2.2 Cancer of the oral cavity and pharyn*x*

The evidence for carcinogenic effects of alcoholic beverage consumption on the risk for cancers of the oral cavity and pharynx in humans was considered to be *sufficient* by a previous IARC Working Group (IARC, 1988). This section evaluates the evidence related to the risk for oral and pharyngeal cancer in humans based on relevant cohort and case–control studies published after 1988.

Exposure to alcoholic beverages is given in many different measurements. For comparability between studies, one drink is equivalent to 14 g, 18 mL or 0.49 oz of alcohol, which generally corresponds to 330 mL of beer, 150 mL of wine and 36 mL of hard liquor. Cancers of the oral cavity and pharynx are predominantly squamous-cell carcinomas. The histology of the tumours is given when available. Generally, studies on pharyngeal cancers are predominantly oropharyngeal and hypopharyngeal cancers, rather than nasopharyngeal cancer. Two case–control studies are, however, specifically focused on nasopharyngeal cancer, as noted in the Tables.

The risks for cancer of the oral cavity and pharynx in relation to total alcoholic beverage consumption are summarized in Tables 2.2–2.5. The effect of alcohol types are presented in Table 2.6, the combined or joint effects of alcohol drinking and tobacco smoking are shown in Table 2.7, and the effect of alcohol cessation and the association between alcoholic beverage consumption and risk for oral and pharyngeal cancers among nonsmokers are presented in Tables 2.8 and 2.9, respectively.

2.2.1 *Cohort studies (Table 2.2)*

Five cohort studies of the general population have been published since 1988 on the relationship between alcoholic beverage consumption and oral or pharyngeal cancer (Boffetta & Garfinkel, 1990; Chyou *et al*., 1995; Murata *et al*., 1996; Kjaerheim

Table 2.2 Cohort studies of cancers of the oral cavity and pharynx combined

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)[a]	Adjustment factors	Comments
Boffetta & Garfinkel (1990), USA, American Cancer Society Prospective Study	Cohort of 276 802 white men from over 25 states; aged 40–59 years; enrolment in 1959; mortality follow-up until 1971; 3% of cohort lost to follow-up	Questionnaire	Oral cavity (ICD 140–145)	*Total alcohol* Non-drinker Occasional drinker 1 drink/day 2 drinks/day 3 drinks/day 4 drinks/day 5 drinks/day ≥6 drinks/day Irregular drinker	 55 10 6 12 13 13 5 26 15	 1.0 (reference) 1.2 (0.6–2.4) 0.4 (0.2–1.0) 1.0 (0.5–1.9) 2.2 (1.2–4.0) 3.2 (1.7–6.1) 2.7 (1.0–6.8) 6.2 (3.7–10.1) 2.0 (1.1–3.5)	Age, smoking	
Adami *et al.* (1992a,b) Uppsala, Sweden,	Cohort of 9353 patients (8340 men, 1013 women) diagnosed with alcoholism in the Inpatient Register; incidence follow-up 1965–83	Inpatient Register records	Oral cavity, pharynx (ICD7 140–148)	Overall *Age at follow-up* <50 years 50–64 years ≥65 years	36 NG NG NG	**SIR** 4.1 (2.9–5.6) 9.4 (1.9–27.3) 10.1 (6.6–14.7) 1.0 (0.4–2.2)	No information on potential confounders	Age-standardized expected rates from local population; confounding by smoking likely

Table 2.2 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)[a]	Adjustment factors	Comments
Kjaerheim *et al.* (1993), Norway	Cohort of 5332 members of the International Organization of Good Templars (signed statement that they will not drink alcoholic beverages), aged ≥10 years; enrolment in 1980; incidence follow-up until 1989		Oral cavity, pharynx (ICD7 141–148)	Non-drinkers	*Men* 2 *Women* 1 *Both sexes* 3	**SIR** [0.11] [0.01–0.40] [0.38] [0.01–2.12] 0.44 (0.09–1.27)	None	Age- and sex-specific expected rates from national incidence

Table 2.2 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)[a]	Adjustment factors	Comments
Day *et al.* (1994a), USA	Nested case–control study of second primary cancers; cohort of 1090 first primary cancers of oral cavity and pharynx; enrolment of first primary cancers in 1984–85; follow-up until 1989; 80 (56 men, 24 women) developed second primary cancers during follow-up; 189 (132 men, 57 women) randomly selected from cohort, matched on sex, study area and survival, free of second primary cancer at the end of follow-up	Interviewer-administered questionnaire	Oral cavity, pharynx, oesophagus (ICD9 141, 143–146, 148–149)	*Total alcohol* <5 drinks/week 5–14 drinks/ week 15–29 drinks/ week ≥30 drinks/ week	 9 10 14 24	**Odds ratio** 1.0 (reference) 1.6 (0.5–5.1) 2.1 (0.7–6.6) 1.5 (0.5–4.5)	Age, stage of disease, lifetime smoking	Nested case–control study of second primary cancers among cases of Blot *et al.* (1988) study; looked at type of alcoholic beverage and cessation of alcoholic beverage consumption

Table 2.2 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)[a]	Adjustment factors	Comments
Tønnesen *et al.* (1994), Copenhagen, Denmark	Cohort of 18 307 (15 214 men, 3093 women) alcoholics from a public outpatient clinic for free treatment; incidence follow-up 1954–87	Interview with a social worker and psychiatrist	Oral cavity, pharynx	Alcoholic	*Men* 112 W*omen* 22	 3.6 (3.0–4.3) 17.2 (10.8–26.0)	None	Age-, sex- and calendar period-specific cohort cancer incidence compared with total Danish population
Chyou *et al.* (1995), Hawaii, USA, American men of Japanese Ancestry	Cohort of 7995 men of Japanese ancestry identified by the Honolulu Heart Program, aged 45–68 years; recruitment in 1965–68, incidence follow-up until 1993; 1–2% lost to follow-up	Interviewer-administered questionnaire	Oral cavity, pharynx, oesophagus, larynx (ICD8 140–150, 161)	*Total alcohol* Non-drinker <4 oz/month 4–24.9 oz/ month ≥25 oz/month *p* for trend	 16 5 18 52	**Hazard ratio** 1.0 (reference) 0.6 (0.2–1.6) 1.7 (0.9–3.4) 4.7 (2.6–8.3) <0.0001	Age, number of cigarettes/ day, years smoked	Study population from Kato *et al.* (1992c); looked at type of alcoholic beverage and joint effects with smoking

Table 2.2 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)[a]	Adjustment factors	Comments
Murata *et al.* (1996), Japan	Nested case–control study among cohort of 17 200 men part of a gastric mass screening survey in 1984; incidence follow-up until 1993; 887 cases and 1774 controls matched on sex, birth year, city/ county	Self-administered questionnaire	Oral cavity, pharynx, oesophagus, larynx (ICD9 140-150, 161)	*Total alcohol*[*]			None	[*]Unit is cup of 180 mL of sake: corresponds to 27 mL ethanol
				0 cups/day	17	1.0 (reference)		
				0.1–1.0 cups/ day	13	1.0 (p>0.05)		
				1.1–2.0 cups/ day	11	1.9 (p>0.05)		
				≥2.1 cups/day	10	9.0 (p<0.01)		
				χ^2 for trend		9.6 (p<0.01)		
				Nonsmoker[*]				
				0 cups/day	7	1.0 (reference)		
				0.1–1.0 cups/ day	6	1.2 (p>0.05)		
				≥1.1 cups/day	5	2.1 (p>0.05)		
				Smoker[*]				
				0 cups/day	10	1.9 (p>0.05)		
				0.1–1.0 cups/ day	7	1.4 (p>0.05)		
				≥1.1 cups/day	16	5.9 (p<0.01)		

Table 2.2 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)[a]	Adjustment factors	Comments
Sigvardsson *et al.* (1996), Sweden	Cohort of 15 508 alcoholic women ascertained through the Temperance Boards and 15 508 non-alcoholic women from population matched individually on region and date of birth; enrolled in 1947–77; follow-up for incidence	Temperance Boards records	Tongue (ICD7 141), mouth (143, 144), tonsil (145), hypo-pharynx (147), Pharynx (148)	*Tongue* Comparisons Alcoholics *Mouth* Comparisons Alcoholics *Tonsil* Comparisons Alcoholics *Hypopharynx* Comparisons Alcoholics *Pharynx* Comparisons Alcoholics	 2 17 1 12 1 11 1 9 0 1	 1.0 (reference) 8.5 (2.0–37) 1.0 (reference) 12.0 (1.6–92) 1.0 (reference) 11.0 (1.4–85) 1.0 (reference) 9.0 (1.1–71) 1.0 (reference) NG	None	

Table 2.2 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)[a]	Adjustment factors	Comments
Kjaerheim *et al.* (1998), Norway	Cohort of 10 960 men born in 1893–1929 who completed two questionnaires sent to a probability sample of the Norwegian population; incidence follow-up 1968–92; mean age at start of follow-up, 59 years	Mailed survey	Oral cavity, pharynx, larynx, oesophagus (ICD7 141, 143–145, 147, 148, 150, 161)	*Total alcohol* Never or <1 time/week Previously 1–3 times/week 4–7 times/week *p* for trend *Beer* Never or <1 time/week Previously 1–3 times/week 4–7 times/week *p* for trend *Spirits* Never or <1 time/week Previously 1–3 times/week 4–7 times/week *p* for trend	 26 4 18 19 37 11 8 14 42 15 5 5 	 1.0 (reference) 0.9 (0.3–2.7) 1.1 (0.6–1.9) 3.9 (2.1–7.1) 0.003 1.0 (reference) 1.0 (0.5–1.9) 1.4 (0.7–3.1) 4.4 (2.4–8.3) <0.001 1.0 (reference) 1.3 (0.7–2.3) 1.4 (0.6–3.6) 2.7 (1.1–7.0) 0.06	Age, smoking	
Sørensen *et al.* (1998), Denmark	Cohort of 11 605 1-year survivors of cirrhosis from the Danish National Registry of Patients; recruitment in 1977–89; incidence follow-up until 1993	Admission records of Danish National Registry of Patients	Oral cavity, pharynx	Overall All cirrhosis Alcoholic cirrhosis Chronic hepatitis cirrhosis	 143 115 8	**SIR** 9.2 (7.8–10.8) 11.6 (9.6–14.0) 4.2 (1.8–8.2)	None	Expected rates from age-, sex- and site-specific national incidence rates

Table 2.2 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)[a]	Adjustment factors	Comments
Boeing (2002), Denmark, France, Germany, Greece, Italy, Norway, Spain, Sweden, Netherlands, UK, European Prospective Investigation into Cancer and Nutrition	Cohort of 417 752 healthy adults; recruitment initiated in 1992; follow-up ongoing	Mailed questionnaire	Oral cavity, pharynx, oesophagus (ICDO C00.0–C10.9, C13.0–13.9, C15.0–15.9)	*Lifelong alcohol* No alcohol >0–30 g/day >30–60 g/day >60 g/day	 4 83 20 17	**Hazard ratio** 1.0 (reference) 1.2 (0.4–3.4) 3.2 (1.0–10.1) 9.2 (2.8–30.9)	Follow-up time, sex, education, body mass index, vegetable and fruit consumption, tobacco smoking, energy intake	Looked at joint effects with smoking and observed a synergistic effect
Dikshit *et al.* (2005), Italy, Spain, Switzerland	Occurrence of second primary tumours among a cohort of 876 male cases of laryngeal/ hypo-pharyngeal cancer from a multicentric population-based case–control study (1979–82); follow-up until 2000	Interviewer-administered questionnaire	Oral cavity, pharynx, oesophagus (ICD9 140–150)	*Total alcohol* 0–40 g/day 41–80 g/day 81–120 g/day ≥21 g/day	 4 4 12 17	**Hazard ratio** 1.0 (reference) 0.8 (0.2–3.3) 3.0 (0.9–9.5) 3.5 (1.1–11.2) p=0.003	Age, centre, occupation, smoking, site of first cancer	

CI, confidence interval; ICD, International Classification of Diseases; NG, not given; SIR, standardized incidence ratio; [a] p-value indicated when CI not presented

et al., 1998; Boeing, 2002), four of which reported smoking-adjusted relative risks but one did not (Murata *et al*., 1996). Increases in risk with consumption of alcoholic beverages were observed in all five cohort studies of populations from the USA, Europe and Asia, and heavy consumption was associated with a significantly increased risk. The adjusted relative risks were 9.22 (95% CI, 2.75–30.93) for more than 60 g (or more than four drinks) per day (Boeing, 2002), 6.2 (95% CI, 3.7–10.1) for more than 60 g (or more than four drinks per day) in the American Cancer Society Prospective Study (Boffetta & Garfinkel, 1990) and 3.9 (95% CI, 2.1–7.1) for consumption of alcoholic beverages four to seven times per week in a study in Norway (Kjaerheim *et al*., 1998). A strong dose–response relationship was reported in three studies (Murata *et al*., 1996; Kjaerheim *et al*., 1998; Boeing, 2002); however, two studies found a J-shaped relationship with an inverse association with low levels of alcoholic beverage consumption (Boffetta & Garfinkel, 1990; Chyou *et al*., 1995). In both studies, an increase in risk was observed with increasing levels of alcoholic beverage consumption thereafter.

Separating the effects of alcoholic beverages and tobacco smoking is generally very difficult. In most of these studies, however, smoking was controlled for in the analyses (Boffetta & Garfinkel, 1990; Chyou *et al*., 1995; Kjaerheim *et al*., 1998; Boeing, 2002). The increases in risk with consumption of alcoholic beverages were consistently seen in situations where smoking was controlled for as well as where smoking was not taken into account.

Five cohort studies were based on special populations (Adami *et al*., 1992a; Kjaerheim *et al*., 1993; Tønnesen *et al*., 1994; Sigvardsson *et al*., 1996; Sørensen *et al*., 1998). This type of study usually does not consider individual exposure levels. The point estimates were either the SIRs or standardized mortality ratios (SMRs) without adjusting for tobacco smoking. Among special cohorts of alcoholics, an increase in risk for cancers of the oral cavity and pharynx compared either with the local population rates (Adami *et al*., 1992a; Tønnesen *et al*., 1994; Sørensen *et al*., 1998) or with a population control group (Sigvardsson *et al*., 1996) has also been shown. Among Swedish alcoholics, Adami *et al*. (1992a) found a fourfold increase in risk (95% CI, 2.9–5.6) for oral cavity and pharyngeal cancers. Tønnesen *et al*. (1994) also found more than a 3.5-fold increase in risk (95% CI, 3.0–4.3) among men and a 17-fold increase (95% CI, 10.8–26.0) among women. In Danish 1-year survivors of cirrhosis, Sørensen *et al*. (1998) found a ninefold increase in risk (95% CI, 7.8–10.8) compared with national incidence rates. Furthermore, among alcoholic cirrhosis patients, the risk was increased more than 11.5-fold (95% CI, 9.6–14.0) compared with fourfold (95% CI, 1.8–8.2) among chronic hepatitis cirrhosis patients. By cancer site, Sigvardsson *et al*. (1996) found 8.5-fold (95% CI, 2.0–37), 12-fold (95% CI, 1.6–92), 11-fold (95% CI, 1.4–85) and ninefold (95% CI, 1.1–71) increases in risk for cancers of the tongue, mouth, tonsil and hypoharynx, respectively, in a Swedish population. Conversely, a cohort study among members of the International Organization of Good Templars in Norway, an organization for which members sign a statement that they will abstain from the consumption of alcoholic beverages, showed a 56% decrease in risk (SIR 0.44; 95% CI,

0.09–1.27) compared with the national incidence rates (Kjaerheim *et al*., 1993). Data on individual alcoholic beverage and tobacco consumption, however, were not obtained, which makes the separation of the protective effects of abstaining from either factor very difficult, especially since the two habits are usually correlated.

Alcoholic beverages have also been shown to be a risk factor for second primary cancers of the oral cavity and pharynx in two prospective studies of patients with a first primary cancer (Day *et al*., 1994a; Dikshit *et al*., 2005). Day *et al*. (1994a) and Dikshit *et al*. (2005) studied the risks for second primary cancers of the upper aerodigestive tract in relation to alcoholic beverage consumption among North Americans and Europeans (from Italy, Spain and Switzerland), respectively. In both studies, an increase in risk was found, although a more dramatic increase was found among Europeans (3–3.5-fold increase in risk among those who drank ≥81 g per day) than among North Americans (1.5–2-fold increase in risk among those who drank ≥15 drinks [≥210 g] per week or ≥30 g per day), which may be attributed to differences in categorization.

Results from prospective cohort studies of the general population provide *sufficient* evidence for the important role of alcoholic beverage consumption in the development of oral and pharyngeal cancer. The strength of the association is demonstrated by significantly increased relative risks that range from 3.5 to 9.2. A strong dose–response relationship was observed in almost all of the studies. Alcoholic beverage consumption was associated with an increase in risk for oral and pharyngeal cancer across different geographic regions and populations, which further supports the evidence.

2.2.2 *Case–control studies*

(a) Cancer of the oral cavity (Table 2.3)

All of the studies listed in Table 2.3 were hospital-based case–control studies (Franceschi *et al*., 1990; Zheng *et al*., 1990; Choi & Kahyo, 1991a; Zheng *et al*., 1997; Rao & Desai, 1998; Balaram *et al*., 2002; Znaor *et al*., 2003; De Stefani *et al*., 2007) and all but one (Rao & Desai, 1998) adjusted for tobacco smoking when evaluating the effect of alcoholic beverage consumption. All six studies of cancer of the oral cavity reported a positive association, with a dose–response relationship with alcoholic beverage consumption in different geographical areas of the world. A study of cancer of the tongue with a relatively large sample size reported increased risks for 20–30 years of alcoholic beverage consumption (odds ratio, 3.3; 95% CI, 1.4–8.9 for men; 2.0; 95% CI, 1.0–4.6 for women) (Rao & Desai, 1998). No obvious association was found in a study of cancer of the tongue with a limited sample size (Zheng *et al*., 1997).

Overall, the increase in risk for oral cancer associated with alcoholic beverage consumption is consistent, even after controlling for smoking. The strength of the association was shown by elevated adjusted odds ratios for heavy consumption that ranged from 3.0 to 14.8. Furthermore, a dose–response relationship was observed with elevated alcoholic beverage consumption and increased risk in most studies with multiple exposure levels when adjusted for tobacco smoking. The association has been observed

Table 2.3 Case-control studies of cancer of the oral cavity and alcoholic beverage consumption

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Odds ratio (95% CI)	Adjustment factors	Comments
Franceschi *et al.* (1990), Milan, Pordenone, Italy, 1986–89	157 men identified from hospitals in Milan and Pordenone; under 75 years of age; histologically confirmed; response rate, 98% overall for cases	1272 hospital-based, male non-cancer patients from same hospitals as cases matched on age, area of residence; excluded patients with alcohol- and tobacco-related conditions; response rate, 97%	Interviewer-administered questionnaire	Oral cavity (ICD9 140, 141, 143–145)	*Total drinks/ week* ≤19 20–34 35–59 ≥60 *p* for trend	 15 14 63 65	 1.0 (reference) 1.1 (0.5–2.5) 3.2 (1.6–6.2) 3.4 (1.7–7.1) <0.01	Age, area of residence, education, occupation, smoking habits	Also looked at pharyngeal cancers; looked at type of alcoholic beverage and joint effects with smoking
Zheng *et al.* (1990), Beijing, China, 1988–89	404 cases (248 men, 156 women) diagnosed at seven participating hospitals in the Beijing area; histologically confirmed; response rate, 100%	404 randomly selected non-cancer, hospital-based controls individually matched on age, sex, hospital; response rate, 100%	Interviewer-administered standardized questionnaire	Oral cavity (ICD9 141, 143–145)	**Men only** *Total alcohol in spirit equivalent* Never drinker <26 g/day 26–49 g/day 50–99 g/day >99 g/day	 42 52 42 39	 1.0 (reference) 1.3 (0.7–2.3) 1.1 (0.6–2.1) 1.4 (0.7–2.6) 2.8 (1.2–6.3)	Age, education, smoking	Assessed type of alcoholic beverage and joint effects with smoking

Table 2.3 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Odds ratio (95% CI)	Adjustment factors	Comments
Choi & Kahyo (1991a), Seoul, Republic of Korea, 1986–89	157 cases (113 men, 44 women) from the Korea Cancer Center Hospital; cytological and/or histopathological confirmation	471 (339 men, 132 women) hospital-based, non-cancer controls matched (3:1 controls:cases) on age, sex, admission date; excluded patients with alcohol- and tobacco-related conditions	Interviewer-administered standardized questionnaire in hospital	Oral cavity (ICDO 140, 141, 143–145)	**Men only** *Total alcohol*[a] Non-drinker <1 hop/day 1–2 hops/day 2–4 hops/day >4 hops/day	 16 9 45 32 11	 1.0 (reference) 0.6 (0.3–1.4) 3.6 (1.8–7.2) 4.2 (2.1–8.4) 14.8 (5.0–43.7)	Smoking	Also looked at pharynx and larynx; [a]1 hop = 90 mL of soju [generally 20% alcohol, 14 g ethanol]; soju is most frequent alcoholic beverage type
Zheng *et al.* (1997), Beijing, China, 1988–89	111 cases (65 men, 46 women) diagnosed at seven participating hospitals in the Beijing area; aged 20–80 years; histologically confirmed	111 randomly selected non-cancer, hospital-based controls individually matched on age, sex, hospital; excluded patients with alcohol- and tobacco-related conditions	Interviewer-administered standardized questionnaire	Tongue	*Total alcohol in spirit equivalent* Never drinker <50 g/day 50 g/day >50 g/day *Spirits frequency* <5 days/week ≥5 days/week	 64 20 8 19 18 27	 1.0 (reference) 1.2 (0.5–3.2) 0.7 (0.2–2.3) 1.6 (0.6–4.4) 0.70 (0.28–1.70) 2.34 (0.90–6.06)	Education, smoking (matched on age, sex)	Same population as Zheng *et al.* (1990); looked at type of alcoholic beverage and joint effects with smoking

Table 2.3 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Odds ratio (95% CI)	Adjustment factors	Comments
Rao & Desai (1998), Bombay, India, 1980–84	637 men from the hospital	635 hospital-based, unmatched controls; free from cancer, infectious disease, benign lesion	Interviewer-administered questionnaire before clinical examination	Tongue (ICD 140–144)	*Total duration of alcoholic beverage consumption*			Age, residence	
				Anterior tongue	Non-user	102	1.0 (reference)		
					1–10 years	11	1.2 (0.6–2.6)		
					11–20 years	12	2.0 (0.9–4.4)		
					21–30 years	12	3.3 (1.4–8.9)		
					≥31 years	4	1.3 (0.3–4.8)		
				Base tongue	Non-user	382	1.0 (reference)		
					1–10 years	38	1.5 (0.9–2.5)		
					11–20 years	35	1.6 (0.9–2.9)		
					21–30 years	32	2.0 (1.0–4.6)		
					≥31 years	8	0.5 (0.2–1.4)		
Balaram *et al.* (2002), southern India, 1996–99	591 cases (309 men, median age 56 years; 282 women, median age 58 years) from three centres in Bangalore, Madras, Trivandrum; response rate, 97%	582 (292 men, 290 women) hospital-based controls from the same hospitals as cases frequency matched by centre, age, sex; response rate, 90%	Interviewer (social worker)-administered questionnaire	Oral cavity	*Men only*			Centre, age, education, paan chewing, smoking	Looked at cessation of alcoholic beverage consumption and joint effects with paan chewing; former drinkers abstained ≥12 months
					Abstainers	102	1.0 (reference)		
					Former drinkers	65	1.78 (0.97–3.28)		
					Current drinkers				
					<3 drinks/week	29	2.17 (1.00–4.69)		
					3–13 drinks/week	22	2.14 (0.89–5.19)		
					≥14 drinks/week	29	1.97 (0.85–4.57)		
					p for trend		0.01		

Table 2.3 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Odds ratio (95% CI)	Adjustment factors	Comments
Znaor *et al.* (2003), Chennai, Trivandrum, India, 1993–99	1563 men from the Cancer Institute (Chennai) and the Regional Cancer Center (Trivandrum); histologically confirmed	1711 male patients with non-tobacco-related cancers from same centres as cases and 1927 healthy male hospital visitors from Chennai only	Interviewer-administered questionnaire	Oral cavity (ICD9 140, 141, 143–5)	*Total alcohol; average amount of ethanol*[a] Never drinker <20 mL/day 20–50 mL/day >50 mL/day	 780 213 256 308	 1.0 (reference) 1.2 (1.0–1.5) 2.4 (1.9–3.1) 3.0 (2.3–3.8)	Age, centre, education, smoking	Looked at pharynx also [a] Reference was new drinkers
De Stefani *et al.* (2007), Montevideo, Uruguay, 1988–2000	335 men identified in the four major hospitals in Montevideo; microscopically confirmed; response rate, 97%	1501 male hospital-based non-cancer controls; excluded patients with alcohol- and tobacco-related conditions with no recent changes in diet; response rate, 97%	Interviewer-administered questionnaire in hospital	Oral cavity (excluding lip)	*Total alcohol* Never drinkers 1–60 mL 61–120 mL 121–240 mL ≥241 mL *p* for trend	 34 47 91 86 77	 1.0 (reference) 1.2 (0.8–2.0) 4.3 (2.7–6.8) 4.9 (3.1–7.9) 7.0 (4.2–11.5) <0.0001	Age, residence, urban/rural status, hospital, year of diagnosis, education, family history of cancer, occupation, vegetable and fruit consumption, maté intake, smoking	Looked at pharynx also; looked at type of alcoholic beverage and joint effects with smoking

CI, confidence interval; ICD, International Classification of Diseases

across different geographical regions and populations, which further supports the key role of alcoholic beverage consumption in oral and pharyngeal carcinogenesis.

(b) Cancer of the pharynx (Table 2.4)

Among nine case–control studies of cancer of the pharynx, three were population-based (Tuyns *et al*., 1988; Nam *et al*., 1992; Cheng *et al*., 1999) and six were hospital-based (Franceschi *et al*., 1990; Choi & Kahyo, 1991a; Maier *et al*., 1994; Znaor *et al*., 2003; De Stefani *et al*., 2004, 2007). All studies adjusted for or were stratified by tobacco smoking. Results from all of the studies showed a strong association with alcoholic beverage consumption, except for one study of nasopharyngeal cancer in Taiwan, China (Cheng *et al*., 1999).

Alcoholic beverage consumption was associated with an increase in risk for cancers of the oropharynx and hypopharynx across different geographical regions and populations and the point estimates of adjusted odds ratios ranged from 3.6 to 125.2. Furthermore, all studies but one (Cheng *et al*., 1999) observed a strong dose–response trend between alcoholic beverage consumption and risk for oro- and hypopharyngeal cancer. A possible explanation for the lack of association in the study from Taiwan may be the categorization of exposure: the highest exposure group contained people who consumed ≥15 g (equivalent to just over one drink) per day, which may be too low a level to detect an association.

(c) Cancer of the oral cavity and pharynx combined (Table 2.5)

A total of 19 studies of cancer of the oral cavity and pharyngeal cancer combined were identified (Blot *et al*., 1988; Merletti *et al*., 1989; Barra *et al*., 1990, 1991; Maier *et al*., 1992a; Marshall *et al*., 1992; Mashberg *et al*., 1993; Kabat *et al*., 1994; Sanderson *et al*., 1997; Hayes *et al*., 1999; Franceschi *et al*., 2000; Garrote *et al*., 2001; Schwartz *et al*., 2001; Altieri *et al*., 2004; Castellsagué *et al*., 2004; Llewellyn *et al*., 2004a,b; Rodriguez *et al*., 2004; Shiu & Chen, 2004). Six were population-based (Blot *et al*., 1988; Merletti *et al*., 1989; Marshall *et al*., 1992; Sanderson *et al*., 1997; Hayes *et al*., 1999; Schwartz *et al*., 2001) and the rest were hospital-based. Tobacco smoking was considered as a potential confounding factor in almost all of the studies. Seventeen studies reported a strong association, with a dose–response trend, between alcoholic beverage consumption and cancers of the oral cavity and pharynx and two reported an increased risk, but the 95% CIs included a null value (Merletti *et al*., 1989; Llewellyn *et al*., 2004b).

An increase in risk for cancers of the oral cavity and pharynx has been observed in most studies across different geographical regions and populations and the point estimates of adjusted odds ratios ranged from 4.1 to 8.8 for heavy consumption of alcoholic beverages when adjusted for tobacco smoking and other confounding factors. The lack of significant associations in two studies (Merletti *et al*., 1989; Llewellyn *et al*., 2004b) may be explained by small sample size (86 male and 36 female cases in the former and

Table 2.4 Case–control studies of pharyngeal cancer and alcoholic beverage consumption

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	OR (95% CI)	Adjustment factors	Comments
Tuyns *et al.* (1988), France, Italy, Spain, Switzerland, 1980–83	281 men from Calvados (France), Turin and Varese (Italy), Navarra and Zaragoza (Spain), Geneva (Switzerland); histologically confirmed; response rate, 75% (Spain, Italy), 92% (Geneva)	3057 men stratified by age from census lists, electoral lists, or population registries; response rate, 75% (64% in Geneva, 56% in Turin)	Interviewer-administered questionnaire	Hypopharynx (ICD9 148.0, 148.1, 148.3, 149.8)	*Total alcohol* 0–20 g/day 21–40 g/day 41–80 g/day 81–120 g/day ≥121 g/day	 NG NG NG NG NG	 1.0 (reference) 1.6 (0.7–3.4) 3.2 (1.6–6.2) 5.6 (2.8–11.2) 12.5 (6.3–25.0)	Age, place, age/place interaction, cigarettes/day	Looked at joint effects with smoking
Franceschi *et al.* (1990), Milan, Pordenone, Italy, 1986-89	134 men, under age 75 years; histologically confirmed; response rate, 98% overall	1272 male hospital-based non-cancer patients from same hospitals as cases matched on age, area of residence; excluded patients with alcohol- and tobacco-related conditions; response rate, 97%	Interviewer-administered questionnaire	Pharynx, hypopharynx/larynx junction included (ICD9 146, 148, 161.1)	*Total alcohol* ≤19 drinks/week 20–34 drinks/week 35–59 drinks/week ≥60 drinks/week *p* for trend	 13 14 34 73	 1.0 (reference) 0.9 (0.4–2.0) 1.5 (0.8–3.1) 3.6 (1.8–7.2) 0.01	Age, area of residence, education, occupation, smoking habits	Also looked at oral cancers; looked at type of alcoholic beverage and joint effects with smoking

Table 2.4 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	OR (95% CI)	Adjustment factors	Comments
Choi & Kahyo (1991a), Seoul, Republic of Korea, 1986–89	152 cases (133 men, 19 women) from the Korea Cancer Centre Hospital; cytological and/or histopathological confirmation	456 (399 men, 57 women) hospital-based non-cancer patients from same hospital matched (3 controls per case) on age, sex, admission date; excluded patients with alcohol- and tobacco-related conditions	Interviewer-administered questionnaire	Pharynx (ICDO 146–149)	**Men only** *Total alcohol*[a] Non-drinker <1 hop/day 1–2 hops/day 2–4 hops/day >4 hops/day	 16 20 44 40 13	 1.0 (reference) 1.2 (0.6–2.5) 2.2 (1.1–4.2 4.1 (2.1–7.9) 11.2 (4.2–29.8)	Smoking	Looked at oral cavity also; [a]1 hop = 90 mL of soju [generally 20% alcohol, 14 g ethanol]; soju is most frequent alcoholic beverage type

Table 2.4 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	OR (95% CI)	Adjustment factors	Comments
Nam *et al.* (1992), USA, 1986	204 (141 men, 63 women) whites from the National Mortality Followback Survey who died of NPC, age <65 years; overall response rate, 89% for whole study population	408 (282 men, 126 women) randomly selected (2:1 controls:cases) whites from the same survey matched on age, sex; died from causes unrelated to smoking or alcoholic beverage use	Questionnaire from next of kin	Nasopharynx	*Total alcohol*			Smoking, sex	Looked at joint effects with smoking
					0–3 drinks/week	107	1.0 (reference)	None	
					4–23 drinks/week	40	0.9 (0.5–1.4)	None	
					≥24 drinks/week	57	1.8 (1.1–3.1)		
					Men only				
					Total alcohol				
					0–3 drinks/week	64	1.0 (reference)		
					4–23 drinks/week	32	1.1 (0.6–1.8)		
					≥24 drinks/week	45	1.9 (1.1–3.2)		
					p for trend		0.007		
					Women only				
					Total alcohol				
					0–3 drinks/week	43	1.0 (reference)		
					4–23 drinks/week	8	1.2 (0.4–3.1)		
					≥24 drinks/week	12	7.3 (2.1–32.5)		
					p for trend		<0.001		

Table 2.4 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	OR (95% CI)	Adjustment factors	Comments
Maier *et al.* (1994), Heidelberg, Germany, 1990–91	105 men from the Otorhinolaryngology-Head and Neck Surgery Department of the University of Heidelberg; histologically confirmed	420 male outpatients without known cancer from the same centre as cases matched (4:1 controls:cases) on age, residential area	Interviewer-administered standardized questionnaire	Oropharynx, hypopharynx	*Total alcohol* <25 g/day 25–50 g/day 50–75 g/day 75–100 g/day >100 g/day *p* for trend	 11 17 22 20 35	 1.0 (reference) 3.5 (1.4–8.6) 12.9 (4.7–35.6) 54.7 (13.5–221.0) 125.2 (28.4–551.6) 0.0001	Tobacco smoking	Beer preferred alcoholic beverage in this area
Cheng *et al.* (1999), Taipei, Taiwan, China, 1991–94	375 cases (260 men, 115 women) from two teaching hospitals in Taipei; histologically confirmed; response rate, 99%	327 (223 men, 104 women) population controls with no history of NPC using the National Household Registration System individually matched on age, sex, residence; response rate, 88%	Interviewer-administered structured questionnaire	Nasopharynx	*Total alcohol (in g ethanol/day)* 0 <15 ≥15 *p* for trend	 270 47 57	 1.0 (reference) 0.7 (0.5–1.2) 1.1 (0.7–1.7) 0.9	Age, sex, race, education, family history of NPC, smoking	
Znaor *et al.* (2003), Chennai, Trivandrum, India, 1993–99	636 men from the Cancer Institute (Chennai) and the Regional Cancer Center (Trivandrum); histologically confirmed	1711 male patients with non-tobacco-related cancers from same centres as cases and 1927 healthy male hospital visitors from Chennai only	Interviewer-administered questionnaire	Pharynx (ICD9 146, 148, 149)	*Total alcohol, average amount of ethanol*[a] Never drinker <20 mL/day 20–50 mL/day >50 mL/day	 297 70 106 162	 1.0 (reference) 1.1 (0.8–1.5) 2.3 (1.7–3.2) 3.6 (2.7–4.8)	Age, centre, education, smoking	Looked at oral cavity also [a] Reference category was new drinkers

Table 2.4 (continued)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	OR (95% CI)	Adjustment factors	Comments
De Stefani *et al.* (2004), Montevideo, Uruguay, 1997–2003	85 men identified in the four major hospitals in Montevideo; microscopically confirmed; response rate, 97.5%	640 hospital-based men from the same hospitals as cases; excluded patients with alcohol- and tobacco-related conditions with no recent changes in diet; frequency matched (2:1 controls:cases) on age, residence; response rate, 97%	Interviewer-administered questionnaire	Hypopharynx	*Total alcohol (in mL ethanol/day)* Never drinkers 1–60 61–120 121–240 ≥241 *p* for trend	 191 175 116 88 70	 1.0 (reference) 2.3 (0.7–8.1) 7.6 (2.3–24.4) 5.6 (1.7–18.6) 12.8 (4.0–41.2) <0.0001	Age, residence, urban/rural status, education, smoking, body mass index	Looked at cessation of alcoholic beverages, type of alcoholic beverages and joint effects with smoking
De Stefani *et al.* (2007), Montevideo, Uruguay, 1988–2000	441 men identified in the four major hospitals in Montevideo; microscopically confirmed; response rate, 97%	1501 male hospital-based non-cancer controls; excluded patients with alcohol- and tobacco-related conditions with no recent changes in diet; response rate, 97%	Interviewer-administered questionnaire in hospital	Pharynx (excluding nasopharynx)	*Total alcohol (in mL ethanol/day)* Never drinkers 1–60 61–120 121–240 ≥241 *p* for trend	 33 53 97 136 122	 1.0 (reference) 1.4 (0.9–2.2) 4.4 (2.8–7.0) 7.9 (5.0–12.3) 11.7 (7.2–18.9) <0.0001	Age, residence, urban/rural status, hospital, year of diagnosis, education, family history of cancer, occupation, vegetable and fruit consumption, maté intake, smoking	Looked at oral cavity also; looked at type of alcoholic beverages and joint effects with smoking

CI, confidence interval; ICD, International Classification of Diseases; NPC, nasopharyngeal carcinoma

Table 2.5 Case–control studies of cancers of the oral cavity and pharynx combined and alcoholic beverage consumption

Reference, study location, period	Characteristics of study population	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Odds ratio (95% CI)	Adjustment factors	Comments
Blot *et al.* (1988), USA, 1984–85	1114 (762 men, 352 women) cases; identified from the population-based registries covering metropolitan Atlanta (GA), Los Angeles, Santa Clara, San Mateo counties (CA), New Jersey; aged 18–79 years; pathologically confirmed; response rate, 75%; 1268 population controls	Interviewer-administered standardized questionnaire	Oral cavity, pharynx (ICD9 141, 143–146, 148, 149), excluding salivary gland, nasopharynx	**Men** *Hard liquor* <1 drink/week 1–4 drinks/week 5–14 drinks/week 15–29 drinks/week ≥30 drinks/week *Beer* <1 drink/week 1–4 drinks/week 5–14 drinks/week 15–29 drinks/week ≥30 drinks/week *Wine* <1 drink/week 1–4 drinks/week 5–14 drinks/week 15–29 drinks/week ≥30 drinks/week	 40 71 99 154 389 146 130 141 134 195 497 114 70 31 35	 1 (reference) 1.0 (0.7–1.3) 1.3 (0.9–1.8) 2.6 (1.7–3.9) 5.5 (3.4–9.1) 1 (reference) 1.2 (0.8–1.7) 1.7 (1.2–2.4) 3.4 (2.7–5.1) 4.7 (3.0–7.3) 1 (reference) 0.7 (0.5–1.0) 0.7 (0.4–1.0) 0.9 (0.5–1.8) 2.5 (0.9–6.5)	Age, race, study location, respondent status (self versus proxy), tobacco smoking, other two types of alcoholic beverages	

Table 2.5 (continued)

Reference, study location, period	Characteristics of study population	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Odds ratio (95% CI)	Adjustment factors	Comments
Blot *et al.* (1988) (contd)	1268 population controls from random-digit dialling; aged 18–64 years, frequency-matched on age, sex, race (black, white); response rate, 79% (under 65 years) and 76% (≥ 65 years)			**Women**				
				Hard liquor		1 (reference)		
				<1 drink/week	135	1.3 (0.9–2.1)		
				1–4 drinks/week	78	1.5 (0.9–2.5)		
				5–14 drinks/ week	65	4.9 (1.6–14.3) 7.8 (2.1–29.2)		
				15–29 drinks/ week	32	1 (reference) 2.2 (1.4–3.6)		
				≥30 drinks/week	41	2.9 (1.5–5.6)		
				Beer		2.3(0.9–6.5)		
				<1 drink/week	180	18.0 (2.1–159)		
				1–4 drinks/week	73	1 (reference)		
				5–14 drinks/ week	48	0.6 (0.4–1.0) 0.8 (0.4–-1.4)		
				15–29 drinks/ week	24	0.5 (0.1–2.3) 1.6 (0.2–13.6)		
				≥30 drinks/week	27			
				Wine				
				<1 drink/week	230			
				1–4 drinks/week	60			
				5–14 drinks/ week	41			
				15–29 drinks/ week	1			
				≥30 drinks/week	7			

Table 2.5 (continued)

Reference, study location, period	Characteristics of study population	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Odds ratio (95% CI)	Adjustment factors	Comments
Merletti *et al.* (1989) Torino, Italy, 1982–84	122 cases (86 men, 36 women); histologically confirmed; response rate, 85% 606 (385 men, 221 women) population-based controls, randomly selected from files of residents, stratified by age, sex; response rate, 55%	Interviewer-administered standardized questionnaire	Oral cavity, oropharynx (ICD9 140.3–140.5, 141, 143–146)	**Total alcohol** *Men* 1–20 g/day 21–40 g/day 41–80 g/day 81–120 g/day >120 g/day *Women* 1–20 g/day 21–40 g/day >40 g/day	 8 9 29 14 22 6 13 12	 1.0 (reference) 0.7 (0.2–2.6) 1.3 (0.4–3.8) 0.6 (0.2–2.1) 2.1 (0.6–6.8) 1.0 (reference) 3.0 (0.9–10.5) 3.4 (0.9–12.9)	Age, education, area of birth, tobacco habits	Looked at type of alcoholic beverage and joint effect of smoking
Barra *et al.* (1990), Milan, Pordenone, Italy, 1986–90	305 men from hospitals in Pordenone and Milan; median age, 58 years; histologically confirmed; refusal rate, 2% 1621 men, hospital-based non-cancer patients; median age, 57 years; matched by area of residence, age; excluded patients with alcohol- and tobacco-related conditions; refusal rate, 3%	Interviewer-administered questionnaire in hospital	Oral cavity, pharynx	*Total alcohol* ≤20 drinks/week 21–55 drinks/week 56–83 drinks/week ≥84 drinks/week	 17 5 12 41	 1 (reference) 0.8 (0.3–2.3) 1.8 (0.8–4.4) 4.1 (2.0–8.2)	Age, area of residence, occupation, tobacco smoking	Includes study population from Franceschi *et al.* (1990); looked at types of alcoholic beverage

Table 2.5 (continued)

Reference, study location, period	Characteristics of study population	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Odds ratio (95% CI)	Adjustment factors	Comments
Barra *et al.* (1991), Pordenone, Italy, 1985–90	272 (236 men, 36 women) cases from hospitals in Pordenone; median age, 60 years; histologically confirmed; refusal rate, 3% 1884 (1122 men, 762 women) non-cancer, hospital-based patients; median age, 58 years; matched by area of residence, age; excluded patients with alcohol- and tobacco-related conditions; refusal rate, 3%	Interviewer-administered questionnaire in hospital	Oral cavity, pharynx	*Total alcohol* ≤20 drinks/week 21–34 drinks/week 35–55 drinks/week 56–83 drinks/week ≥84 drinks/week *p* for trend	 24 28 21 31 83 106	Non-cancer controls 1.0 (reference) 2.2 (1.2–4.0) 2.4 (1.2–4.7) 6.6 (3.5–12.5) 11.4 (6.0–21.4) ≤ 0.01	Age, sex, education, occupation, tobacco	Includes study population from Barra *et al.*(1990) study; also compared results with cancer control group with similar results; looked at types of alcoholic beverage

Table 2.5 (continued)

Reference, study location, period	Characteristics of study population	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Odds ratio (95% CI)	Adjustment factors	Comments
Maier *et al.* (1992a), Giessen & Heidelberg, Germany	200 male patients selected from ENT departments from University of Heidelberg and Giessen with squamous cells cancer of the head and neck; 800 male subjects without known cancer served as controls selected from out patients clinics	Interviewer-administered questionnaire	Head and neck	Total alcohol <25 g/day 25–50 g/day 50–75g/day 75–100 g/day >100 g/day		 1.0 (reference) 1.7 (1.0–2.7) 6.7 (3.9–11.3) 16.2 (7.1–36.8) 21.4 (11.2–40.6)	Tobacco	Females excluded due to low number of cases

Table 2.5 (continued)

Reference, study location, period	Characteristics of study population	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Odds ratio (95% CI)	Adjustment factors	Comments
Marshall *et al.* (1992), New York, USA, 1975–83	290 (201 men, 89 women) identified from pathology records of 20 major hospitals in Erie, Niagara, Monroe (New York); aged 45 years or younger; pathologically confirmed; response rate of those contacted, 60% 290 (201 men, 89 women) population-based individually matched on age, sex, neighborhood; response rate, 41%	Interviewer-administered standardized questionnaire	Oral cavity, pharynx	Quantity–frequency–duration derived quintiles 1 2 3 4 5 *p* for trend		 1 (reference) 2.4 (1.1–5.2) 2.7 (1.2–6.1) 3.4 (1.6–7.4) 14.8 (6.8–32.3) <0.0001		Black cases excluded from analysis

Table 2.5 (continued)

Reference, study location, period	Characteristics of study population	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Odds ratio (95% CI)	Adjustment factors	Comments
Mashberg *et al.* (1993) New Jersey, USA, 1972–83	359 white and black male veterans with invasive cancer and in-situ carcinoma identified in the Department of Veterans Affairs Medical Center; median age, 57 years; histologically confirmed 2280 white or black male patients from the same centre as cases of the same age range as cases (37–80 years); median age, 58 years; excluding patients with cancer or dysplasia of the pharynx, larynx, lung, oesophagus	Interviewer-administered standardized questionnaire	Oral cavity, oropharynx	*Total alcohol (in whiskey equiv./ day)*[a] Minimal drinking 2–5 per day 6–10 per day 11–21 per day ≥22 per day Former drinker (abstained ≥2 years)	 17 37 91 112 98 4	 1 (reference) 2.6 (1.4–4.7) 6.4 (3.7–11.0) 7.9 (4.6–13.4) 7.1 (4.1–12.2) 1.9 (0.6–5.7)	Age, race, tobacco smoking	Looked at type of alcoholic beverage and joint effects with smoking; 1 whiskey equivalent = 10.2 g alcohol

Table 2.5 (continued)

Reference, study location, period	Characteristics of study population	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Odds ratio (95% CI)	Adjustment factors	Comments
Kabat *et al.* (1994), USA, 1977–90	1560 (1097 men, 463 women) enrolled in 28 hospitals in eight US cities 2948 (2075 men, 873 women) hospital-based; matched on age, sex, race, hospital, date of interview	Interviewer-administered questionnaire	Oral cavity, pharynx (excluding nasopharynx)	*Total alcohol (whiskey equiv.)*		*Men*	Age, education, smoking, race, time period, type of hospital	Looked at type of alcoholic beverage and joint effects of smoking; 1 oz whiskey equivalent = 10.2 g alcohol
				Non-drinker	50	1		
				Occasional	142	1.4 (0.9–2.0)		
				1–2.9 oz/day	246	2.9 (2.0–4.2)		
				4–6.9 oz/day	169	4.7 (3.2–7.1)		
				≥7 oz/day	466	7.3 (5.1–10.7)		
Kabat *et al*. (1994) (contd)						*Women*		
				Non-drinker	123	1 (reference)		
				Occasional	130	1.2 (0.9–1.6)		
				1–3.9 oz/day	108	1.8 (1.3–2.6)		
				4–6.9 oz/day	98	4.8 (2.9–7.8)		
				≥7 oz/day	–	–		
Maier *et al.* (1994), Heidelberg, Giessen, Germany, 1987–88	200 men from the ENT departments of the Universities of Heidelberg and Giessen; histologically confirmed 800 male outpatients without known cancer; matched on age, residential area (4:1 controls:cases)	Interviewer-administered questionnaire	Oral cavity, pharynx, larynx	*Total alcohol*			Tobacco smoking	Beer preferred alcoholic beverage in the area; looked at joint effect of smoking
				<25 g/day		1 (reference)		
				25–50 g/day		1.7 (1.0–2.7)		
				50–75 g/day		6.7 (3.9–11.3)		
				75–100 g/day		16.2 (7.1–36.8)		
				>100 g/day		21.4 (11.2–40.6)		

Table 2.5 (continued)

Reference, study location, period	Characteristics of study population	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Odds ratio (95% CI)	Adjustment factors	Comments
Sanderson *et al.* (1997) Netherlands, 1980–90	303 women aged ≥40 years from the University Hospital's Head Cancer Centre 1779 women from a national survey by National Central Bureau of Statistics; matched on age	Hospital records (cases) and national survey (controls)	Oral cavity, oropharynx (excluding salivary glands and lip)	*Total alcohol* Non-drinker 1–5 units/day >5 units/day	 153 104 46	 1 (reference) 3.5 (2.5–4.8) 20.8 (11.4–37.8)	Age	Looked at joint effect of smoking
Hayes *et al.* (1999), Puerto Rico, 1992–95	342 (286 men, 56 women) identified through pathology laboratories and Central Cancer Registry; aged 21–79 years; histologically confirmed; response rate, 70% 521 (417 men, 104 women) population-based; frequency-matched by age, gender; response rate, 83%	Interviewer-administered questionnaire	Oral cavity, pharynx (ICD9 141–143–146, 148, 149)	*Total alcohol*[a] Non-drinker 1–7 drinks/week 8–21 drinks/week 22–42 drinks/week >42 drinks/week *p* for trend Non-drinker 1–7 drinks/week 8–21 drinks/week 22–42 drinks/week >42 drinks/week *p* for trend	 9 19 28 49 164 26 13 1 12 – 	*Men* 1 (reference) 0.8 (0.3–2.1) 1.4 (0.6–3.4) 3.3 (1.4–8.0) 7.7 (3.3–17.9) <0.0001 *Women* 1 (reference) 0.8 (0.3–2.1) 0.9 (0.0–17.0) 9.1 (0.9–94.2) – (–) 0.02	Age, tobacco use	Looked at cessation of alcoholic beverage consumption and joint effect of smoking

Table 2.5 (continued)

Reference, study location, period	Characteristics of study population	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Odds ratio (95% CI)	Adjustment factors	Comments
Franceschi *et al.* (2000), Italy, Switzerland, 1992–97	754 (638 men, 116 women) from major teaching and general hospitals in Pordenone, Rome, Latina (Italy) and Vaud (Switzerland); aged 22–77 years; histologically confirmed; response rate, 95% 1775 (1254 men, 521 women) hospital-based non-cancer from the same network of hospitals as cases; excluded tobacco- and alcohol-related conditions; frequency-matched (5:1 for women, 2:1 for men controls:cases) on age, sex, area of residence; response rate, 95%	Interviewer-administered questionnaire	Oral cavity, pharynx (excluding lip, salivary glands, nasopharynx)	*Total alcohol* Current drinkers Never 1–20 drinks/week 21–62 drinks/week 63–90 drinks/week ≥91 drinks/week χ^2 for trend	 32 82 271 145 98	 1 (reference) 0.7 (0.4–1.2) 2.6 (1.6–4.2) 8.9 (5.0–15.9) 16.7 (8.6–32.7) 160.5 $p < 0.001$	Age, sex, study centre, education, interviewer, tobacco smoking, drinking status	Study population from Franceschi *et al.* (1999); looked at alcoholic beverage consumption cessation

Table 2.5 (continued)

Reference, study location, period	Characteristics of study population	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Odds ratio (95% CI)	Adjustment factors	Comments
Garrote *et al.* (2001), Havana, Cuba, 1996–99	200 (143 men, 57 women) from the Instituto Nacional de Oncologia y Radiobiologia of Havana; age, 64 years; response rate, 88%. 200 (136 men, 64 women) hospital-based controls admitted to same hospital and three other major hospitals in Havana; excluded patients with alcohol- and tobacco-related conditions; frequency-matched on age, sex; median age, 62 years; response rate, 79%	Interviewer (dentist)-administered questionnaire	Oral cavity, oropharynx	*Total alcohol* Abstainers Former drinkers (abstained ≥12 months) *Current drinkers* <7 drinks/week 7–20 drinks/week 21–69 drinks/week ≥70 drinks/week χ^2 for trend	 83 36 15 25 21 20	 1 (reference) 1.04 (0.5-2.1) 1.1 (0.5–2.6) 1.6 (0.7–3.7) 2.2 (0.9–5.5) 5.7 (1.8–18.5) 8.75 p <0.01	Age, sex, area of residence, education, tobacco smoking	Looked at cessation, type of alcoholic beverage and joint effect of smoking

Table 2.5 (continued)

Reference, study location, period	Characteristics of study population	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Odds ratio (95% CI)	Adjustment factors	Comments
Schwartz *et al.* (2001), Washington, USA, 1985–95	333 (237 men, 96 women) in-situ and invasive cancers ascertained through the population-based Cancer Surveillance System (participant of SEER); aged 18–65 years from two original studies; response rates, 54% and 63%. 541 (387 men, 154 women) population-based; frequency-matched on age, sex; response rates, 63% and 61%	Interviewer-administered structured questionnaire	Oral cavity, oropharynx (excluding lip)	*Total alcohol* <1 drink/week 1–7 drinks/week 8–14 drinks/week 15–42 drinks/week ≥43 drinks/week		1 (reference) 1.0 (0.6–1.5) 1.7 (1.0–2.9) 2.8 (1.7–4.8) 4.7 (2.4–9.4)	Age, sex, race, tobacco smoking	Looked at joint effect of smoking and *ADH3*

Table 2.5 (continued)

Reference, study location, period	Characteristics of study population	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Odds ratio (95% CI)	Adjustment factors	Comments
Altieri *et al.* (2004), Italy, Switzerland, 1992–97	749 (634 men, 115 women) from Pordenone, Rome, Latina (Italy) and Vaud (Switzerland) admitted to major teaching and general hospitals in area under surveillance; aged 22–77 years; histologically confirmed 1772 (1252 men, 520 women) hospital-based from the same network of hospitals as cases; aged 20–78 years; excluded patients with alcohol- and tobacco-related conditions	Interview-administered structured questionnaire	Oral cavity, pharynx	*Total alcohol* Non-drinkers 1–2 drinks/day 3–4 drinks/day 5–7 drinks/day 8–11 drinks/day ≥12 drinks/day χ^2 for trend	 33 93 95 132 199 196	 – 1 (reference) 2.1 (1.5–2.9) 5.0 (3.5–7.1) 12.2 (8.4–17.6) 21.1 (14.0–31.8) 272.07 p<0.0001	Age, sex, study centre, education, tobacco smoking	

Table 2.5 (continued)

Reference, study location, period	Characteristics of study population	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Odds ratio (95% CI)	Adjustment factors	Comments
Castellsagué *et al.* (2004), Spain, 1996–99	375 (304 men, 71 women) identified from hospitals in Granada, Sevilla, Barcelona; mean age, 60 years; histologically confirmed; response rate, 76.5% 375 (304 men, 71 women) non-cancer hospital-based from same hospitals as cases; frequency-matched on age, sex; mean age, 60 years; excluded patients with alcohol- and tobacco-related diagnoses; response rate, 91%	Interviewer-administered standardized questionnaire in hospital	Oral cavity, oropharynx (ICDO C1-C10)	*Average no. of drinks/day* Never drinker 1 2 3–4 5–6 7–10 ≥11 *p* for trend	 35 59 27 49 55 68 82	 1 (reference) 2.0 (1.1–3.8) 3.7 (1.6–8.6) 6.2 (2.8–13.7) 10.6 (4.6–24.5) 10.3 (4.6–23.2) 13.7 (6.0–31.0) <0.0001	Age group, sex, education, tobacco smoking, centre	Looked at type of alcoholic beverage and joint effect of smoking

Table 2.5 (continued)

Reference, study location, period	Characteristics of study population	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Odds ratio (95% CI)	Adjustment factors	Comments
Llewellyn *et al.* (2004a), United Kingdom, 1999–2001	53 (28 men, 25 women) from 14 participating hospitals in the Southeast of England; aged ≤ 45 years; response rate, 80% 91 (45 men, 46 women) non-cancer patients; matched (2:1 controls:cases when feasible) on age, sex, area of residence	Interviewer-administered standardized questionnaire and self-completed questionnaire	Oral cavity, oropharynx (ICD-10 C00-C06, C0, C10)	**Total alcohol** *Men* Within recommended levels[a] Over recommended levels *Women* Within recommended levels[a] Over recommended levels		 1 (reference) 8.1 (1.6–40.1) 1 (reference) 3.8 (0.7–20.7)	Social class, race, ever smoking (matching variables: age, sex, area of residence)	[a]Recommended levels: for men, ≤21 units/ week; for women, ≤14 units/ week
Llewellyn *et al.* (2004b), United Kingdom, 1990–97	116 (65 men, 51 women) identified by the Thames Cancer Registry; aged ≤ 45 years; response rate, 59% 207 (112 men, 95 women) non-cancer patients; matched (2:1 controls:cases when feasible) on age, sex, area of residence	Self-completed questionnaire	Oral cavity, oropharynx (ICD-10 C00-C06, C0, C10)	**Total alcohol** *Men* Within recommended levels[a] Over recommended levels *Women* Within recommended levels[a] Over recommended levels		 1 (reference) 1.6 (0.8–3.1) 1 (reference) 1.6 (0.6–4.2)	Social class, race, ever smoking (matching variables: age, sex, area of residence)	[a]Recommended levels : for men, ≤21 units/ week; for women, ≤14 units/ week

Table 2.5 (continued)

Reference, study location, period	Characteristics of study population	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Odds ratio (95% CI)	Adjustment factors	Comments
Rodriguez *et al.* (2004), Italy, Switzerland, 1984–93, 1992–97	137 (113 men, 24 women) from Milan and Pordenone, Italy (1984–93) and Vaud, Switzerland (1992–97), under age 46 years; histologically confirmed; response rate, 95%. 298 (226 men, 72 women) non-cancer hospital-based; matched 2:1 (control:case) for men and 3:1 for women on age, sex, study centre; below age 46 years; excluded patients with alcohol- and tobacco-related conditions; response rate, 95%	Interviewer-administered questionnaire	Oral cavity, pharynx	*Total alcohol* Non-drinkers <3 drinks/day 3–<6 drinks/day 6–<10 drinks/day ≥10 drinks/day χ^2 for trend	 13 20 19 37 46	 1 (reference) 0.7 (0.3–1.8) 1.0 (0.4–2.8) 3.7 (1.2–11.1) 4.9 (1.6–15.1) 17.5 p<0.0001	Age, sex, study centre, education, marital status, body mass index, tobacco smoking, coffee consumption	Study populations from Franceschi *et al.* (1990, 2000)

Table 2.5 (continued)

Reference, study location, period	Characteristics of study population	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Odds ratio (95% CI)	Adjustment factors	Comments
Shiu & Chen (2004), Taipei, Taiwan, 1988–98	74 (71 men, 3 women) randomly selected from 1688 cancers identified at a medical centre; response rate, 74% 187 patients with periodontal disease free of leukoplakia and oral cancer, randomly selected from 25 882 patients; response rate, 94%	Interviewer-administered questionnaire	Oral cavity, pharynx (140–149, except 142 and 147)	**Total alcohol** *Leukoplakia versus normal* No Yes *Oral cancer versus leukoplakia* No Yes		 1 (reference) 0.76 (0.4–1.4) 1 (reference) 2.37 (1.5–3.8)	Tobacco smoking, betel-quid chewing	

ADH3, alcohol dehydrogenase 3 gene; CI, confidence interval; ICD, International Classification of Diseases; SEER, Surveillance, Epidemiology and End Result

65 male and 51 female cases in the latter), which limits the power to detect an association, as well as the inclusion of light drinkers in the baseline comparison group (1–20 g per day in the former and within the recommended level in the latter).

2.2.3 *Types of alcoholic beverage (Table 2.6)*

In a study not described previously, Schildt *et al*. (1998) investigated the effects of snuff, smoking and alcoholic beverage consumption on the risk for cancer of the oral cavity. Among 354 histologically confirmed cases reported to the Cancer Registry from Norrbotten, Vasterbotten, Jamtland and Vasternorrland, Sweden, between 1980 and 1989 and 354 individually matched population controls, beer and liquor were found to be the types of alcoholic beverage associated with a higher risk (odds ratio for beer, 1.5; 95% CI, 0.7–3.2; odds ratio for liquor, 1.5; 95% CI, 0.9–2.3) in a model that contained snuff, smoking and the other types of alcohol. Self-completed questionnaires were completed by proxies for 60% of the participants.

Assessment of risk associated with different types of alcoholic beverage is a difficult task; drinkers rarely consume only one type of alcoholic beverage, and isolating the effects of a single type in the presence of the other types is not easy to accomplish. Furthermore, heterogeneity of effects across different populations further complicates the interpretation of results. Overall, among studies in the USA, the ranking from highest to lowest risk by alcoholic beverage type is beer, hard liquor and wine (Blot *et al*., 1988; Mashberg *et al*., 1993; Day *et al*., 1994b; Kabat *et al*., 1994). Among the Italian studies, the highest risk was associated with wine consumption (Franceschi *et al*., 1990). In Latin America, hard liquor was associated with the highest risk among Cuban (Garrote *et al*., 2001) and Brazilian populations (Schlecht *et al*., 2001), and wine was associated with the highest risk among Uruguayans (De Stefani *et al*., 2004). In several studies, the other types of alcoholic beverage were not controlled for in the analyses which may distort the association under study. Generally, the types of alcoholic beverage that are the largest contributors to alcoholic beverage consumption are usually associated with the greatest increases in risk.

2.2.4 *Joint effects (Table 2.7)*

The joint effects of alcoholic beverage consumption and tobacco smoking on cancers of the oral cavity and pharynx have been assessed extensively. The studies varied in their methods and in the approaches used to assess effect modification, which ranged from descriptive to formal estimation of interaction in multivariate models.

For cancers of the oral cavity and pharynx, the evidence comes almost entirely from case–control studies carried out in Asia, Australia, Europe and the USA. Two prospective cohort studies have reported joint effects of alcoholic beverage consumption and tobacco smoking including the European Prospective Investigation into Cancer and Nutrition (EPIC) study (Boeing, 2002) and a cohort study of Japanese men (Chyou

Table 2.6 Consumption of different types of alcoholic beverage and incidence of cancers of the oral cavity and pharynx

Reference, study location, period	Characteristics of study population	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment factors	Comments
Blot *et al.* (1988), USA, 1984–85	1114 (762 men, 352 women) cases; identified from the population-based registries covering metropolitan Atlanta (GA), Los Angeles, Santa Clara, San Mateo counties (CA), New Jersey; aged 18–79 years; pathologically confirmed; response rate, 75%; 1268 population controls	Interviewer-administered standardized questionnaire	Oral cavity, pharynx (ICD9 141, 143–146, 148, 149), excluding salivary gland and nasopharynx	**Men** *Hard liquor* <1 drink/week 1–4 drinks/week 5–14 drinks/week 15–29 drinks/week ≥30 drinks/week *Beer* <1 drink/week 1–4 drinks/week 5–14 drinks/week 15–29 drinks/week ≥30 drinks/week *Wine* <1 drink/week 1–4 drinks/week 5–14 drinks/week 15–29 drinks/week ≥30 drinks/week	 40 71 99 154 389 146 130 141 134 195 497 114 70 31 35	 1 (reference) 1.0 (0.7–1.3) 1.3 (0.9–1.8) 2.6 (1.7–3.9) 5.5 (3.4–9.1) 1 (reference) 1.2 (0.8–1.7) 1.7 (1.2–2.4) 3.4 (2.7–5.1) 4.7 (3.0–7.3) 1 (reference) 0.7 (0.5–1.0) 0.7 (0.4–1.0) 0.9 (0.5–1.8) 2.5 (0.9–6.5)	Age, race, study location, respondent status (self versus proxy), tobacco smoking, other two types of alcoholic beverage	

Table 2.6 (continued)

Reference, study location, period	Characteristics of study population	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment factors	Comments
Blot *et al*. (1988) (contd)	Population controls from random-digit dialling; aged 18–64 years; frequency-matched on age, sex, race (black, white); response rate, 79% (under 65 years) and 76% (≥65 years)			**Women**				
				Hard liquor				
				<1 drink/week	135	1 (reference)		
				1–4 drinks/week	78	1.3 (0.9–2.1)		
				5–14 drinks/week	65	1.5 (0.9–2.5)		
				15–29 drinks/week	32	4.9 (1.6–14.3)		
				≥30 drinks/week	41	7.8 (2.1–29.2)		
				Beer				
				<1 drink/week	180	1 (reference)		
				1–4 drinks/week	73	2.2 (1.4–3.6)		
				5–14 drinks/week	48	2.9 (1.5–5.6)		
				15–29 drinks/week	24	2.3 (0.9–6.5)		
				≥30 drinks/week	27	18.0 (2.1–159)		
				Wine				
				<1 drink/week	230	1 (reference)		
				1–4 drinks/week	60	0.6 (0.4–1.0)		
				5–14 drinks/week	41	0.8 (0.4–-1.4)		
				15–29 drinks/week	1	0.5 (0.1–2.3)		
				≥30 drinks/week	7	1.6 (0.2–13.6)		

Table 2.6 (continued)

Reference, study location, period	Characteristics of study population	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment factors	Comments
Merletti *et al.* (1989), Torino, Italy, 1982–84	122 (86 men, 36 women) cases; histologically confirmed; response rate, 85%. 606 (385 men, 221 women) population-based controls randomly selected from files of residents; stratified by age, sex; response rate, 55%	Interviewer-administered questionnaire	Oral cavity, oropharynx (ICD9 140.3–140.5, 141, 143–146)	Wine only Beer Aperitifs Liquor Wine only Beer Aperitifs Liquor		**Men** 1 (reference) 2.1 (1.1–4.0) 1.4 (0.7–2.6) 0.7 (0.4–1.4) **Women** 1 (reference) 6.1 (1.4–26.5) 0.4 (0.1–1.7) 0.8 (0.3–2.3)	Age, education, area of birth, smoking habits, alcoholic beverage consumption	

Table 2.6 (continued)

Reference, study location, period	Characteristics of study population	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment factors	Comments
Barra *et al.* (1990), Milan, Pordenone, Italy, 1986–90	305 cases (all men); median age, 58 years; histologically confirmed; refusal rate, 2% 1621 (all men) hospital-based controls; median age, 57 years; matched by area of residence, age; excluded patients with alcohol- and tobacco-related conditions; refusal rate, 3%	Interviewer-administered standardized questionnaire	Oral cavity, pharynx	*Wine only* ≤20 glasses wine/week 21–55 drinks/week 56–83 drinks/week ≥84 drinks/week *Wine and beer* ≤20 glasses wine/wk 21–55 drinks/week 56–83 drinks/week ≥84 drinks/week *Wine and spirits* ≤20 glasses wine/wk 21–55 drinks/week 56–83 drinks/week ≥84 drinks/week	 17 44 48 14 17 3 13 21 17 13 34 32	 1 1.9 (1.0–3.4) 7.3 (3.8–14.1) 11.2 (3.8–33.1) 1 0.7 (0.2–2.5) 3.9 (1.6–9.6) 7.4 (3.2–17.3) 1 1.1 (0.5–2.4) 3.5 (1.7–6.9) 9.9 (4.3–22.7)	Age, area of residence, occupation, smoking and drinking habits	Includes study population from Franceschi *et al.* (1990); area of very high wine intake

Table 2.6 (continued)

Reference, study location, period	Characteristics of study population	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment factors	Comments
Franceschi *et al.* (1990), Milan, Pordenone, Italy, 1986–89	157 male cases; below age 75 years; histologically confirmed; response rate, 98% 1272 hospital-based non-cancer male controls from same hospitals as cases, matched on age, area of residence; excluded patients with alcohol- and tobacco-related conditions; response rate, 97%	Interviewer-administered questionnaire	Oral cavity (ICD9 140, 141, 143–145)	*Wine (glasses/week)*			Age, area of residence, education, occupation, smoking habits	Study population from Barra *et al.* (1990); area of very high wine intake
				0–6	12			
				7–20	6	1		
				21–34	20	1.1 (0.5–2.3)		
				35–55	27	1.9 (0.9–3.7)		
				56–83	68	4.9 (2.6–9.5)		
				≥84	24	8.5 (3.6–20.2)		
				χ^2 for trend		47.68 (p<0.01)		
				Beer (glasses/week)				
				0	111	1		
				1–13	20	1.0 (0.6–1.8)		
				≥14	26	0.8 (0.5–1.4)		
				χ^2 for trend		0.30 (NS)		
				Hard liquor (glasses/week)				
				0	91	1		
				1–6	19	0.7 (0.4–1.3)		
				≥7	47	0.9 (0.6–1.3)		
				χ^2 for trend		0.66 (NS)		

Table 2.6 (continued)

Reference, study location, period	Characteristics of study population	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment factors	Comments
Franceschi *et al.* (1990) (contd)	134 male cases, below age 75 years; histologically confirmed; response rate, 98%		Pharynx (ICD9 146, 148, 161.1)	*Wine (glasses/week)*				
				0–6	9			
				7–20	6	1		
				21–34	16	0.7 (0.3–1.6)		
				35–55	28	1.9 (0.9–3.7)		
				56–83	45	3.1 (1.6–6.1)		
				≥84	30	10.9 (4.7–25.3)		
				χ^2 for trend		46.44 (p<0.01)		
				Beer (glasses/week)				
				0	94	1		
				1–13	11	0.5 (0.3–1.0)		
				≥14	28	0.9 (0.5–1.5)		
				χ^2 for trend		0.47 (NS)		
				Hard liquor (glasses/ week)				
				0	73	1		
				1–6	10	0.4 (0.2–0.9)		
				≥7	51	1.2 (0.8–1.8)		
				χ^2 for trend		0.24 (NS)		

Table 2.6 (continued)

Reference, study location, period	Characteristics of study population	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment factors	Comments
Zheng *et al.* (1990), Beijing, China, 1988–89	404 (248 men, 156 women) cases diagnosed at seven participating hospitals in the Beijing area; histologically confirmed; response rate, 100%; 404 randomly selected non-cancer hospital-based controls; individually matched on age, sex, hospital; response rate, 100%.	Interviewer-administered questionnaire	Oral cavity (ICD9 141, 143-145)	*Type of alcohol* None Spirits only Beer/wine only Mixed	 83 144 7 14	 1 1.5 (0.9–2.3) 1.0 (0.3–3.1) 1.1 (0.5–2.8)	Age, sex, education, smoking	Most alcoholic beverages in study population were consumed in form of spirits.

Table 2.6 (continued)

Reference, study location, period	Characteristics of study population	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment factors	Comments
Barra *et al.* (1991), Pordenone, Italy, 1985–90	272 (236 men, 36 women) cases; median age, 60 years; histologically confirmed; refusal rate, 3% 1884 (1122 men, 762 women) non-cancer, hospital-based controls; median age, 58 years; matched by area of residence, age; excluded patients with alcohol- and tobacco-related conditions; refusal rate, 3%	Interviewer-administered standardized questionnaire	Oral cavity, pharynx	*Wine* ≤20 drinks/week 21–34 drinks/week 35–55 drinks/week 56–83 drinks/week ≥84 drinks/week χ^2 for trend *Beer* 0 drink/week 1–13 drinks/week ≥14 drinks/week χ^2 for trend *Spirits* 0 drink/week 1–13 drinks/week ≥14 drinks/week χ^2 for trend	 31 35 46 99 61 168 32 72 137 69 28 	 1 1.7 (1.0–3.1) 3.3 (1.8–5.9) 6.8 (3.9–12.1) 15.6 (8.2–29.7) 107.9 (p<0.01) 1 0.7 (0.4–1.0) 1.4 (1.0–1.9) 1.5 (NS) 1 0.8 (0.6–1.1) 1.6 (1.1–2.3) 1.1 (NS)	Age, sex, education, occupation, tobacco	Area of very high wine intake; no mention of controlling for other types of alcoholic beverage; includes participants from Barra *et al.* (1990)
Mashberg, *et al.* (1993), New Jersey, USA, 1972–83	359 white and black men with invasive cancer and in-situ carcinoma 2280 white or black male controls from the same centre as cases	Interviewer-administered questionnaire	Oral cavity, oropharynx	*Type of alcohol* Minimal drinking Mixed consumption Whiskey only Whiskey predominantly Beer only Beer predominantly	 17 125 32 77 40 61	 1 (reference) 8.3 (4.7–14.8) 3.8 (1.8–8.1) 5.3 (1.1–26.3) 2.6 (1.3–5.2) 8.3 (3.4–20.2)	Age, race, tobacco smoking, average total alcoholic beverage consumption	

Table 2.6 (continued)

Reference, study location, period	Characteristics of study population	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment factors	Comments
Ng *et al.* (1993), USA	173 (100 men, 73 women) non smoking cases 613 (254 men, 359 women) nonsmoking hospital-based controls; matched on age, sex, date of interview		Oral cavity	*Men only*				
				Beer				
				Non-drinker	24	1 (reference)		
				<1 oz/day	24	1.9 (0.9–3.8)		
				1–2.9 oz/day	16	2.6 (1.1–5.9)		
				≥3 oz/day	9	5.1 (1.8–14.2)		
				χ^2 for trend		13.6 ($p < 0.001$)		
				Wine				
				Non-drinker	38	1 (reference)		
				<1 oz/day	28	0.9 (0.5–1.8)		
				1–2.9 oz/day	6	1.5 (0.5–4.9)		
				≥3 oz/day	0	1.6 (0.0–29.7)		
				χ^2 for trend		0.01 (NS)		
				Liquor				
				Non-drinker	13	1 (reference)		
				<1 oz/day	20	1.1 (0.6–2.2)		
				1–2.9 oz/day	19	2.0 (0.7–5.3)		
				≥3 oz/day	13	0.4 (0.0–7.1)		
				χ^2 for trend		0.25 (NS)		

Table 2.6 (continued)

Reference, study location, period	Characteristics of study population	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment factors	Comments
Day *et al.* (1994a), USA, 1984–85	80 (56 men, 24 women) cases with second primary cancers from cohort of 1090 first primary cancers) 189 (132 men, 57 women) controls randomly selected from the cohort that were free of second primary cancer at the end of follow-up (1989)	Interviewer-administered standardized questionnaire	Oral cavity, pharynx, oesophagus, larynx	*Beer*			Age, stage of disease, lifetime smoking, other two types of alcoholic beverage	Nested case–control study of second primary cancers among cases of Blot *et al.* (1988) study
				<1 drink/week	14	1 (reference)		
				1–14 drinks/week	18	2.4 (0.8–7.1)		
				≥15 drinks/week	25	3.8 (1.2–12.0)		
				Liquor				
				<1 drink/week	16	1 (reference)		
				1–14 drinks/week	26	1.2 (0.5–2.9)		
				≥15 drinks/week	15	0.4 (0.1–1.1)		
				Wine				
				<1 drink/week	46	1 (reference)		
				≥1 drink/week	11	0.6 (0.2–1.3)		
	921 cases and 900 controls who drank hard liquor			*Dark liquor*			Age, sex, race, study location, education, smoking, intake of beer and wine	
				<1 drink/week	138	1 (reference)		
				1–4 drinks/week	120	1.1 (0.7–1.5)		
				5–14 drinks/week	142	1.2 (0.9–1.8)		
				15–29 drinks/week	111	2.7 (1.7–4.3)		
				≥30 drinks/week	139	4.6 (2.7–7.9)		
				Light liquor				
				<1 drink/week	50	1 (reference)		
				1–4 drinks/week	37	1.4 (0.8–2.5)		
				5–14 drinks/week	53	1.7 (0.9–3.0)		
				15–29 drinks/week	42	5.6 (2.5–12.5)		
				≥30 drinks/week	74	13.2 (5.2–33.5)		

Table 2.6 (continued)

Reference, study location, period	Characteristics of study population	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment factors	Comments
Kabat *et al.* (1994), USA, 1977–90	1560 (1097 men, 463 women) cases enrolled in 28 hospitals in eight US cities 2948 (2075 men, 873 women) hospital-based controls; matched on age, sex, race, hospital, date of interview	Interviewer-administered standardized questionnaire	Oral cavity, pharynx (excluding nasopharynx)	*Whiskey equivalents/day* **Men** *Beer* Non-drinker Occasional 1–3.9 oz/day 4–6.9 oz/day ≥7 oz/day *Wine* Non-drinker Occasional 1–3.9 oz/day 4–6.9 oz/day ≥7 oz/day	 178 254 240 136 279 646 300 83 13 50	 1 (reference) 1.5 (1.2–1.9) 2.5 (2.0–3.3) 4.1 (2.9–5.7) 5.3 (4.0–7.0) 1 (reference) 0.8 (0.7–1.0) 1.3 (0.9–1.8) 1.0 (0.5–2.3) 2.7 (1.6–4.6)	Age, education, smoking, race, time period, type of hospital	1 oz whiskey equivalent = 10.2 g of alcohol

Table 2.6 (continued)

Reference, study location, period	Characteristics of study population	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment factors	Comments
Kabat *et al.* (1994) (contd)				*Hard liquor*				
				Non-drinker	303	1		
				Occasional	228	1.0 (0.8–1.3)		
				1–3.9 oz/day	214	1.7 (1.4–2.3)		
				4–6.9 oz/day	103	2.6 (1.8–3.7)		
				≥7 oz/day	235	3.1 (2.4–4.1)		
				Women				
				Beer				
				Non-drinker	290	1 (reference)		
				Occasional	90	1.3 (1.0–1.9)		
				1–3.9 oz/day	46	1.9 (1.1–3.1)		
				4–6.9 oz/day	37	3.6 (1.7–7.5)		
				Wine				
				Non-drinker	284	1 (reference)		
				Occasional	130	0.8 (0.6–1.1)		
				1–3.9 oz/day	31	0.8 (0.5–1.4)		
				4–6.9 oz/day	16	2.7 (1.0–7.7)		
				Hard liquor				
				Non-drinker	217	1 (reference)		
				Occasional	112	1.1 (0.8–1.5)		
				1–3.9 oz/day	64	1.9 (1.2–2.9)		
				4–6.9 oz/day	70	7.6 (3.9–14.8)		

Table 2.6 (continued)

Reference, study location, period	Characteristics of study population	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment factors	Comments
Chyou *et al.* (1995), Hawaii, USA, 1965-93	Cohort of 7995 men of Japanese ancestry, aged 45–68 years; recruitment from 1965–68, incidence follow-up until 1993; 1–2% lost to follow-up.	Interviewer-administered questionnaire	Oral cavity, pharynx, oesophagus, larynx (ICD8 140–150, 161)	*Beer*			Age, number of cigarettes/ day, years smoked	
				Non-drinker	161	1 (reference)		
				<49 oz/month	5	0.7 (0.3–1.8)		
				49–360 oz/month	17	1.9 (1.0–3.8)		
				≥361 oz/month	39	3.7 (2.0–6.7)		
				p for trend	<0.0001			
				Wine				
				Non-drinker	16	1 (reference)		
				≤4 oz/month	10	2.5 (1.2–5.6)		
				>4 oz/month	12	3.8 (1.8–8.2)		
				p for trend	0.0001			
				Spirits				
				Non-drinker	16	1 (reference)		
				≤4 oz/month	18	1.6 (0.8–3.2)		
				>4 oz/month	34	3.6 (2.0–6.6)		
				p for trend	<0.0001			

Table 2.6 (continued)

Reference, study location, period	Characteristics of study population	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment factors	Comments
Zheng *et al.* (1997), Beijing, China, 1988–89	111 (65 men, 46 women) cases diagnosed at seven participating hospitals in the Beijing area; aged 20–80 years; histologically confirmed; 111 randomly selected non-cancer hospital-based controls; individually matched on age, sex, hospital	Interviewer-administered questionnaire	Tongue	*Type of alcohol* None Spirits only Beer/wine	 64 41 6	 1 (reference) 1.2 (0.3–4.0) 1.2 (0.6–2.4)	Education, smoking (age and sex matched on)	Part of Zheng *et al.* (1990)

Table 2.6 (continued)

Reference, study location, period	Characteristics of study population	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment factors	Comments
Grønbaek *et al.* (1998), Denmark, 1975–94	Cohort of 15 117 men and 13 063 women from prospective population studies of the Copenhagen city heart study the Copenhagen male study, and the Copenhagen county centre of preventive medicine; aged 20–98 years; cases identified by linkage with the Danish Cancer registry; follow-up through to 1993 (mean follow-up, 13.5 years).	Self-administered questionnaire	Oral cavity, pharynx, oesophagus (ICD7 140.0–149.0, 150.0)	*Beer* 0 drink/week 1–6 drinks/week ≥7 drinks/week *Wine* 0 drinks/week 1–6 drinks/week ≥7 drinks/week *Spirits* 0 drinks/week 1–6 drinks/week ≥7 drinks/week		 1 (reference) 1.5 (0.9–2.5) 2.9 (1.8–4.8) 1 (reference) 0.8 (0.5–1.1) 0.4 (0.2–0.8) 1 (reference) 0.7 (0.5–1.1) 1.5 (1.2–1.9)	Age, sex, smoking, education, other types of alcoholic beverage	One drink = 12 g ethanol

Table 2.6 (continued)

Reference, study location, period	Characteristics of study population	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment factors	Comments
Schildt *et al.* (1998), Sweden, 1980–89	410 (276 men, 134 women) cases from Norrbotten, Vasterbotten, Jamtland, Vasternorrland reported to the Cancer Registry (175 living, 235 deceased); histologically confirmed; response rate, 96% (11 living, seven proxies refused). 410 (276 men, 134 women) population controls; individually matched on age, sex, county; response rate, 91% (21 living, 17 proxies refused); after refusals, 354 (237 men, 117 women) matched pairs	Self-completed questionnaire	Oral cavity (ICD7 140, 141, 143–145)	*Overall* Light beer Beer Wine Liquor *Amount*frequency score* *Wine* Low Medium High *Liquor* Low Medium High	 150 25 8 125 60 42	 1.2 (0.7–1.7) 1.5 (0.7–3.2) 1.0 (0.6–1.5) 1.5 (0.9–2.3) 1.3 (0.9–1.8) 0.9 (0.5–1.8) 8.6 (1.0–70.0) 1.3 (0.9–2.0) 1.6 (1.0–2.7) 3.6 (1.8–7.2)	Snuff and smoking in addition to types of alcoholic beverage listed	Proxies used for 60% of participants; looked at joint effects of smoking and liquor

Table 2.6 (continued)

Reference, study location, period	Characteristics of study population	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment factors	Comments
Garrote *et al.* (2001), Havana, Cuba, 1996–99	200 (143 men, 57 women) cases identified in the Instituto Nacional de Oncologia y Radiobiologia of Havana; median age, 64 years; response rate, 88% 200 (136 men, 64 women) hospital-based controls admitted to same institute and three other major hospitals in Havana; excluded patients with alcohol- and tobacco-related conditions; frequency-matched on age, sex; median age, 62 years; response rate, 79%	Interviewer (dentist)-administered questionnaire	Oral cavity, oropharynx	*Hard liquor* 0 drink/week 1–7 drinks/week 8–20 drinks/week 21–69 drinks/week ≥70 drinks/week χ^2 for trend *Beer* 0 drink/week <7 drinks/week ≥7 drinks/week χ^2 for trend *Wine* 0 drink/week <2 drinks/week ≥2 drinks/week χ^2 for trend	 86 19 25 15 15 98 36 29 129 26 9 	 1 (reference) 1.3 (0.5–3.3) 1.0 (0.4–2.4) 4.2 (1.1–16.5) 5.1 (1.1–23.3) 4.58 ($p < 0.05$) 1 (reference) 1.5 (0.6–3.9) 1.5 (0.5–4.6) 0.85 ($p = 0.36$) 1 (reference) 1.0 (0.4–2.4) 0.8 (0.2–3.2) 0.15 ($p = 0.70$)	Age, sex, area of residence, education, smoking, other two types of alcoholic beverage	Looked at cessation, type of alcoholic beverage and joint effect of smoking

Table 2.6 (continued)

Reference, study location, period	Characteristics of study population	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment factors	Comments
Schlecht *et al.* (2001), Brazil, 1986–89	784 cases selected from hospitals in Sao Paulo, Curitiba, Goiania; histopathologically confirmed 1578 hospital-based non-cancer controls; matched (2:1 controls:case) on age, sex, hospital area, admission period	Interviewer-administered questionnaire	Oral cavity, pharynx, larynx (ICD9 140–149, 161; excluding 142 and 147)	Lifetime consumption **Oral cavity** *Beer* Non-drinker 1–10 g 11–100 g >100 g Other than beer *Wine* Non-drinker 1–10 g 11–100 g >100 g Other than wine *Hard liquor* Non-drinker 1–10 g 11–100 g >100 g Other than hard liquor *Cachaca* Non-drinker 1–10 g 11–100 g 101–500 g 501–1000 g 1001–2000 g >2000 g Other than cachaca		 1 (reference) 3.6 (1.9–7.0) 2.8 (1.4–5.6) 3.7 (1.4–10.3) 3.1 (1.6–5.8) 1 (reference) 3.4 (1.8–6.5) 4.3 (1.9–10.1) 3.0 (1.2–7.3) 2.9 (1.6–5.5) 1 (reference) 3.3 (1.3–8.2) 3.1 (1.5–6.6) 6.9 (2.8–17.1) 3.2 (1.7–5.8) 1 (reference) 1.4 (0.4–5.4) 2.0 (1.0–4.2) 4.5 (2.2–9.2) 7.2 (3.5–14.7) 8.7 (4.3–17.6) 9.9 (3.8–25.5) 3.7 (1.8–7.8)	Remaining alcohol consumption, tobacco smoking, income, education, race, beverage temperature, religion, wood stove use, spicy food (matched variables: age, sex, study location, admission period)	Same study population as Schlecht *et al.* (1999)

Table 2.6 (continued)

Reference, study location, period	Characteristics of study population	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment factors	Comments
Schlecht *et al.*(2001) (contd)				**Pharynx**				
				Beer				
				Non-drinker		1 (reference)		
				1–10 g		3.2 (1.1–9.2)		
				11–100 g		3.4 (1.1–10.4)		
				>100 g		1.1 (0.3–4.1)		
				Other than beer		3.1 (1.0–9.2)		
				Wine				
				Non-drinker		1 (reference)		
				1–10 g		3.1 (1.0–9.2)		
				11–100 g		2.8 (0.8–9.4)		
				>100 g		3.0 (0.8–11.1)		
				Other than wine		3.6 (1.3–10.5)		
				Hard liquor				
				Non-drinker		1 (reference)		
				1–10 g		4.1 (1.0–17.7)		
				11–100 g		4.6 (1.5–14.1)		
				>100 g		2.5 (0.7–9.8)		
				Other than hard liquor		3.1 (1.1–8.8)		
				Cachaca				
				Non-drinker		1 (reference)		
				1–10 g		2.8 (0.4–19.6)		
				11–100 g		2.9 (0.9–9.1)		
				101–500 g		5.4 (1.7–17.5)		
				501–1000 g		9.2 (2.9–29.3)		
				1001–2000 g		14.3 (4.4–45.8)		
				>2000 g		12.5 (2.9–53.7)		
				Other than cachaca		2.1 (0.6–7.8)		

Table 2.6 (continued)

Reference, study location, period	Characteristics of study population	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment factors	Comments
Huang *et al.* (2003), Puerto Rico, 1992–95	286 male cases identified through the Central Cancer Registry and by abstracting patients' medical records; aged 21–79 years; histologically confirmed; response rate, 70% 417 male population controls selected from among all Puerto Ricans; frequency-matched on age; response rate, 83%.	Interviewer-administered questionnaire	Oral cavity, pharynx (ICD9 141, 143–146, 148, 149)	*Beer* Non-drinker >0–<8 drinks/week 8–<43 drinks/week ≥43 drinks/week *p* for trend *Wine* Non-drinker >0–<8 drinks/week ≥8 drinks/week *p* for trend *Liquor* Non-drinker >0–<8 drinks/week 8–<43 drinks/week ≥43 drinks/week *p* for trend	 47 70 119 42 0.004 194 62 27 0.2 22 40 90 128 <0.0001	 1 (reference) 0.5 (0.3–1.0) 1.1 (0.6–2.0) 1.8 (0.8–4.1) 1 (reference) 1.0 (0.6–1.7) 1.8 (0.8–4.3) 1 (reference) 1.7 (0.9–3.2) 3.5 (1.8–6.7) 13.2 (6.5–26.6)	Age, tobacco use, raw fruit and vegetable intake, education, other types of alcoholic beverage	Same population as Hayes *et al.* (1999)

Table 2.6 (continued)

Reference, study location, period	Characteristics of study population	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment factors	Comments
Altieri *et al.* (2004), Italy, Switzerland, 1992–97	749 (634 men, 115 women) cases from Pordenone, Rome, Latina (Italy) and Vaud (Switzerland) admitted to major teaching and general hospitals in area under surveillance; aged 22–77 years; histologically confirmed 1772 (1252 men, 520 women) hospital controls from the same network of hospitals as cases; aged 20–78 years; excluded patients with alcohol- and tobacco-related conditions	Interview-administered structured questionnaire	Oral cavity, pharynx	*Beer* Non-drinkers 1–2 drinks/day ≥3 drinks/day χ^2 for trend *Wine* Non-drinkers 1–2 drinks/day 3–4 drinks/day 5–7 drinks/day 8–11 drinks/day ≥12 drinks/day χ^2 for trend *Spirits* Non-drinkers 1–2 drinks/day ≥3 drinks/day χ^2 for trend	 284 380 84 43 110 127 157 177 134 297 386 66 	 1 (reference) 1.2 (1.0–1.5) 2.3 (1.4–3.7) 9.86 (p = 0.02) – – 1 (reference) 2.2 (1.6–3.0) 7.1 (5.0–10.1) 11.8 (8.1–17.2) 16.1 (10.2–25.3) 221.83 (p <0.0001) 1 (reference) 1.0 (0.8–1.2) 1.9 (1.1–3.3) 1.14 (p = 0.29)	Age, sex, study centre, education, smoking habit, other types of alcoholic beverage	

Table 2.6 (continued)

Reference, study location, period	Characteristics of study population	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment factors	Comments
Castellsagué et al. (2004), Spain, 1996–99	375 (304 men, 71 women) cases identified from hospitals; histologically confirmed; response rate, 76.5% 375 (304 men, 71 women) non-cancer hospital controls from same hospitals as cases; frequency-matched on age, sex; mean age, 60 years; excluded patients with alcohol- and tobacco-related diagnoses; response rate, 91%	Interviewer-administered questionnaire	Oral cavity, oropharynx (ICDO C1-C10)	*Type of alcohol* Only beer Only wine and beer Only wine Spirits with or without wine/beer *p* for trend	 12 47 32 248 <0.0001	 1.2 (0.5–2.8) 2.0 (1.0–4.0) 2.7 (1.3–5.6) 7.3 (3.7–14.5)	Age group, sex, education, tobacco smoking, centre	

Table 2.6 (continued)

Reference, study location, period	Characteristics of study population	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment factors	Comments
De Stefani *et al.* (2004), Montevideo, Uruguay, 1997–2003	85 male cases identified in the four major hospitals in Montevideo; microscopically confirmed; response rate, 97.5% 640 hospital-based male controls from the same hospitals as cases; excluded patients with alcohol- and tobacco-related conditions with no recent changes in diet; frequency matched (2:1 controls:cases) on age, residence; response rate, 97%	Interviewer-administered questionnaire	Hypopharynx	**Ethanol/day (mL)** *Beer* Beer abstainers 1–60 ≥61 *p* for trend *Red wine* Wine abstainers 1–60 61–120 ≥121 *p* for trend *Hard liquor* Liquor abstainers 1–60 61–120 ≥121 *p* for trend	 75 8 2 0.08 9 20 29 27 0.0001 45 12 10 18 0.0008	 1 (reference) 0.8 (0.3–1.9) 0.2 (0.1–1.1) 1 (reference) 2.3 (0.9–5.5) 5.2 (2.2–12.4) 4.5 (1.9–10.8) 1 (reference) 0.9 (0.4–1.9) 2.2 (0.9–5.2) 3.3 (1.6–6.8)	Age, residence, urban/rural status, education, body mass index, smoking, other types of alcoholic beverage	

Table 2.6 (continued)

Reference, study location, period	Characteristics of study population	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment factors	Comments
De Stefani *et al.* (2007), Montevideo, Uruguay, 1988–2000	335 male cases identified in the four major hospitals in Montevideo; microscopically confirmed; response rate, 97% 1501 hospital-based non-cancer male controls; excluded patients with alcohol- and tobacco-related conditions with no recent changes in diet; response rate, 97%	Interviewer-administered questionnaire	Oral cavity (excluding lip)	**Ethanol/day (mL)** *Beer* Beer abstainers 1–22 ≥23 *p* for trend *Wine* Wine abstainers 1–60 61–120 ≥121 *p* for trend *Hard liquor* Liquor abstainers 1–60 61–120 ≥121 *p* for trend		 1 (reference) 0.5 (0.3–0.9) 0.4 (0.2–0.9) 0.004 1 (reference) 0.8 (0.6–1.2) 1.5 (1.0–2.1) 1.4 (0.9–2.4) 0.03 1 (reference) 0.8 (0.6–1.2) 1.8 (1.2–2.7) 1.4 (0.8–2.2) 0.03	Age, residence, urban/ rural status, hospital, year of diagnosis, education, family history of cancer, occupation, vegetable and fruit consumption, mate, smoking, total alcoholic beverage	

Table 2.6 (continued)

Reference, study location, period	Characteristics of study population	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment factors	Comments
De Stefani *et al.* (2007) (contd)	441 male cases identified in the four major hospitals in Montevideo; microscopically confirmed; response rate, 97%		Pharynx (excluding nasopharynx	*Beer*				
				Beer abstainers		1 (reference)		
				1–22		0.8 (0.4–1.3)		
				≥23		0.3 (0.2–0.7)		
				p for trend		0.001		
				Wine				
				Wine abstainers		1 (reference)		
				1–60		1.1 (0.8–1.5)		
				61–120		2.7 (1.9–3.8)		
				≥121		2.5 (1.6–3.9)		
				p for trend		<0.0001		
				Hard liquor				
				Liquor abstainers		1 (reference)		
				1–60		0.9 (0.7–1.3)		
				61–120		1.6 (1.1–2.3)		
				≥121		0.9 (0.5–1.4)		
				p for trend		0.5		

CI, confidence interval; ICD, International Classification of Diseases; NS, not significant

Table 2.7 Joint effects of alcoholic beverage consumption and tobacco smoking on cancers of the oral cavity and pharynx

Reference, study location, period	Tobacco	Alcoholic beverages					Comments/ adjustment factors
Blot *et al.* (1988), USA, 1984–85		No. of cases (odds ratio)					[a]Quit for ≥10 years or smoked for <20 years; adjusted for age, race, study location, respondent status (self vs next-of-kin)
		<1 drink/week	1–4 drinks/week	5–14 drinks/week	15–29 drinks/week	≥30 drinks/week	
	Men						
	Nonsmoker	12 (1)	12 (1.3)	15 (1.6)	5 (1.4)	6 (5.8)	
	Short duration/ former[a]	8 (0.7)	24 (2.2)	21 (1.4)	25 (3.2)	43 (6.4)	
	1–19/day for ≥20 years	2 (1.7)	7 (1.5)	8 (2.7)	16 (5.4)	22 (7.9)	
	20–39/day for ≥20 years	8 (1.9)	17 (2.4)	28 (4.4)	52 (7.2)	145 (23.8)	
	≥40/day for ≥20 years	9 (7.4)	6 (0.7)	19 (4.4)	43 (20.2)	148 (37.7)	
	Pipe/cigar only	1 (0.6)	5 (1.0)	8 (3.7)	13 (4.7)	25 (23.0)	
	Women						
	Nonsmoker	36 (1)	11 (0.7)	7 (1.3)	0 (0.0)	0 (0.0)	
	Short duration/ former[a]	7 (1.0)	8 (1.6)	4 (0.4)	3 (1.1)	3 (~)	
	1–19/day for ≥20 years	4 (0.9)	22 (5.1)	11 (2.8)	3 (4.6)	9 (11.0)	
	20–39/day for ≥20 years	12 (2.2)	20 (2.7)	35 (6.9)	31 (12.4)	38 (46.0)	
	≥40/day for ≥20 years	4 (~)	14 (9.3)	15 (7.8)	18 (18.0)	37 (107.9)	

Table 2.7 (continued)

Reference, study location, period	Tobacco	Alcoholic beverages				Comments/ adjustment factors
Tuyns *et al.* (1988), France, Italy, Spain, Switzerland, 1980–83		No. of cases/odds ratio (95% CI)				Adjusted for age, place, age/place interaction
		0–40 g/day	41–80 g/day	81–120 g/day	≥121 g/day	
	0–7 cigarettes/ day	4 (1)	10 (3.0)	7 (5.5)	11 (15.0	
	8–15 cigarettes/ day	9 (4.7)	32 (14.6)	28 (27.5)	39 (71.6)	
	16–25 cigarettes/ day	27 (13.9)	42 (19.5)	52 (48.3)	56 (67.8)	
	≥26 cigarettes/ day	5 (4.9)	15 (18.4)	22 (37.6)	50 (135.5)	
Merletti *et al.* (1989), Torino, Italy, 1982–84		No. of cases/odds ratio (95% CI)				Adjusted for age, education, area of birth
		0–40g/day	41–120g/day	>120g/day		
	Men					
	0–7 g/day	4/1.0 (reference)	4/0.6 (0.2–2.0) (categories combined)			
	8–15 g/day	7/3.3 (0.9–12.4)	15/3.6 (1.1–12.0)	5/8.6 (1.9–39.0)		
	>16 g/day	10/2.5 (0.7–8.5)	25/3.6 (1.2–11.3)	16/21.4 (5.9–77.7)		
	Women					
	0 g/day	6/1.0 (reference)	5/1.1 (0.3–4.1)	2/0.8 (0.1–4.2)		
	≥1 g/day	5/2.8 (0.7–11.1)	8/6.5 (1.7–24.5)	10/21.3 (5.1–88.6)		

Table 2.7 (continued)

Reference, study location, period	Tobacco	Alcoholic beverages				Comments/ adjustment factors
Franceschi *et al.* (1990), Milan, Pordenone, Italy, 1986–89		No. of cases (odds ratio)				Adjusted for age, area of residence, education, occupation; oral cavity and pharynx cases combined
		<35 drinks/week	35–59 drinks/week	≥60 drinks/week		
	Nonsmoker	3 (1)	2 (1.6)	1 (2.3)		
	Light smoker	7 (3.1)	7 (5.4)	12 (10.9)		
	Intermediate smoker	39 (10.9)	79 (26.6)	102 (36.4)		
	Heavy smoker	7 (17.6)	8 (40.2)	19 (79.6)		
Zheng *et al.* (1990), Beijing, China, 1988–89		No. of cases (odds ratio)				Adjusted for age, education
		Lifetime consumption of spirit equivalents				
		0 kg	<217 kg	217–801 kg	>801 kg	
	0 pack–years	20 (1)	9 (1.2)	4 (0.8)	4 (2.4)	
	1–18 pack–years	15 (1.4)	15 (2.8)	13 (5.6)	4 (15.2)	
	19–32 pack–years	12 (2.1)	14 (4.9)	9 (1.7)	19 (10.1)	
	>32 pack–years	13 (2.5)	2 (5.9)	14 (5.9)	31 (17.4)	
Nam *et al.* (1992), USA, 1986		Odds ratio (*p*-value)				Adjusted for sex
		0–3 drinks/week	4–23 drinks/week	≥24 drinks/week		
	≤30 pack–years	1	0.6	1.4		
	31–59 pack–years	1.5	2.3 (<0.05)	2.6 (<0.01)		
	≥60 pack–years	2.2 (<0.05)	2.3 (<0.05)	5.2 (<0.01)		

Table 2.7 (continued)

Reference, study location, period	Tobacco	Alcoholic beverages					Comments/ adjustment factors
Maier *et al.* (1994), Heidelberg, Giessen, Germany, 1987–88		No. of cases/odds ratio (95% CI)					
		<25 g/day	25–75 g/day	>75 g/day			
	<5 tobacco–years	5/1	5/2.3 (0.6–8.8)	3/10.3 (1.9–55.8)			
	5–50 tobacco–years	27/5.7 (1.9–17.3)	50/14.6 (4.8–43.9)	44/153.2 (44.1–532)			
	>50 tobacco–years	14/23.3 (6.6–82.5)	27/52.8 (15.8–176.6)	25/146.2 (37.7–566)			
Mashberg *et al.* (1993), New Jersey, USA, 1972–83		No. of cases (odds ratio)					Adjusted for age, race
		Minimal drinkers	2–5 WE/day	6–10 WE/day	11–21 WE/day	≥22 WE/day	
	Minimal smokers	1 (1)	1 (2.7)	2 (11.9)	3 (12.5)	2 (8.3)	
	Cigar/pipe	6 (20.5)	6 (17.0)	13 (53.4)	6 (27.3)	5 (23.1)	
	6–15 cigarettes/day	3 (10.8)	7 (24.2)	17 (50.9)	8 (30.9)	6 (27.5)	
	16–25 cigarettes/day	4 (7.6)	16 (29.7)	23 (28.9)	34 (44.8)	31 (61.7)	
	26–35 cigarettes/day	0 (–)	2 (5.3)	18 (61.9)	18 (79.5)	22 (70.3)	
	≥36 cigarettes/day	1 (3.2)	4 (10.2)	17 (26.8)	40 (98.4)	30 (32.0)	

Table 2.7 (continued)

Reference, study location, period	Tobacco	Alcoholic beverages				Comments/ adjustment factors
Kabat *et al.* (1994), USA, 1977–90		Odds ratio (95% CI)				
		Non-drinker/ occasional	1–3.9 oz/day	4–6.9 oz/day	≥7 oz/day	
	Men					
	Never	1	1.6 (0.9–2.7)	1.2 (0.4–3.7)	2.9 (1.1–8.1)	
	Former smoker (abstained for ≥12 months)	1 (0.7–1.6)	1.7 (1.1–2.6)	3.1 (1.9–5.2)	5.1 (3.3–7.8)	
	1–20 cigarettes/ day	1.5 (0.9–2.51)	5.8 (3.7–9.1)		11.9 (7.7–18.4)	
	21–30 cigarettes/ day	2.2 (1.1–4.3)	6.8 (3.6–12.7)		13.5 (7.9–23.2)	
	≥31 cigarettes/ day	2.0 (1.1–3.7)	6.9 (3.9–12.4)		20.1 (12.9–31.5)	

Table 2.7 (continued)

Reference, study location, period	Tobacco	Alcoholic beverages			Comments/ adjustment factors
		Non-drinker/ occasional	≥4 oz/day	1–3.9 oz/day	
Kabat *et al.* (1994) (cont)	**Women**				Adjusted for age, education, race, time period, type of hospital
	Never	1	3.5 (0.9–13.4)	0.7 (0.3.–1.4)	
	Former smoker (abstained for ≥12 months)	1.3 (0.9–2.0)	2.7 (1.0–7.9)	2.1 (1.2–3.8)	
	1–20 cigarettes/ day	2.9 (1.9–4.3)	17.6 (8.1–37.5)	5.8 (3.5–9.8)	
	≥21 cigarettes/ day	3.8 (2.3–6.2)	26.7 (12.3–58.6)	22.3 (9.6–51.8)	
Chyou *et al.* (1995), Hawaii, USA		No. of cases/odds ratio (95% CI)			Study population from Kato *et al.* (1992c); adjusted for age
		0 oz/month	>0–<14 oz/month	≥14 oz/month	
	0 cigarette/ day	3/1 (reference)	3/1.3 (0.3–6.3)	6/6.5 (1.6–26.0)	
	>0–≤20 cigarettes/ day	8/3.0 (0.8–11.3)	6/1.9 (0.5–7.7)	24/10.7 (3.2–35.4)	
	>20 cigarettes/ day	5/3.2 (0.8–13.4)	7/4.6 (1.2–17.7)	28/14.4 (4.4–47.4)	

Table 2.7 (continued)

Reference, study location, period	Tobacco	Alcoholic beverages				Comments/ adjustment factors
Murata *et al.* (1996), Japan 1984–93		No. of cases (odds ratio; *p*-value)				In sake-equivalents (180 mL sake contains ~27 mL ethanol)
		0 cup/day	0.1–1.0 cup/day	≥1 cup/day		
	Nonsmoker	7 (1)	6 (1.2)	5 (2.1)		
	Smoker	10 (1.9)	7 (1.4)	16 (p <0.01)		
Sanderson, *et al.* (1997), Netherlands, 1980–90		No. of cases/odds ratio (95% CI)				
		Non-drinker	1–5 units/day	>5 units/day		
	Nonsmoker	125 Ref	39/2.4 (1.6–3.6)			
	Smoker	28/1 (0.6–1.5)	65/6.5 (4.4–9.7)			
	Nonsmoker and smoker			46/32.9 (18.3–59.2)		
Zheng *et al.* (1997), Beijing, China, 1988–89		No. of cases (odds ratio; *p*-value) (Lifetime intake, spirit equivalents in kg)				Adjusted for education (matching variables: age, sex)
		Never	≤255 kg	>255 kg		
	Never	39 (1)	6 (1.9)	3 (2.4)		
	≤ 20 pack–years	10 (1.2)	9 (1.6)	4 (3.0)		
	>20 pack–years	15 (7.6; p<0.05)	8 (23.3; p<0.05)	17 (4.1)		
Schildt *et al.* (1998), Sweden, 1980–89		No. of cases/odds ratio (95% CI)				
		Never liquor	Low liquor intake	Medium liquor intake	High liquor intake	
	Never	80/1.0	50/1.2 (0.8–1.9)	7/1.4 (0.8–2.6)	4/4.2 (1.8–9.4)	
	Low consumption	15/1.0 (0.6–1.6)	26/1.2 (0.6–2.1)	19/1.4 (0.7–2.7)	4/4.0 (1.6–9.8)	
	High consumption	8/1.4 (0.8–2.3)	30/1.6 (0.9–2.9)	27/2.0 (1.0–3.6)	30/5.7 (2.4–14)	

Table 2.7 (continued)

Reference, study location, period	Tobacco	Alcoholic beverages					Comments/ adjustment factors
Schlecht *et al.* (1999), Brazil, 1986–89		Odds ratio (95% CI) for lifetime consumption					Same study population as Schlecht *et al.* (2001); adjusted for race, beverage temperature, religion, wood stove use, spicy food intake (matching variables: age, sex, study location, admission period)
		0–10 kg	11–530 kg	>530 kg			
	Oral cavity						
	0–5 pack–years	1	1.2 (0.4–3.4)	2.3 (0.6–9.1)			
	6–42 pack–years	2.9 (1.2–6.8)	6.2 (2.7–14.1)	19.5 (2.6–147)			
	>42 pack–years	7.8 (2.9–21.0)	11.2 (4.8–26.3)	20.3 (9.0–45.3)			
	Pharynx						
	0–5 pack–years	1	6.2 (0.7–56.6)	22.3 (2.1–238)			
	6–42 pack–years	2.4 (0.2–24.0)	21.7 (2.6–180)	66.3 (1.7–2,556)			
	>42 pack–years	69.4 (6.9–694)	43.0 (4.9–340)	77.3 (9.2–625)			
Hayes *et al.* (1999), Puerto Rico, 1992–95		No. of cases/odds ratio (95% CI)					Adjusted for age
		None	1–7 drinks/week	8–21 drinks/week	22–42 drinks/week	≥42 drinks/week	
	None	6/1.00 (reference)	1/0.2 (0.0–1.5)	2/0.6 (0.1–3.5)	2/1.6 (0.3–9.6)	4/6.4 (1.3–31.9)	
	Low	0	10/1.6 (0.5–4.8)	3/1.3 (0.3–5.7)	11/3.7 (0.8–16.4)	9/5.5 (1.6–19.0)	
	10–19 cigarettes/ day	1/11.3 (0.6–213.0)	2/1.3 (0.2–7.2)	3/1.8 (0.4–8.3)	8/18.6 (4.1–84.0)	10/12.2 (3.3–45.6)	
	20–39 cigarettes/ day	1/1.8 (0.2–19.0)	10/3.8 (1.2–12.0)	13/6.2 (2.0–19.3)	19/11.3 (3.7–34.0)	60/50.2 (16.6–152.0)	
	≥40 cigarettes/ day	1/2.4 (0.2–27.6)	6/4.3 (1.1–16.7)	4/7 (0.9–18.7)	10/10.5 (2.9–37.9)	67/38.7 (13.6–110.0)	

Table 2.7 (continued)

Reference, study location, period	Tobacco	Alcoholic beverages				Comments/ adjustment factors
Franceschi *et al.* (1999), Italy, Switzerland, 1992–97		No. of cases/odds ratio (95% CI)				Study population from Franceschi *et al.* (2000); adjusted for age, area of residence, interviewer, education, vegetable and fruit intake, total energy intake *categories combined
		0–20 drinks/week	21–48 drinks/week	49–76 drinks/week	≥77 drinks/week	
	Oral cavity					
	Never smoker	3/1 (reference)	5/2.7 (0.6–11.6)	3/4.5 (0.8–24.2)*	3/4.5 (0.8–24.2)*	
	1–14 cigarettes/ day	2/2.2 (0.4–13.5)	6/5.9 (1.4–25.1)	11/30.6 (7.3–128.2)	8/52.4 (10.4–264.2)	
	15–24 cigarettes/ day	4/3.0 (0.6–13.8)	28/22.9 (66.6–79.4)	35/62.5 (17.4–224.2)	31/110.3 (29.1–418.1)	
	≥25 cigarettes/ day	4/5.6 (1.2–26.3)	12/22.7 (5.9–86.9)	25/103.1 (26.4–402.7)	31/227.8 (54.6–950.7)	
	Former smoker (abstained ≥12 months)	12/3.9 (1.1–14.1)	20/6.0 (1.7–21.0)	17/10.5 (2.9–38.6)	17/25.4 (6.7–96.0)	

Table 2.7 (continued)

Reference, study location, period	Tobacco	Alcoholic beverages				Comments/ adjustment factors
Franceschi *et al.* (1999) (contd)	*Pharynx*					*Categories combined
	Never smoker	6/1 (reference)	2/0.4 (0.1–2.3)	1/0.5 (0.1–4.3)*	1/0.5 (0.1–4.3)*	
	1–14 cigarettes/ day	4/2.3 (0.6–8.4)	11/4.5 (1.5–13.4)	17/16.3 (5.3–50.5)	13/27.5(7.2–105.1)	
	15–24 cigarettes/ day	12/4.4 (1.6–12.5)	32/11.7 (4.6–30.2)	40/26.9 (10.0–72.3)	48/58.3 (20.3–167.3)	
	≥25 cigarettes/ day	7/5.5 (1.7–17.8)	22/18.6 (6.8–51.3)	18/32.2 (10.3–100.4)	36/100.4 (30.8–327.7)	
	Former smoker (abstained ≥12 months)	11/1.7 (0.6–4.9)	22/2.7 (1.0–7.1)	31/6.8 (2.6–17.8)	31/14.8 (5.4–40.9)	
Schwartz *et al.* (2001), Washington, USA, 1985–95		No. of cases/odds ratio (95% CI)				Adjusted for age, sex, race
		<1 drink/week	1–14 drinks/week	≥15 drinks/week		
	Never	26/1 (reference)	19/0.8 (0.4–1.5)	5/1.2 (0.4–3.6)		
	1–20 pack–years	9/0.8 (0.3–1.8)	27/0.9 (0.5–1.6)	13/3.8 (1.5–9.4)		
	≥ 20 pack–years	10/1.8 (0.7–4.5)	94/3.3 (1.9–5.7)	130/9.9 (5.5–17.9)		

Table 2.7 (continued)

Reference, study location, period	Tobacco	Alcoholic beverages			Comments/ adjustment factors
Garrote *et al.* (2001), Havana, Cuba, 1996–99		No. of cases/odds ratio (95% CI)			Adjusted for age, sex, area of residence, education, smoking (former smokers only)
		0 drink/week	<21 drinks/week	≥21 drinks/week	
	Never smokers	14/1 (reference)	1	0	
	1–29 cigarettes/ day	35/6.6 (2.8–15.7)	17/11.0 (3.7–32.8)	15/26.7 (7.2–99.9)	
	≥ 30 cigarettes/ day	15/10.5 (2.9–38.2)	15/42.3 (8.4–212.3)	21/111.2 (22.7–543.7)	
Balaram *et al.* (2002); southern India, 1996–99		No. of cases/odds ratio (95% CI)			Adjusted for age, centre, education, oral hygiene, smoking, chewing, drinking habits
		Never drinker	Current drinker		
	Never paan chewer	64/1 (reference)	48/2.8 (1.6–5.1)		
	Current paan chewer	48/7.3 (3.8–14.1)	46/8.6 (4.1–18.1)		
Boeing (2002), Denmark, France, Germany, Greece, Italy, Norway, Spain, Sweden, Netherlands, United Kingdom		No. of cases/hazard rate ratio (95% CI)			Adjusted for sex, follow-up time, education, body mass index, vegetable and fruit intake, energy intake
		0–30 g/day	>30–60 g/day	>60 g/day	
	Nonsmoker	58/1 (reference)	7/2.6 (1.1–6.0)	4/6.9 (2.3–2.7)	
	1–20 cigarettes/ day	22/2.0 (1.2–3.5)	6/5.1 (2.1–12.7)	6/22.0 (8.3–58.1)	
	>20 cigarettes/ day	7/6.8 (3.0–15.5)	7/20.7 (8.7–49.0)	7/48.7 (20.0–118.9)	

Table 2.7 (continued)

Reference, study location, period	Tobacco	Alcoholic beverages				Comments/ adjustment factors
Rodriguez *et al.* (2004), Italy, Switzerland, 1984–93, 1992–97		No. of cases/odds ratio (95% CI)				Study populations from Franceschi *et al*. (1990, 1999); adjusted for education, marital status, body mass index, coffee consumption (matched variables: age, sex, study centre)
		<6 drinks/day	6–<10 drinks/day	≥10 drinks/day		
	Never/ former smokers (abstained ≥ 12 months)	22/1 (reference)	4/1.9 (0.5–7.1)	5/15.7 (3.6–67.9)		
	1–15 cigarettes/ day	9/2.4 (0.9–6.4)	9/21.2 (5.2–87.7)	2/8.1 (1.0–64.8)		
	>15 cigarettes/ day	20/8.3 (3.3–20.6)	24/44.2 (14.9–131.2)	39/48.1 (17.6–131.0)		
Castellsagué *et al.* (2004), Spain, 1996–99		No. of cases/ odds ratio (95% CI)				Adjusted for age, sex, centre, education
		Never drinker	1–2 drinks/day	3–5 drinks/day	≥6 drinks/day	
	Never smoker	28/1 (reference)	23/2.0 (0.9–4.4)	2/1.1 (0.9–6.4)	2/6.2 (1.0–39.2)	
	1–10 cigarette/ day	3/2.9 (0.6–14.8)	14/4.7 (1.7–12.9)	10/32.2 (8.1–127.1)	1/2.7 (0.3–26.5)	
	11–20 cigarette/ day	2/1.0 (0.2–6.0)	27/11.1 (4.0–30.6)	22/26.6 (8.6–82.0)	46/43.1 (15.0–123.8)	
	≥21 cigarettes/ day	2/1.9 (0.3–11.1)	22/8.2 (2.9–22.9)	40/22.0 (8.0–61.0)	131/50.7 (19.1–134.2)	

Table 2.7 (continued)

Reference, study location, period	Tobacco	Alcoholic beverages			Comments/ adjustment factors
De Stefani, *et al.* (2004), Montevideo, Uruguay, 1997–2003		Odds ratio (95% CI)			Adjusted for age, residence, urban/ rural status, education, body mass index
		0–60 mL/day	61–120 mL/day	≥121 mL/day	
	0–14 cigarettes/ day	1 (reference)	5.1 (1.1–23.3)	4.6 (0.8–25.6)	
	15–24 cigarettes/ day	1.9 (0.3–12.8)	16.3 (4.2–62.9)	22.3 (5.8–86.3)	
	≥25 cigarettes/ day	4.3 (0.8–23.5)	5.6 (2.4–13.1)	43.9 (11.5–116.8)	

Table 2.7 (continued)

Reference, study location, period	Tobacco	Alcoholic beverages				Comments/ adjustment factors
De Stefani *et al.* (2007), Montevideo, Uruguay, 1988–2000		Odds ratio (95% CI)				Adjusted for age, residence, urban/ rural status, hospital, year at diagnosis, education, family history of cancer, occupation, vegetable and fruit intake, mate intake
		0–60 mL/day	61–120 mL/day	121–240 mL/day	≥ 241 mL/day	
	Oral cavity					
	0–9 cigarettes/ day	1	3.5 (1.2–10.5)	2.9 (90.8–11.2)	1.9 (0.2–15.9)	
	10–19 cigarettes/ day	4.4 (2.1–9.4)	8.9 (3.9–20.4)	14.5 (6.1–34.2)	24.5 (8.3–72.1)	
	20–29 cigarettes/ day	4.8 (2.3–10.2)	24.1 (11.5–50)	21.2 (9.6–46.8)	50.5 (21–119)	
	≥30 cigarettes/ day	6.5 (3.1–13.8)	29.6 (13.7–64)	42.5 (19.9–90)	33.4 (15.8–70)	
	Pharynx					
	0–9 cigarettes/ day	1	0.9 (0.2–4.4)	2.5 (0.8–8.2)	9.8 (3.7–26.3)	
	10–19 cigarettes/ day	2.8 (1.4–5.6)	8.8 (4.3–17.9)	18.6 (9.1–38.0)	12.4 (4.0–38.7)	
	20–29 cigarettes/ day	3.7 (1.9–7.1)	16.8 (8.6–33	31.4 (16.0–62)	53.2 (25–114)	
	≥30 cigarettes/ day	4.7 (2.4–9.2)	24.0 (12.8–48)	36.4 (18.7–71)	43.8 (23.0–84)	

CI, confidence interval; WE whiskey equivalent

et al., 1995). The evaluation of effect modification was descriptive, without formal assessment of multiplicative interaction in most of studies.

Overall, a large majority of studies on joint exposure to alcoholic beverage and tobacco consumption demonstrated a synergistic effect. Many studies demonstrated a greater than multiplicative interaction (Tuyns *et al*., 1988; Merletti *et al*., 1989; Franceschi *et al*., 1990; Zheng *et al*., 1990; Mashberg *et al*., 1993; Kabat *et al*., 1994; Franceschi *et al*., 1999; Hayes *et al*., 1999; Schlecht *et al*., 1999; Garrote *et al*., 2001; Schwartz *et al*., 2001; Boeing, 2002; Castellsagué *et al*., 2004; De Stefani *et al*., 2007). In contrast, some other studies demonstrated a greater than additive but less than multiplicative interaction (Maier *et al*., 1992a; Chyou *et al*., 1995; Schildt *et al*., 1998). Among tobacco chewers in India, there appears to be no interaction between chewing and alcoholic beverage consumption (Balaram *et al*., 2002).

2.2.5 *Effect of cessation of alcoholic beverage consumption (Table 2.8)*

Studies of cessation of alcoholic beverage consumption may be confounded by the fact that precursors and early malignancies of the oral cavity and pharynx may lead to such cessation. Nevertheless, this type of confounding may result in underestimation of the effect of cessation. For recent quitters, the risk for oral and pharyngeal cancers increases above that of current drinkers; as the number of years since quitting increases, however, that elevated risk gradually drops to below that of current drinkers and near to the levels of non-drinkers in some studies. Hayes *et al*. (1999) observed that risk could drop to near the levels of non-drinkers after 20 years of quitting among men. Castellsagué *et al*. (2004) showed that risk can be reduced to near levels of never drinkers after 14 years and De Stefani *et al*. (2004) showed that this occurs after 10 years of quitting. In contrast, Franceschi *et al*. (2000) showed that a reduction in risk with quitting compared with current drinkers is not attained even 11 years after quitting.

2.2.6 *Effect of alcoholic beverage consumption in nonsmokers (Table 2.9)*

Because tobacco smoking is a major risk factor for oral and pharyngeal cancer, the study of nonsmoking subjects can avoid the strong confounding effect of tobacco smoking. Of the studies that focused on the effects of alcoholic beverage consumption in nonsmokers, an increase in risk in relation to alcoholic beverages was consistent. Talamini *et al*. (1990a) compared 27 nonsmoking cases identified between 1986 and 1989 in Milan and Pordenone and 572 nonsmoking hospital-based controls matched on age and area of residence. A significant dose–response relationship between alcoholic beverage consumption and cancer of the oral cavity and pharynx was observed (P=0.04). Ng *et al*. (1993) identified 173 white nonsmoking cases of oral and hypopharyngeal cancer between 1977 and 1991 in eight US cities and compared them with 613 hospital-based controls matched on age, sex and date of interview. A significant dose–response relationship was also observed in this study (P<0.001). Sixty nonsmoking

Table 2.8 Effect of cessation of alcoholic bevarage consumption on the incidence of cancers of the the oral cavity and pharynx

Reference, study location, period	Characteristics of study population	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment factors	Comments
Day *et al.* (1994a), USA, 1984–85	80 (56 men, 24 women) with second primary cancers from cohort of 1090 (first primary cancers) 189 (132 men, 57 women) randomly selected from cohort that were free of second primary cancer at the end of follow-up (1989)	Interviewer-administered questionnaire	Oral cavity, pharynx, oesophagus, larynx	*Years since last drank alcohol* Current drinker <5 years ≥5 years	 29 17 7	 1 (reference) 5.4 (1.6–18.0) 1.9 (0.6–6.7)	Age, stage of disease, amount smoked and drunk	

Table 2.8 (continued)

Reference, study location, period	Characteristics of study population	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment factors	Comments
Hayes *et al*. (1999), Puerto Rico, 1992–95	342 (286 men, 56 women) identified through pathology laboratories and Central Cancer Registry; aged 21–79 years; histologically confirmed; response rate, 70% 521 (417 men, 104 women) population-based controls; frequency-matched by age, gender; response rate, 83%	Interviewer-administered questionnaire	Oral cavity, pharynx (ICD9 141–143–146, 148, 149)	*Years since last drink* **Men** Non-drinker Recent use Quit 2–9 years Quit 10–19 years Quit ≥20 years **Women** Non-drinker Recent use Quit 2–9 years Quit 10–19 years Quit ≥20 years	 9 163 60 34 20 26 15 6 5 4	 1 (reference) 2.4 (.0–5.4) 3.6 (1.5–9.0) 2.7 (1.0–7.0) 1.3 (0.5–3.6) 1 (reference) 1.2 (0.4–3.4) 1.0 (0.2–5.4) 1.1 (0.2–6.4) 0.9 (0.2–4.8)	Age, tobacco use	

Table 2.8 (continued)

Reference, study location, period	Characteristics of study population	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment factors	Comments
Franceschi *et al.* (2000), Italy, Switzerland, 1992–97	754 (638 men, 116 women) cases from major teaching and general hospitals in Pordenone, Rome, Latina (Italy) and Vaud (Switzerland); aged 22–77 years; histologically confirmed; response rate, 95% 1775 (1254 men, 521 women) hospital-based non-cancer controls from the same network of hospitals as cases; excluded tobacco- and alcohol-related conditions; frequency-matched (5:1 for women, 2:1 for men controls:cases) on age, sex, area of residence; response rate, 95%	Interviewer-administered questionnaire	Oral cavity, pharynx (excluding lip, salivary glands, nasopharynx)	*Years since quit drinking* 1–3 years 4–6 years 7–10 years ≥11 years χ^2 for trend	 27 37 36 26	 1.2 (0.6–2.4) 1.8 (1.0–3.5) 3.3 (1.5–7.3) 1.9 (1.0–3.8) 1.6 (p = 0.21)	Age, sex, study centre, education, interviewer, tobacco smoking, total alcoholic beverage consumption	Study population from Franceschi *et al.* (1999)

Table 2.8 (continued)

Reference, study location, period	Characteristics of study population	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment factors	Comments
Garrote *et al.* (2001), Havana, Cuba, 1996–99	200 (143 men, 57 women) cases identified in the Instituto Nacional de Oncologia y Radiobiologia of Havana; median age, 64 years; response rate, 88% 200 (136 men, 64 women) hospital-based controls admitted to same institute and three other major hospitals in Havana; excluded patients with alcohol- and tobacco-related conditions; frequency-matched on age, sex; median age, 62 years; response rate, 79%	Interviewer (dentist)-administered questionnaire	Oral cavity, oropharynx	*Years since quit drinking* Current drinker <10 years ≥10 years χ^2 for trend	 81 21 14	 1 0.7 (0.3–1.8) 0.3 (0.1–0.8) 5.00 (p=0.03)	Age, sex, area of residence, education, smoking	

Table 2.8 (continued)

Reference, study location, period	Characteristics of study population	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment factors	Comments
Balaram, *et al.* (2002), southern, India, 1996–99	591 (309 men, median age, 56 years; 282 women, median age, 58 years) from three centres in Bangalore, Madras, Trivandrum; response rate, 97% 582 (292 men, 290 women) hospital-based from the same hospitals as cases; frequency-matched by centre, age, sex; response rate, 90%	Interviewer-administered questionnaire	Oral cavity	**Men only** *Years since quit drinking* Current drinkers <10 years ≥ 10 years *p* for trend	 84 49 16	 1 0.94 (0.43–2.09) 0.62 (0.19–2.05) 0.55	Centre, age, education, paan chewing, smoking, drinking	
Castellsagué, *et al.* (2004), Spain, 1996–99	375 (304 men, 71 women); mean age, 60 years; response rate, 76.5% 375 (304 men, 71 women); mean age, 60 years; response rate, 91%	Interviewer-administered questionnaire	Oral cavity, oropharynx	*Years since quit drinking* Never drinker Current drinker 1–2 years 3–7 years 8–13 years ≥14 years *p* for trend	 35 251 28 22 20 19	 1 (reference) 3.5 (1.9–6.5) 3.9 (1.7–9.1) 1.7 (0.8–3.9) 2.3 (1.0–5.3) 1.5 (0.7–3.3) 0.003	Age group, sex, education, centre, average number of cigarettes per day	

Table 2.8 (continued)

Reference, study location, period	Characteristics of study population	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment factors	Comments
De Stefani *et al.* (2004), Montevideo, Uruguay, 1997–2003	85 men identified in the four major hospitals in Montevideo; microscopically confirmed; response rate, 97.5% 640 hospital-based men from the same hospitals as cases; excluded patients with alcohol- and tobacco-related conditions with no recent changes in diet; frequency-matched (2:1 controls:cases) on age, residence; response rate, 97%	Interviewer-administered questionnaire	Hypopharynx	*Years since quit drinking* Current drinker 1–4 years 5–9 years ≥10 years Never drinker *p* for trend	 66 8 4 3 4	 1 (reference) 1.4 (0.6–3.2) 1.3 (0.4–4.3) 0.4 (0.1–1.5) 0.2 (0.1–0.5) 0.0007	Age, residence, urban/ rural status, education, body mass index, smoking	Looked at oral cavity, type of alcoholic beverage and joint effect of smoking

CI, confidence interval; ICD, International Classification of Diseases

Table 2.9 Risk of consumption of alcoholic beverages for cancers of the oral cavity and pharynx among nonsmokers

Reference, study location, period	Characteristics of study population	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment factors	Comments
Talamini *et al.* (1990a), Milan, Pordenone, Italy, 1986–89	27 (six men, 21 women) 572 (288 men, 284 women) hospital-based; matched on age, area of residence	Interviewer-administered questionnaire	Oral cavity, pharynx	*Total alcohol* <14 drinks/ week 14–55 drinks/ week >55 drinks/ week χ^2 for trend	 11 14 2	 1 (reference) 1.5 (0.6–3.7) 2.2 (0.2–27.9) 4.08 (p=0.04)	Age, sex	Includes study population from Franceschi *et al.* (1990); reference group included '0' drinks/ week and <14 drinks/ week

Table 2.9 (continued)

Reference, study location, period	Characteristics of study population	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment factors	Comments
Ng *et al.* (1993), USA, 1977–91	173 (100 men, 73 women) whites in eight US cities; histologically confirmed 613 (254 men, 359 women) hospital-based; matched (up to 4:1 controls:cases) on age, sex, date of interview; excluded patients with tobacco-related conditions	Interviewer-administered questionnaire	Oral cavity, pharynx (ICD9 141, 143–146, 148, 149)	*Total alcohol (oz. of whiskey equiv./day)*				Nonsmokers of study from Kabat *et al.* (1994)
				Men				
				Non-drinker	13	1 (reference)		
				<1 oz/day	20	1.3 (0.6–3.1)		
				1–2.9 oz/day	19	2.4 (1.0–5.6)		
				3–6.9 oz/day	13	2.9 (1.1–7.6)		
				≥7 oz/day	8	4.4 (1.4–13.7)		
				χ^2 for trend		11.7 (p<0.001)		
				Women				
				Non-drinker	55	1 (reference)		
				<1 oz/day	34	0.9 (0.5–1.6)		
				1–2.9 oz/day	7	0.9 (0.3–2.6)		
				3–6.9 oz/day	1	0.4 (0.0–7.1)		
				≥7 oz/day	3	2.6 (0.5–13.3)		
				χ^2 for trend		0.00 (NS)		

Table 2.9 (continued)

Reference, study location, period	Characteristics of study population	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment factors	Comments
Talamini *et al.* (1998), Italy, Switzerland, 1992–97	60 (20 men, 40 women) from Pordenone, Rome, Latina (Italy) and Vaud (Switzerland); aged 22–77 years; histologically confirmed; response rate, 95% 692 (346 men, 346 women) hospital-based; response rate, 95%	Interviewer-administered questionnaire	Oral cavity, pharynx	*Total alcohol* Never drinkers <21 drinks/ week 21–34 drinks/ week 35–55 drinks/ week ≥56 drinks/ week Former drinkers (abstain ≥1 year) χ^2 for trend	 16 23 4 7 3 7	 1 (reference) 0.8 (0.4–1.6) 0.8 (0.2–2.7) 5.0 (1.5–16.1) 5.3 (1.1–24.8) 2.0 (0.7–5.4) 6.2 (0.01)	Age, sex, education, study centre	Study population from Franceschi *et al.* (2000)

Table 2.9 (continued)

Reference, study location, period	Characteristics of study population	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment factors	Comments
Fioretti *et al.* (1999), Milan, Pordenone, Italy, 1984–93	42 (10 men, 32 women) lifelong nonsmokers from a network of general and teaching hospitals in Milan and Pordenone; histologically confirmed 864 (442 men, 422 women) hospital-based non-cancer nonsmokers; matched on age, area of residence; excluded patients with tobacco-related conditions	Interviewer-administered questionnaire	Oral cavity, pharynx	*Total alcohol* Non-drinkers >0–<3 drinks/day ≥3 drinks/day Wine drinkers Beer drinkers Spirit drinkers	 4 25 13 37 7 5	 1 (reference) 3.4 (1.1–10.1) 2.6 (0.7–9.3) 3.3 (1.1–9.6) 3.3 (0.7–16.4) 1.0 (0.2–6.1)	Age, sex, education, study centre	Study population from Franceschi *et al.* (1990)

Table 2.9 (continued)

Reference, study location, period	Characteristics of study population	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment factors	Comments
Hashibe *et al.* (2007a), International Consortium of Head and Neck Cancer; combined analysis of 15 studies from USA, South and Central American, European countries	383 who never used tobacco 5775 who never used tobacco	Interview or self-administered questionnaire	Oral cavity (ICD9 140, 141, 143–5)	*Total alcohol*			Adjusted for age, sex, race/ ethnicity, education, study centre	
				Never	243	1.00 (reference)		
				Ever	137	1.17 (0.92–1.48)		
				<1 drink/day	44	1.14 (0.8–1.63)		
				1–2 drinks/day	60	1.64 (1.19–2.25)		
				3–4 drinks/day	10	1.11 (0.57–2.15)		
				≥5 drinks/day	8	1.23 (0.59–2.57)		
				p for trend		0.032		
				Duration				
				1–10 years	21	2.36 (1.43–3.88)		
				11–20 years	17	1.09 (0.65–1.85)		
				21–30 years	19	0.81 (0.49–1.33)		
				31–40 years	35	1.29 (0.88–1.9)		
				>40 years	32	1.15 (0.77–1.73)		
				p for trend		<0.001		

Table 2.9 (continued)

Reference, study location, period	Characteristics of study population	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment factors	Comments
Hashibe *et al.* (2007a) (contd)	369 who never used tobacco 5775 who never used tobacco		Oro-pharynx/ hypo-pharynx (ICD9 146, 148)	*Total alcohol*				
				Never	153	1.00 (reference)		
				Ever	216	1.38 (0.99–1.94)		
				<1 drink/day	73	1.39 (0.99–1.96)		
				1–2 drinks/day	83	1.66 (1.18–2.34)		
				3–4 drinks/day	24	2.33 (1.37–3.98)		
				≥5 drinks/day	29	5.50 (2.26–13.36)		
				p for trend		<0.001		
				Duration				
				1–10 years	18	1.76 (0.99–3.14)		
				11–20 years	28	1.34 (0.81–2.11)		
				21–30 years	63	1.95 (1.37–2.77)		
				31–40 years	61	1.44 (0.78–2.66)		
				>40 years	37	1.51 (0.68–3.37)		
				p for trend		<0.001 (0.003)		

Table 2.9 (continued)

Reference, study location, period	Characteristics of study population	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment factors	Comments
Hashibe *et al*. (2007a) (contd)	155 who never used tobacco 4983 who never used tobacco		Oral cavity or pharynx NOS (ICD9)	*Total alcohol*				
				Never	80	1.00 (reference)		
				Ever	72	1.09 (0.77–1.54)		
				<1 drink/day	25	1.08 (0.67–1.75)		
				1–2 drinks/day	26	1.24 (0.77–1.99)		
				3–4 drinks/day	13	2.32 (1.24–4.34)		
				≥5 drinks/day	4	0.77 (0.27–2.18)		
				p for trend		<0.891		
				Duration				
				1–10 years	13	2.59 (1.38–4.86)		
				11–20 years	11	1.09 (0.56–2.11)		
				21–30 years	18	1.26 (0.73–2.17)		
				31–40 years	14	0.86 (0.47–1.57)		
				>40 years	13	0.92 (0.49–1.71)		
				p for trend		<0.014		

CI, confidence interval; ICD, International Classification of Diseases; NOS, not otherwise specified; NS, not significant

cases from Pordenone, Rome, Latina (Italy) and Vaud (Switzerland) were identified from 1992 to 1997 and compared with 692 hospital-based controls (Talamini *et al*., 1998). Again, a dose–response relationship was seen between alcoholic beverage consumption and cancer of the oral cavity and pharynx (P=0.01). The Pooling Project, the International Head and Neck Cancer Epidemiology Consortium, reported associations between alcoholic beverage consumption and oral and pharyngeal cancer among nonsmokers (Hashibe *et al*., 2007a). The study included 384 cases of oral cancer, 369 oropharyngeal or hypopharyngeal cancers, 155 cases of oral and pharyngeal (not otherwise specified) cancer and 5775 controls. A significant dose–response relationship was observed for oro- and hypopharyngeal cancer for both frequency and duration of alcoholic beverage consumption. The adjusted odds ratios were 1.66 (95% CI, 1.18–2.34) for 1–2 drinks per day, 2.33 (95% CI, 1.37–3.98) for 3–4 drinks per day and 5.5 (95% CI, 2.26–13.36) for five or more drinks per day. The association was weaker for cancer of the oral cavity.

In addition, among 25 studies of effect modification listed in Table 2.7, the effect of alcoholic beverage consumption was presented in 17 (Blot *et al*., 1988; Franceschi *et al*., 1990; Zheng *et al*., 1990; Kabat *et al*., 1994; Chyou *et al*., 1995; Murata *et al*., 1996; Sanderson *et al*., 1997; Zheng *et al*., 1997; Schildt *et al*., 1998; Franceschi *et al*., 1999; Hayes *et al*., 1999; Schlecht *et al*., 1999; Garrote *et al*., 2001; Schwartz *et al*., 2001; Balaram *et al*., 2002; Boeing, 2002; Castellsagué *et al*., 2004). The majority of these studies found a strong association with alcoholic beverage consumption among nonsmokers with a dose–response relationship. A strong association and a dose–response relationship between alcoholic beverage consumption and the risk for oral and pharyngeal cancers demonstrated strong evidence for the carcinogenic effect of alcoholic beverage consumption.