5–17.7)
Muscat & Wynder (1992)	>207 mL/day vs never/<29.6			33	9.6 (3.3–27.6)	72	2.5 (1.0–6.2)
Dosemeci *et al*. (1997)	>141 cL/week vs never drinker			385	1.3 (0.6–2.8)	183	1.5 (0.6–3.6)
Talamini *et al*. (2002)	≥56 drinks/week vs 0–13			49	11.7 (3.2–42.3)	95	4.9 (2.1–11.7)
Menvielle *et al*. (2004)	>13 glasses/day vs 1–2	13	6.6 (2.4–17.7)	12	4.1 (1.4–11.5)	14	2.9 (1.1–7.1)

CI, confidence interval

cancer of the glottis/subglottis. Conversely, other studies reported similar risks for both supraglottis and glottis/subglottis (Flanders & Rothman, 1982; Tuyns *et al*., 1988; Hedberg *et al*., 1994). In a multicentric study in France, Italy, Spain and Switzerland (Tuyns *et al*., 1988) and in two French studies (Brugère *et al*., 1986; Menvielle *et al*., 2004), a stronger effect of alcoholic beverage consumption was found for the epilarynx.

The available evidence thus indicates that the highest risks related to the consumption of alcoholic beverages tend to occur in tissues that come into close contact with both alcoholic beverages and tobacco smoke. Thus, alcoholic beverage consumption may influence the risk for laryngeal cancer particularly through its direct contact or solvent action, perhaps by enhancing the effects of tobacco or other environmental carcinogens.

2.3.4 *Types of alcoholic beverage (Table 2.13)*

Several studies have investigated whether the risk for laryngeal cancer depends on the type of alcoholic beverage consumed. In a cohort study in Hawaii (Chyou *et al*., 1995) of 93 cancers of the upper digestive and respiratory tract, no substantial difference in risk was found between the highest levels of consumption of beer (relative risk, 3.7), wine (relative risk, 3.8) or spirits (relative risk, 3.6). Another prospective study in Norway (Kjaerheim *et al*., 1998) of upper digestive and respiratory tract cancers found a higher risk for elevated consumption of beer (relative risk, 4.4) compared with that of spirits (relative risk, 2.7). However, due to the limited number of cases, specific analysis of laryngeal cancer was not possible in these two cohort studies.

Among case–control studies, a Canadian study (Burch *et al*., 1981) found an increase in risk among heavy beer drinkers (odds ratio, 4.8), but no consistent increase for spirit (odds ratio, 1.3) or wine drinkers (odds ratio, 0.5). Similarly, a case–control study from Denmark (Olsen *et al*., 1985) of 326 cases of laryngeal cancer and 1134 controls reported a higher risk in drinkers who preferably consumed beer (odds ratio, 1.4) than in those who preferred wine (odds ratio, 0.6) or spirits (odds ratio, 1.0). A case–control study in Uruguay (De Stefani *et al*., 1987) of 107 cases of laryngeal cancer and 290 controls showed a higher risk for wine (odds ratio, 7.4) than for hard liquors (odds ratio, 4.0). In an Italian study (Franceschi *et al*., 1990), wine was associated with the highest risk (odds ratio, 4.2), whereas a lower risk was reported for beer (odds ratio, 1.5) and hard liquors (odds ratio, 0.8). In a case–control study conducted in the USA (Muscat & Wynder, 1992), based on 250 cases, an increased risk for laryngeal cancer was found for heavy drinkers of beer (odds ratio, 2.7) and hard liquors (odds ratio, 2.2), but not for wine drinkers (odds ratio, 1.1). No strong differences were seen between consumption of beer, hard liquors or wine in a case–control study in Brazil (Schlecht *et al*., 2001) that included 194 cases of laryngeal cancer: the relative risk was 1.8 for high consumption of hard liquors and beer and 1.5 for that of wine. Higher risks were observed for cachaça (relative risk, 9.9), a typical Brazilian hard liquor. In a case–control study in Italy and Switzerland (Talamini *et al*., 2002),

Table 2.13 Selected case–control studies of laryngeal cancer and consumption of different types of alcohol beverage

Reference, study location	Level of alcohol intake	Relative risk (95% CI)					
		No. of cases	Beer	No. of cases	Wine	No. of cases	Hard liquors
Burch *et al.* (1981), Canada	Beer/spirits: ≥4 drinks/day versus non-drinker Wine: ever used versus never		4.8 (2.4–9.8)		0.5 (0.2–0.9)		1.3 (0.5–3.4)
Olsen *et al.* (1985), Denmark	Preferred type of alcohol		1.4 (1.1–1.9)		0.6 (0.4–0.9)		1.0 (0.6–1.8)
De Stefani *et al.* (1987), Uruguay	>201 mL/day versus non-drinker		–		7.4 (3.0–18.1)		4.0 (1.9–8.2)
Franceschi *et al.* (1990), Italy	Beer: >14 drinks/week versus 0 Wine: ≥84 versus 0–6 Hard liquors: >7 versus 0	25	1.5 (0.8–2.5)	10	4.2 (1.6–10.6)	35	0.8 (0.5–1.3)
Freudenheim *et al.* (1992), USA	Beer: ≥1873 drinks/year versus 0–32 Wine: ≥139 versus 0 Hard liquors: ≥438 versus 0	123	2.7 (1.4–5.1)	67	1.1 (0.6–2.0)	117	2.2 (1.2–4.0)
Schlecht *et al.* (2001), Brazil	>100 kg of lifetime consumption versus non-drinkers	39	1.8 (0.6–5.7)	60	1.5 (0.6–4.0)	61	1.8 (0.6–5.4)
Talamini *et al.* (2002), Italy, Switzerland	Beer: >1 drinks/week versus 0–1 Wine: ≥42 versus 0–13 Hard liquors: >3 versus 0–3	167	3.3 (1.8–6.1)	210	5.2 (2.8–9.9)	182	2.9 (1.5–5.8)
Garavello *et al.* (2006), Italy	Beer: ≥3 drinks/day Wine: ≥12 drinks/day Spirits: ≥3 drinks/day	37	1.3 (0.9–2.2)	56	5.9 (3.5–10.0)	37	1.2 (0.7–2.0)

CI, confidence interval

the risk was slightly higher for wine drinkers than for beer and hard liquor drinkers (odds ratios, 5.2, 3.2 and 2.9, respectively). Case–control studies conducted in Italy between 1986 and 2000 (Franceschi *et al*., 1990; Talamini *et al*., 2002; Garavello *et al*., 2006) included 672 cases of laryngeal cancer and 3454 hospital controls, admitted for acute, non-neoplastic conditions that were unrelated to smoking or alcoholic beverage consumption. Significant trends in risk were found for total alcoholic beverage intake, with multivariate odds ratios of 1.12 for drinkers of 3–4 drinks per day, 2.43 for 5–7, 3.65 for 8–11 and 4.83 for >12 drinks per day compared with abstainers or light drinkers. Corresponding odds ratios for wine drinkers were 1.12, 2.45, 3.29 and 5.91. After allowance was made for wine intake, the odds ratios for beer drinkers were 1.65 for 1–2 drinks per day and 1.36 for ≥3 drinks per day compared with non-beer drinkers; corresponding values for spirit drinkers were 0.88 and 1.15. Thus, in the Italian population which is characterized by frequent wine consumption, wine is the beverage most strongly related to the risk for laryngeal cancer.

Taken together, these data suggest, however, that the most frequently consumed beverage in each population tends to be that which yields the highest risk, and that ethanol is the main component of alcoholic beverages that determines the risk for cancer.

2.3.5 *Joint effects*

Several investigations have considered the combined effect of tobacco smoking and alcoholic beverage consumption on the etiology of cancer of the larynx (Flanders & Rothman, 1982; Elwood *et al*., 1984; Olsen *et al*., 1985; De Stefani *et al*., 1987; Guénel *et al*., 1988; Tuyns *et al*., 1988; Franceschi *et al*., 1990; Choi & Kahyo, 1991a; Zatonski *et al*., 1991; Maier *et al*., 1992a; Zheng *et al*., 1992; Chyou *et al*., 1995; Dosemeci *et al*., 1997; Schlecht *et al*., 1999; Bagnardi *et al*., 2001; Talamini *et al*., 2002). These studies gave risk estimates for the highest level of consumption for both factors compared with the lowest level of between approximately 10 and over 100, and indicated that a multiplicative model rather than an additive model or risk could explain the level of risk from combined exposure to both factors. Separating the effects of alcoholic beverages and tobacco remains difficult, however, since heavy drinkers tend to be heavy smokers and vice versa. Furthermore, most studies included very few cases who neither smoked nor drank.

An example of the combined effect of alcoholic beverages and tobacco on laryngeal cancer was given by Talamini *et al*. (2002). Compared with never smokers/abstainers or light drinkers, the relative risk for laryngeal cancer increased with increasing alcoholic beverage consumption in each stratum of smoking habit to reach 177.2 in heavy drinkers and smokers compared with moderate drinkers and nonsmokers. Similar results were found for smoking within strata of alcoholic beverage intake. The odds ratio for the highest level of alcoholic beverage consumption and current smoking was 177.2. In a French study (Guénel *et al*., 1988), the relative risk for combined heavy alcoholic beverage and tobacco consumption was 289.4 (95% CI, 83.0–705.8) for glottic and 1094.2

(95% CI, 185.8–2970.7) for supraglottic cancers. In a case–control study in Taiwan, China, the odds ratio for users of alcoholic beverages, betel quid and cigarettes compared with non-users was 40.3 (95% CI, 14.8–123.6) (Lee *et al*., 2005).

2.3.6 *Effect of cessation of alcoholic beverage consumption*

The risk for laryngeal cancer declines steeply with time since stopping smoking (Olsen *et al*., 1985; Guénel *et al*., 1988; Tuyns *et al*., 1988; Franceschi *et al*., 1990; Freudenheim *et al*., 1992; Kjaerheim *et al*., 1993; Bosetti *et al*., 2006). Data exist from only one study on time since stopping alcoholic beverage consumption. In a case–control study in Italy (Altieri *et al*., 2002) that included a total of 59 former drinkers, the odds ratios were 1.24 for 1–5 years, 1.29 for 6–19 years and 0.53 for ≥20 years since cessation of drinking compared with current drinking. The risk approached that of never drinkers only after 20 years since cessation (odds ratio, 0.56).

Thus, while the favourable effect of stopping smoking is evident within a few years after cessation, that of stopping drinking becomes apparent only in the long term. Among current smokers that have stopped drinking, the persistence of exposure to tobacco may play an important role in limiting the benefits from cessation of drinking. These findings must, however, be interpreted with caution, since former drinkers may represent a select group of individuals whose average alcoholic beverage intake had exceeded that of current drinkers.

2.3.7 *Effect of Alcoholic beverage consumption in nonsmokers (Table 2.14)*

An independent role of alcoholic beverages on the incidence of laryngeal cancer has been suggested, but is difficult to quantify (Austin & Reynolds, 1996). In developed countries, cancer of the larynx is rare in nonsmokers, and only a few studies have included enough cases to provide useful information on the effect of alcoholic beverages in nonsmokers.

A case–control study form Canada (Burch *et al*., 1981) of 204 cases and 204 matched controls reported an increased risk for laryngeal cancer in relation to alcoholic beverage consumption (odds ratio, 7.7 for ≥26 000 oz ethanol in a lifetime) in never smokers based, however, on three case–control pairs only. A multicentric case–control study in France, Italy, Spain and Switzerland (Tuyns *et al*., 1988) reported odds ratios of 1.7 for ≥80 g per day of alcohol among nine never-smoker cases of cancer of the endolarynx and of 6.7 for ≥40 g per day of alcohol among 22 nonsmoking cases of cancer of the epilarynx/hypopharynx. In a case–control in Italy conducted on 40 never-smoking cases, an excess risk (odds ratio, 2.5) for ≥8 drinks per day was found (Bosetti *et al*., 2002).

A pooled analysis of never-tobacco users from 11 case–control studies, including 121 cases of laryngeal cancer and 4602 controls, showed an increased risk for laryngeal

Table 2.14 Selected case–control studies of laryngeal cancer and alcoholic beverage consumption in nonsmokers

Reference, study location	Exposure Categories	Number of cases	Relative risk (95% CI)
Burch *et al*. (1981), Canada	0 oz ethanol in lifetime	3	1[a] (3)
	<10 000 oz ethanol in lifetime	3	2.0 (3)
	10 000–25 000 oz ethanol in lifetime	3	3.9 (3)
	≥26 000 oz ethanol in lifetime	3	7.7 (3)
Tuyns *et al*. (1988)[b], France, Italy, Spain, Switzerland	0–40 g/day	7	1[a] (7)
	40–80 g/day	3	1.5 (3)
	≥80 g/day	6	1.7 (6)
Bosetti *et al*. (2002), Italy, Switzerland	<8 drinks/day	31	1[a] (31)
	≥8 drinks/day	9	2.5 (9)
Hashibe *et al*. (2007b), pooled analysis	Never drinkers		1.00[a]
	<1 drink/day		0.92 (0.50–1.69)
	1–2 drinks/day		1.26 (0.77–2.07)
	3–4 drinks/day		1.24 (0.62–2.45)
	≥5 drinks/day		2.98 (1.72–5.17)
			p for trend <0.001

CI, confidence interval [a] Reference category [b] Relative risks are presented for endolarynx.

cancer with the consumption of ≥5 drinks per day (odds ratio, 2.98; 95% CI, 1.72–5.17) (Hashibe *et al*., 2007b).

Thus, these studies confirmed that, even in a population of never smokers, elevated alcoholic beverage consumption increases the risk for laryngeal cancer. There is, however, no reason to suppose that tobacco smoking is the only carcinogenic agent to which the human upper respiratory and digestive tract is exposed, and ethanol may facilitate the effect of other unrecognized carcinogenic agents in nonsmokers, just as it commonly facilitates the effect of tobacco smoking (Doll *et al*., 1999).