Pergamon

Oral Oncol, Eur J Cancer Vol. 32B, No. 5, pp. 293–305, 1996

Printed in Great Britain
0964-1955/96 $15.00+0.00

PII: S0964-1955(96)00002-4

Epidemiology of Laryngeal Cancer

M.S. Cattaruzza, P. Maisonneuve and P. Boyle

Division of Epidemiology and Biostatistics, European Institute of Oncology, via Ripamonti 435, 20141 Milan, Italy

Laryngeal cancer is the second most common respiratory cancer after lung cancer. Its incidence is increasing over time in much of the world and this increase is generally accepted to be related to changes in tobacco and alcohol consumption. It is a relatively common cancer in men, but rarer in women. Moreover, interesting new issues have been raised recently about the influence of other possible risk factors. Evidence from epidemiological studies which supports the involvement of new risk factors in the aetiology of larynx cancer, as well as new perspectives in therapy, must be taken into consideration in order to realise primary and tertiary prevention. However, it remains clear that, even as new evidence continues to amass about a wide range of risk factors, primary prevention of the great majority of laryngeal cancers could be achieved by elimination of tobacco smoking and reduction of consumption of alcoholic beverages. With an additional contribution from adoption of a diet rich in fruits and vegetables, the great majority of laryngeal cancer appears to be preventable within our current epidemiological knowledge.

Key words: larynx cancer, epidemiology, tobacco smoking, alcohol consumption, diet, prevention

Oral Oncol, Eur J Cancer, Vol. 32B, No. 5, pp. 293–305, 1996

INTRODUCTION

Laryngeal cancer is the second most common respiratory cancer after lung cancer. Its incidence is increasing over time in much of the world and this increase is generally accepted to be related to changes in tobacco and alcohol consumption. It is a relatively common cancer in men, but rarer in women. Moreover, interesting new issues have been raised recently about the influence of other possible risk factors. Here, the most important research findings from analytical epidemiological studies as well as the most recent trends from descriptive epidemiological analysis are reviewed in light of the most recently published articles (from 1990 onwards with few exceptions).

PROBLEMS ABOUT CLASSIFICATION

It is now well known that cancer of the epilarynx and endolarynx differ in many ways, including in their descriptive epidemiology and aetiology. The epilarynx, being at the junction between the respiratory system and the digestive tract, is exposed both to inhaled and ingested agents. There are good reasons, *a priori*, to believe that a change in alcohol intake could have a greater effect on epilarynx cancer, while a change in tobacco consumption could be reflected more in changes in endolarynx cancer. Prognostic and therapeutic benefits could also rise from a more detailed classification. Therefore, when evaluating larynx cancer, it would be highly desirable to adopt a new classification which could at least distinguish between the epilarynx and endolarynx [1–6]. Unfortunately, there is no such classification in common usage and it remains virtually impossible to investigate the separate epidemiology of the different anatomic parts of the larynx.

DESCRIPTIVE EPIDEMIOLOGY

Laryngeal cancer is the eleventh most common cancer in men world-wide with an estimate of 121 000 new cases in 1985 [7]. The highest incidence rates recorded in men around the mid-1980s, from over 160 population-based cancer registries, were from Spain, France, Italy, Brazil and Poland (Table 1). In women, the highest rates were much lower, being highest in population groups in North America. In both sexes, the lowest rates were recorded in a diverse series of population groups around the world.

From around 1950 onwards, laryngeal cancer has been seen to increase in occurrence in many countries, both in men and women (Table 2). Incidence is higher among black than in white residents of the same geographical region, and is slightly more common in urban than in rural areas [8, 9].

Correspondence to P. Boyle.
Received and accepted 9 Jan. 1996.

Table 1. Ten highest and ten lowest incidence rates of cancer of the larynx (ICD-9 161) recorded in men and women around the mid-1980s

Male registry	Period	Cases*	Rate†	Female registry	Period	Cases*	Rate†
Spain, Basque Country	86–87	520	20.36	U.S., New Orleans: Black	83–87	36	3.75
Spain, Navarra	83–86	238	17.84	U.S., Connecticut: Black	83–87	21	3.44
France, Somme	83–84	110	17.53	Thailand, Chiang Mai	83–87	51	2.57
Spain, Granada	85–87	219	16.15	U.S., Detroit: Black	83–87	65	2.55
Spain, Zaragoza	83–85	269	16.06	U.S., New Orleans: White	83–87	57	2.37
Brazil, Porto Alegre	87–87	68	15.98	U.S., Los Angeles: Black	83–87	58	2.36
Italy, Trieste	84–85	78	15.00	Canada, PEI	83–87	8	2.30
Poland, Lower Silesia	84–87	486	15.30	Cuba	86–86	111	2.25
Spain, Murcia	84–87	339	15.25	U.S., Alameda: Black	83–87	12	2.18
Italy, Varese	83–87	377	14.88	U.S., Bay Area: Black	83–87	24	2.15
U.S., Los Angeles: Chinese	83–87	5	1.75	China, Qidong	83–87	0	—
Thailand, Khon Kaen	88–89	14	1.74	U.S. Hawaii: Chinese	83–87	0	—
U.S., Hawaii: Chinese	83–87	4	1.71	The Gambia	87–89	0	—
Bermuda: White and Other	83–87	2	1.43	Bermuda: Black	83–87	0	—
U.S., Los Angeles: Filipino	83–87	5	1.41	Canada, NWT & Yukon	83–87	0	—
Singapore: Malay	83–87	7	1.20	Kuwait: Kuwaitis	83–87	0	—
U.S., Los Angeles: Japanese	83–87	4	0.93	U.S., Los Angeles: Chinese	83–87	0	—
Mali, Bamako	87–89	4	0.93	Thailand, Khon Kaen	88–89	0	—
The Gambia	87–89	6	0.88	Peru, Trujillo	84–87	0	—
China, Qidong	83–87	3	0.13	U.S., Los Angeles: Japanese	83–87	0	—

Data abstracted from [7].
*Number of incident cases over the time period.
†Age standardised (world) rates per 100 000.

Laryngeal cancer refers almost exclusively to squamous carcinomas, even if the larynx may be a potential site for all histological types of neoplasms; the incidence peak is in the sixth and seventh decade of life [10–12], but some cases have also been reported in children [13].

In the United States (Texas), the incidence has increased from 5.6 to 9.0 per 100 000 in men and from 0.5 to 1.5 per 100 000 in women during the period 1947–1984 [14]. In Canada, in men, both the truncated and overall age-adjusted mortality rates showed an increase between 1955 and 1980. Male birth cohort analysis indicated an increase in mortality rates in successive birth cohorts for age groups over 50, while for age groups before 50 there is no remarkable change in rates in successive birth cohorts [15].

In Australia, between 1955 and 1975, the standardised (truncated) mortality rates in men showed an increase which thereafter stabilised. No clear time trend was observed for overall age-adjusted mortality rates in either men or women. Birth cohort analysis therefore, revealed an increase in rates in successive birth cohorts for age groups

Table 2. Incidence of cancer of the larynx (ICD-9 161) in selected cancer registries, 1960–1985

Cancer	Males						Females					
registry	Vol. 1	Vol. 2	Vol. 3	Vol. 4	Vol. 5	Vol. 6	Vol. 1	Vol. 2	Vol. 3	Vol. 4	Vol. 5	Vol. 6
Canada, Manitoba	3.29	4.73	3.72	4.20	5.59	5.49	0.24	0.57	0.41	0.70	0.96	0.87
Canada, Saskatchewan	0.65	3.01	2.41	3.11	4.53	4.43	0.00	0.42	0.39	0.45	0.60	0.80
U.S., Alameda, White		6.10	7.89	7.14	6.51	6.86		0.61	1.11	1.25	1.20	1.73
U.S., Alameda, Black		4.33	12.88	10.81	9.70	12.78		0.00	1.66	1.26	1.25	2.18
U.S., Connecticut,	7.07	7.47	7.80	8.20			0.59	0.81	0.93	1.17		
U.S., Connecticut, White					7.74	7.42					1.67	1.38
U.S., Connecticut, Black					12.59	9.99					2.70	3.44
India, Bombay		13.76	13.62	12.86	9.96	8.94		2.83	2.57	2.64	2.00	1.58
Japan, Miyagi	2.82	2.41	2.05	2.20	2.23	3.45	0.73	0.33	0.20	0.32	0.23	0.20
Denmark	1.48	2.54	3.51	4.24	5.25	5.56	0.20	0.31	0.50	0.73	0.84	1.20
Finland	6.84	6.65	7.06	5.47	4.51	4.30	0.42	0.31	0.38	0.30	0.35	0.27
Norway	1.60	2.03	2.41	2.82	3.13	3.53	0.04	0.21	0.22	0.20	0.30	0.30
Sweden	1.84	2.05	2.39	2.79	2.77	2.66	0.21	0.19	0.25	0.27	0.33	0.34
U.K., Birmingham	3.52	3.78	3.87	4.05	3.69	4.36	0.31	0.48	0.52	0.54	0.55	0.75
New Zealand, Non-Maori		3.38	3.35	3.95	4.09	4.02		0.19	0.38	0.45	0.46	0.53

Data are abstracted from *Cancer Incidence in Five Continents*, Vols 1–6.
The time periods covered are Vol. 1 (around 1960–1963), Vol. 2 (around 1963–1966). Vol. 3 (around 1968–1972), Vol. 4 (around 1973–1977), Vol. 5 (around 1978–1982), Vol. 6 (around 1983–1987).

between 40 and 59 in men but, for all other age groups, the rates were similar in successive birth cohorts [15].

In Europe, Spain is one of the countries with the highest incidence in the world and with a large number of regions involved: the Basque region has an incidence rate of 20.4, Navarra 17.8, Granada 16.2 and Zaragoza 16.1 [16–18]. From a recent study, it seems that in Segovia province the incidence is increasing too. In Murcia, the supraglottic region was the most common location (67%) [20].

Other countries with high rates of laryngeal cancer include: France, Poland, Italy and Brazil (for Brazil, the possible relationship with mate drinking (a tea-like infusion) is discussed in the risk factors section below).

In Poland (Warsaw), the incidence per 100 000 has risen in men from 7.6 in 1970 to 11.4 in 1980 and during the same period mortality has also risen (both truncated and overall age-adjusted mortality rates have risen in the whole of Poland) [21]. In less than 30 years, the standardised (truncated) rates experienced a more than six-fold increase from 2.4 per 100 000 in 1959 to 15.2 per 100 000 in 1988. Birth cohort analysis showed an increase in mortality rates in successive birth cohorts for age groups older than 39 years in men and in almost all age groups in women [15].

In Italy, an increasing trend in incidence and a decreasing trend in mortality has been reported. In particular, in the male population, the world-standardised mortality rates per 100 000 dropped from 4.8 in 1970 to 4.2 in 1989, a decrease of about 13%, while estimated age-standardised incidence rates per 100 000 increased from 10.0 in 1970 to 12.2 in 1989, corresponding to an increase of 22%. These features have been the subject of an investigation from which a 3% annual increase in survival for larynx carcinoma has been estimated [22]. Birth cohort analysis suggested an increase in mortality rates in successive male birth cohorts until the cohort born in 1930. For cohorts after 1930 the mortality rates have been decreasing [15]. As the highest incidence is the seventh decade of life, the addition of 70 years to the year 1930 (the birth year with the higher risk) implies that at the end of the century there will be the highest number of new cases. After the year 2010 the incidence rate should decline [23].

In Italy, the north has incidence rates higher than the central and south. This north/south gradient in incidence and mortality was consistently observed in geographical and migrant studies on respiratory cancer in Italy, but it is restricted to men only. For women, the rate fluctuates around 1 per 100 000. However, there does not seem to be any relationship with latitude [24–27].

In Denmark, only recently has the truncated and overall age-adjusted mortality rates showed an increase for both sexes. In men, the rates peaked in 1984 and started to decrease thereafter; the analysis of birth cohorts showed an increase in rates in successive birth cohorts for age groups over 40 [15]. The 5-year survival rates are 61% and 62%, respectively, in men and women in the 1980s [28].

In Germany and Czechoslovakia, an increase in mortality rates (both truncated and the overall age-adjusted) has been observed since 1955 and examination by birth cohort showed a current increasing trend in successive birth cohorts born after 1915 for German men [15].

In general, the situation in Central Europe presents a very interesting and consistent pattern of dramatic increases in the mortality of laryngeal cancer by birth cohort (Fig. 1). There are important increases notable in the neighbouring countries of Switzerland, Austria, Germany, Poland, Hungary and Czechoslovakia. These increases are remarkably consistent given the cultural differences which exist between the groups of countries and provide an aetiological lead of considerable potential significance.

Finally, in the United Kingdom, mortality rates declined between 1955 and 1970 in both sexes; thereafter they have been relatively stable. Consequently the birth cohort examination showed a decline in rates in successive birth cohorts in men until the cohort born in 1925, and relatively stable rates for recent birth cohorts [15].

Gender

Larynx cancer has traditionally been considered to be a disease with a high incidence in men, but the male-to-female ratio has been seen to decrease in many countries (e.g. Belgium, United States), because of an increasing incidence in women. Moreover, the male-to-female ratio varies according to the site, being higher for carcinoma of the glottis [10, 29].

In Italy (Trieste), for example, between 1979 and 1988, the overall crude incidence rate was 31.06 per 100 000 in men and 2.29 per 100 000 in women with a male/female ratio of 10.2 for supraglottic cancer compared to 21.4 for glottic cancer [4]. Similar incidence rates are recorded for other areas of Italy, France, and Spain where wine production and consumption is very high.

In Poland, in a study which covered the years from 1960 to 1987, the reported male to female incidence ratio was 11.5 [30]. A different study [15], which took into consideration data from 1959 to 1988, showed a slow but steady increase in mortality for women, although the rates were very low.

In Eastern Austria, the incidence of laryngeal cancer for women became somewhat greater during the last two decades [31]. In Germany, no clear time trend was observed for female mortality rates, either using truncated or overall age-adjustment; an increase in the rate in successive birth cohorts was evident only for age groups between 40 and 59. In Czechoslovakia, female mortality rates have been fairly stable since 1955 [15]. In the United Kingdom, the mortality rates have been decreasing in successive birth cohorts for age groups below 55, but above this age each 5-year age group had recorded an increase in recent time periods [15].

Outside Europe, the situation does not seem to differ very much. In the United States, in Colorado, a review of the Colorado Central Cancer Registry from 1979 to 1990 showed a significant trend of an increasing proportion of female cases. For total larynx cancer, the observed male to female ratio was 4.3, but for glottic carcinoma, it was 7.6 [29]. In Texas, again through a review of the Cancer Registry files from 1959 to 1973 and from 1974 to 1988, a decrease in the male-to-female ratio was noted: from 5.6 in the first 15-year period to 4.5 to 1 in the second 15-year period, reflecting an increasing incidence in women [14].

In Canada, since 1955 a modest but steady increase in both the truncated and overall age-adjusted mortality rate was observed for women [15]. In Malaysia (Kuala Lumpur) between 1981 and 1988, in a retrospective study to investigate larynx cancer, a male to female ratio of 7.6 was found

[32]. In Cuba (Camaguey), in a study conducted between 1985 and 1992 based on 168 cases in total, cases were predominantly men, but the relative frequency among women was high (15.4%), exceeding that usually reported in the literature [11, 33].

ANALYTICAL EPIDEMIOLOGY

Classically, cigarette smoking and alcohol drinking have been considered the most important risk factors for laryngeal cancer due to the magnitude of the relative risk estimates and the consistency of the findings among the variety of epidemiological studies. There has generally been a consistent finding of an interaction between cigarette smoking and alcohol consumption on laryngeal cancer risk, i.e. the joint effects of both cigarette smoking and alcohol consumption are greater than the sum of the individual effects. Nevertheless, the nature and biological aspects of the interaction between tobacco and alcohol are still not clear.

Other risk factors have been assessed and the advancement of research in these areas has raised some interesting issues which merit attention. The most important and recent results are reviewed below together with a broad account of those already known.

Tobacco smoking

Tobacco smoking has long been recognised as a major cause of larynx cancer and especially of the endolarynx [34–37].

Tuyns *et al.* [1] published results regarding tobacco and alcohol consumption from a large, multicentre, case–control study comprising 1147 male cases (cancer of the larynx and hypopharynx) and 3057 male controls. The risk associated with cigarette smoking was approximately 10 for all subsites of the larynx and hypopharynx considered. The risks for alcohol drinking, however, varied by site, being higher for the epilarynx and hypopharynx (OR = 4.3 for 80 g/day or more) but lower at the same dose for the endolarynx (OR = 2.1). Risk decreased within 10 years of quitting cigarette smoking and smokers of blond tobacco were found to have about half the risk of smokers of black tobacco. The authors also reported that the risks associated with joint exposure to alcohol and tobacco were consistent with a multiplicative relative risk model.

Franceschi *et al.* [38] report of a hospital-based, case–control study conducted in two regions of Northern Italy: Pordenone province and the Greater Milan area conducted between June 1986 and June 1989. It comprised 157 male

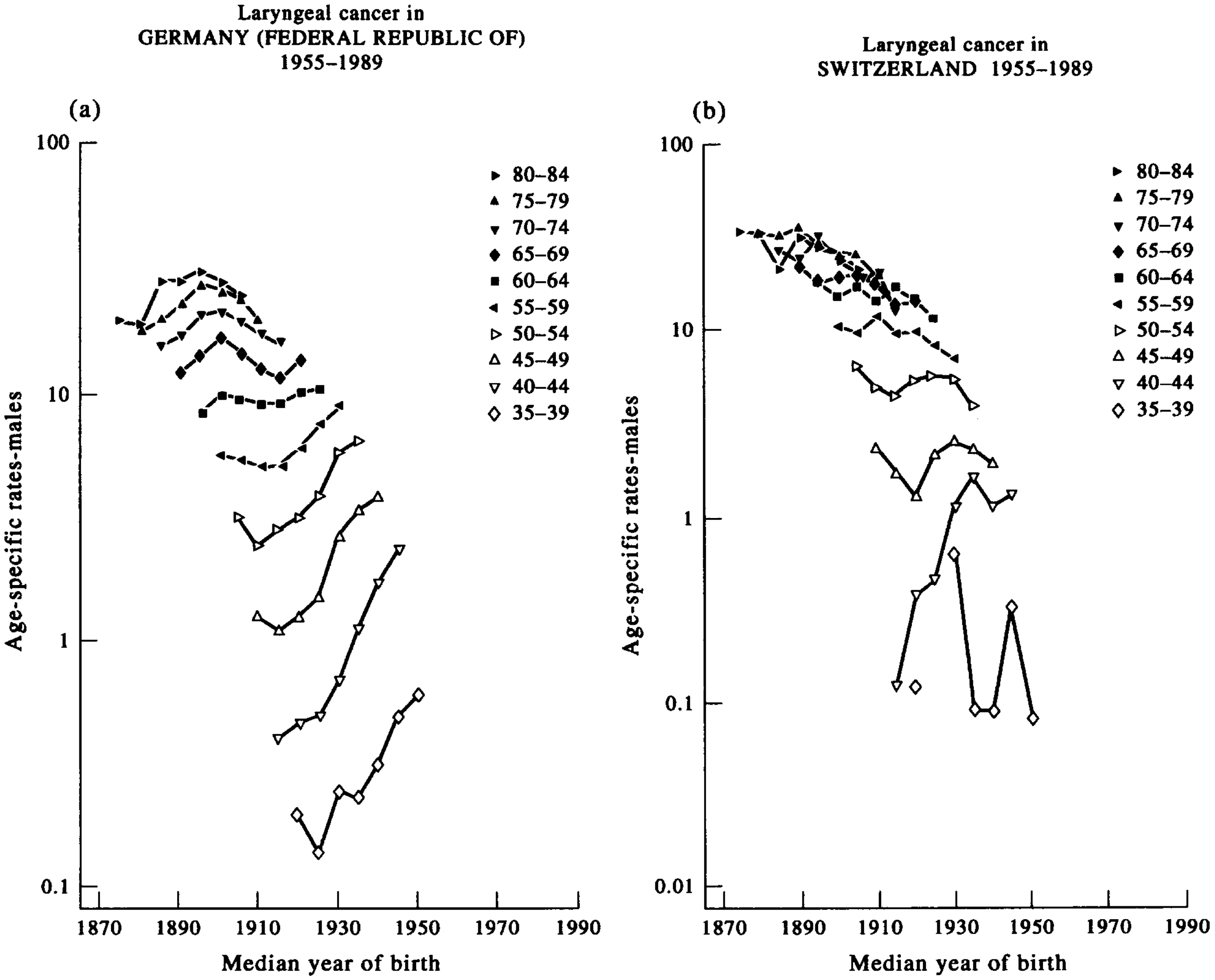

Fig. 1a, b.

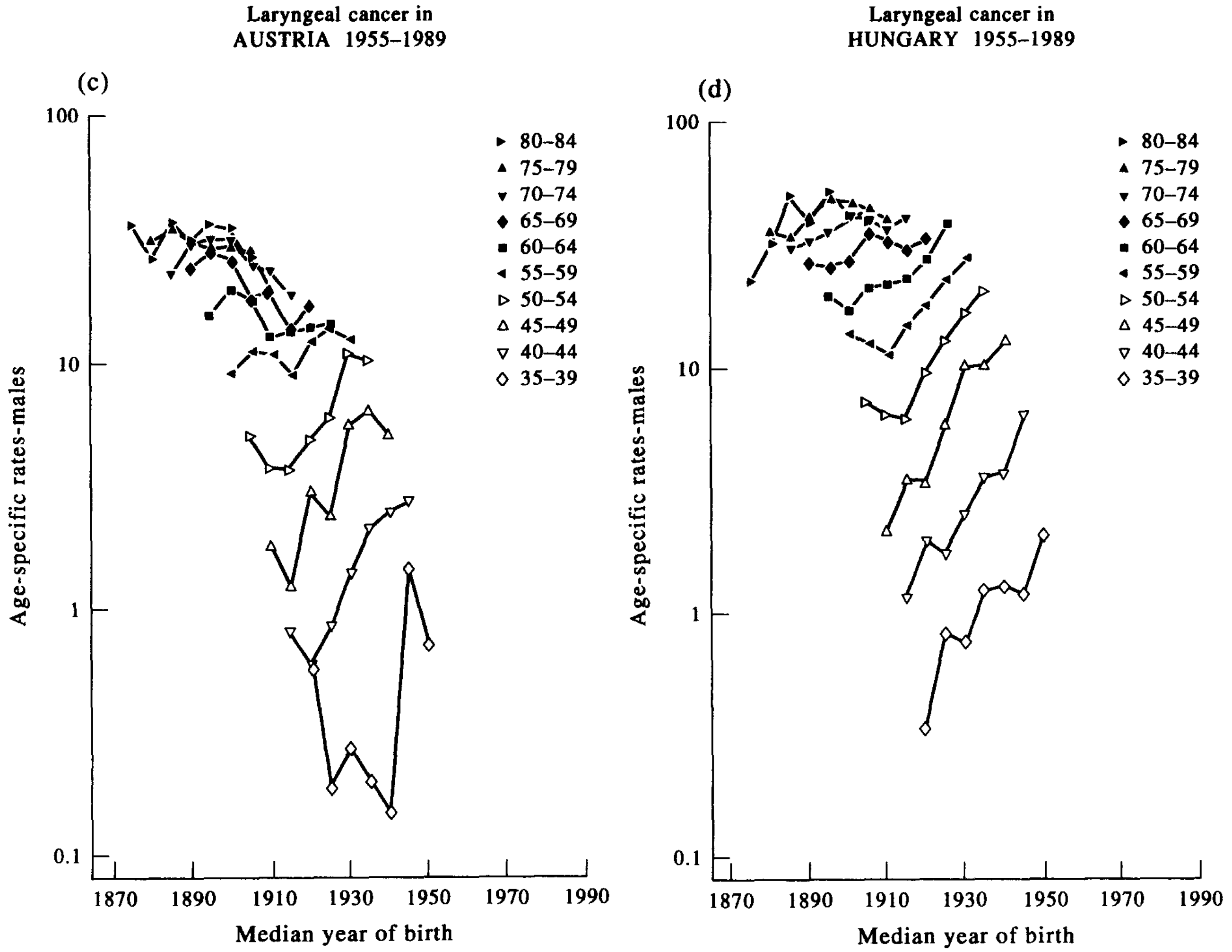

Fig. 1c, d.

cases of oral cancer (lip, tongue and mouth), 134 pharyngeal cancer (oropharynx, hypopharynx and the hypopharynx/larynx junction) and 1272 male in-patient controls. Odds ratios for current smokers of cigarettes were 11.1 for oral cavity and 12.9 for pharynx. For both sites, the risk increased with increasing number of cigarettes smoked and the duration of the smoking habit and decreased with time since quitting smoking. Smokers of pipes and cigars showed a more elevated risk of oral cancer than did cigarette smokers. Significantly elevated risks also emerged in heavy drinkers with the OR = 3.4 for oral cavity and 3.6 for pharyngeal cancer for drinkers of >60 compared to ⩾19 drinks per week deriving mainly from wine consumption. The risk of oral cancer and pharyngeal cancer for the highest levels of alcohol and smoking was 80-fold relative to the lowest levels of both factors.

The relationship between type of cigarettes smoked and the risk of cancer of the oral cavity and pharynx (excluding salivary gland and nasopharynx) was examined in a hospital-based case–control study involving 291 male cases and 1272 controls conducted in Pordenone Province and Greater Milan in Northern Italy (same study base as above) [39]. As the basis of classification, the authors used tar-yield and the brand smoked for the longest time (< 22 mg, low to medium tar; ⩾22 mg, high tar). After adjustment for other risk factors, relative to non-smokers the risk among ever-smokers for oral and pharyngeal cancers were 8.5 (95% C.I. (3.7, 19.4)) for low/medium and 16.4 (7.1, 38.2) for high tar cigarettes. For larynx cancer, the corresponding results were 4.8 (2.3, 10.1) and 7.1 (3.2, 15.6) relative to non-smokers. The authors concluded that these data provided further quantitative evidence of the importance of type of cigarette smoked on the risk of oral cancers as well as other cancers of the upper digestive and respiratory tract.

The incidence and mortality rates of laryngeal cancer in Poland are notably high and have been increasing for 25 years. Zatonski and Becker [21] report a study among persons under the age of 65 years in Lower Silesia, in south-west Poland, based on 249 newly-diagnosed cases and 965 controls. For smoking more than 30 cigarettes per day, the relative risk (RR) was 59.7 (13, 274) compared to non-smokers and the risk for consuming vodka regularly for 30 or more years was 10.4 (4, 27.2). Exposures to tobacco and alcohol showed a clear multiplicative effect in all categories of exposure. The risk of laryngeal cancer was shown to be reduced by quitting smoking or by having a history of intermittent smoking. Poor nutrition was identified as a strong independent risk factor in this study. It was estimated that smoking alone accounts for 95% of all cases of laryngeal cancer in this population.

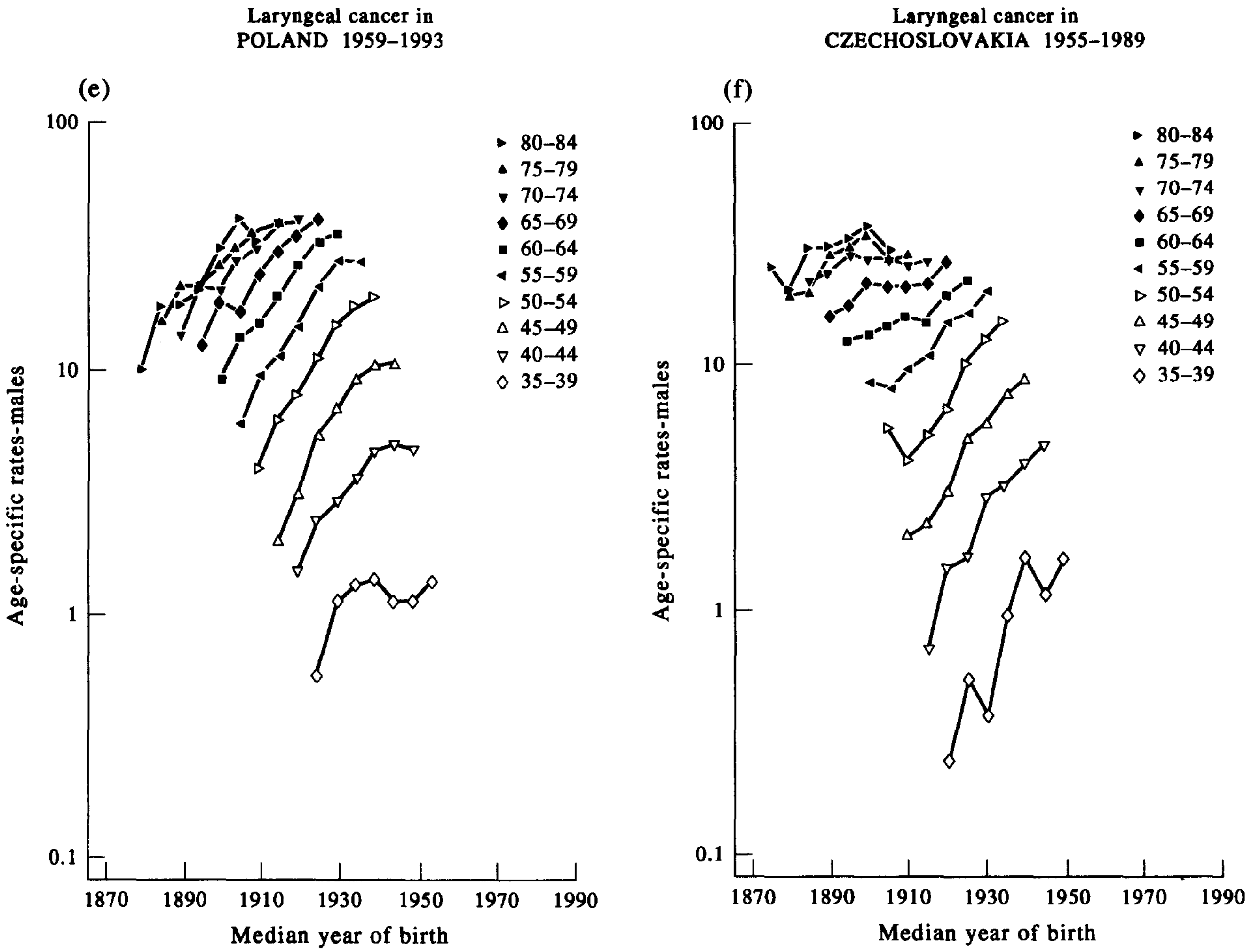

Fig. 1. Time trends in mortality from laryngeal cancer in birth cohorts of men in countries of central Europe. (a) Germany; (b) Switzerland; (c) Austria; (d) Hungary; (e) Poland; (f) Czechoslovakia.

According to a large population-based case–control study in Southern Europe, about 90% of the current incidence of larynx cancer could be prevented by avoiding smoking and alcohol consumption, tobacco being responsible for most of the risk [2, 27]. A case–control study conducted in Poland estimated that smoking alone accounted for 95% of all cases of laryngeal cancer [21]. Similar conclusions have been drawn from an Italian study aimed at evaluating the impact of a reduction of cigarette smoking on mortality [35].

From a case–control study conducted in Liaoning province (China) between 1991 and 1992, smoking was the most important risk factor with an OR of 16.8 and tobacco smoking in particular had an OR of 30.4 [40]. A different Chinese population-based case–control study conducted in Shanghai between 1988 and 1990, confirmed that cigarette smoking was the main risk factor for laryngeal cancer accounting for 86% of the male and 54% of the female cases. The adjusted (for age and education) OR was 8.7 (95% CI 3.8–19.6) for ever versus never smoking. The risk increased with both the quantity and duration of smoking, with a 25-fold excess in the heaviest consumption categories; it declined following cessation [41].

Tobacco smoking was found to be connected with an increased incidence of larynx cancer risk both among natives and immigrants in a case–control study conducted in Poland [42]. From a different Polish study, smoking more than 30 cigarettes per day gave an OR of 59.7 with a 95% confidence interval (C.I.) between 13 to 274 [43].

A case–control study conducted in Beograd, found that smoking more than 10 cigarettes per day resulted in an OR of 18.17 (95% CI 1.95–169.76). Also passive smoking was investigated and for an extended stay in closed space filled with cigarette smoke an OR of 2.67 was obtained (95% CI 1.08–6.60) [44].

Similarly in Spain, laryngeal cancer was found to be significantly associated with tobacco smoking; the association was found for smoking more than 15 cigarettes per day (filter tipped as well as non-filter tipped cigarettes) and having been smoking for more than 15 years [17].

Hand-rolled cigarettes have been found to be a greater risk of laryngeal cancer than commercial ones, in a study conducted in Uruguay (Montevideo) [45].

The analysis of data from a case–control study conducted in Northern Italy between 1986 and 1992 showed an OR of 8.8 (95% CI 5.2–14.8) for heavy current smokers compared to never smokers and an OR of 3.3 (95% CI 1.9–5.5) for ex- or moderate smokers. Estimates of attributable risk implied that 77% of laryngeal cancers in men were due to smoking [46].

In Heidelberg (Germany) for heavy smokers (greater than 60 pack-years) a RR of 23.4 (alcohol adjusted) was found [47, 48].

The risk of larynx cancer has been noted to increase with the intensity of the smoking habit: precocious age at the beginning, long duration, high number of pack-years, black tobacco use, deep inhalation of smoke, absence of quitting [12].

A dose-dependent effect for current cigarette smoking was observed in data from a hospital-based case–control study conducted in New York between 1985 and 1990. Estimates of the risk were calculated separately for supraglottic (OR from 21.6 to 68) and glottic cancer (OR from 5.5 to 20.7). Elevated risks were registered for ex-smokers (OR 4.8) and pipe and cigar smokers (OR 4.3) but they did not vary by subsite [49].

Similar results were obtained by another American case–control study (Seattle Western Washington): assuming as a reference category those who never smoked or those who quitted more than 15 years ago, the risk for those who quitted less than 15 years ago, for those who currently smoked less than 20 cigarettes per day, 20–39 cigarettes per day and 40 or more cigarettes per day were, respectively, 2.5 (1.4–4.3), 6.3 (3.1–11.8), 10.6 (6.5–18.7) and 23.1 (9.4–52.6) [9].

The risk of laryngeal cancer was shown to be reduced by smoking cessation [16]; having a history of intermittent smoking also seems to reduce the risk of laryngeal cancer compared with continual smoking, but this new finding, of considerable interest and potential importance with regard to possible mechanisms of laryngeal carcinogenesis, needs validation from further studies [43].

Finally, the results from a Japanese study (with an immunohistochemical and molecular approach) of a series of 41 laryngeal carcinomas, suggested that p53 abnormalities may be more likely to be related to smoking history than to infection with human papilloma virus (see below).

Alcohol drinking

The relationship between increased laryngeal cancer risk and alcohol consumption has been consistently demonstrated by a variety of epidemiological studies [50].

A large population-based case–control study in Southern Europe, found that reducing only alcohol consumption could prevent a quarter of the cases of laryngeal carcinoma [27].

The results from a case–control study conducted in Northern Italy were an OR of 1.5 (95% CI 1.0–2.2) for drinkers of six to seven alcoholic drinks per day and a OR of 2.2 (95% CI 1.6–3.0) for drinkers of eight or more drinks per day compared to teetotalers or moderate drinkers. Estimates of AR implied that alcohol intake accounted for 25% of cases [46]. Other estimates showed ORs for men and women, respectively, of 2.0 and 2.6 for people in the highest intake category (42 or more drinks/week in women and 42–55 drinks/week in men) as compared to light drinkers [51].

A dose-dependent effect for alcohol has often been noted [49, 52]. In a case–control study conducted in New York between 1985 and 1990, estimates of the risk, different for supraglottic and glottic cancer, were, respectively, 9.6 and 2.5 for heavy drinkers (207 ml or more/daily). Interestingly, binge drinkers had higher ORs: 28.4 and 8.3 for supraglottic and glottic cancer, respectively [49].

Similar results were obtained by another American case–control study (Seattle Western Washington): for 7–13, 14–20, 21–41 and 42 or more drinks per week the OR were respectively, 1.9 (95% CI 1.1–3.2), 2.1 (95% CI 1.0–4.4), 2.8 (95% CI 1.4–5.7) and 3.1 (95% CI 1.2–7.9) when compared to drinkers of less than seven drinks per week [9].

A Chinese case–control study revealed that there was little increase in risk associated with drinking alcoholic beverages after adjusting for smoking [41]. From a Polish case–control study, it has been estimated that consuming vodka regularly for 30 or more years is associated with an increased risk of laryngeal cancer (OR = 10.4, 95% CI (4–27.2)) [43]. It may be of further value to pursue such differences in countries where the consumption of alcoholic beverages is so contrasting.

A similar study (of laryngeal and hypopharyngeal cancer) from the United States classified liquour consumption roughly into 'dark' or 'light'. The relative effect on hypopharyngeal cancer risk was much stronger for those who reported high consumption of dark liquour (OR = 4.4, 95% CI (2.9, 6.8)) than for those reporting consumption of a comparable amount of light liquour (OR = 1.3, 90% CI (0.8, 2.1)). For laryngeal cancer, consumption of dark liquour was found to have a smaller effect with little distinction between the effects of light and dark. Rothman *et al.* [53] concluded that the results are consistent with non-alcoholic content of distilled alcoholic beverages being a determinant of cancer risk and that alcoholic beverages act topically rather than systemically.

Finally, the relationship between alcoholism and cancer of the larynx has been evaluated by a case–control study conducted in the United States [9]. The aim of the study was to determine if alcoholism (as measured by responses to the Michigan Alcoholism Screening Test (MAST)) was a risk factor for laryngeal cancer independently from alcohol consumption. They found an OR of 1.9 (95% CI 1.1–3.4) for a score of 5 or more compared with a score of 0, after having been adjusted for age, gender, average alcohol consumption and summary cigarette use. To investigate if there was a higher association for tissues that come into more direct contact with alcohol, they evaluated different multiple logistic regression models and obtained an OR of 1.9 (95% CI 1.0–3.7) for glottic and subglottic tumours and an OR of 2.3 (95% CI 0.9–5.5) for supraglottic tumours after having been adjusted for the same factors listed above. Possible explanations for the association between alcoholism and laryngeal cancer include the possibility that the MAST score may be serving as an additional measure of alcohol consumption, that is, measure of alcoholism improves the accuracy of assessment of alcohol consumption; that alcoholism is associated with a pattern of alcohol consumption (e.g. alcoholics may gulp drinks instead of sipping them, perhaps leading to a smaller amount of alcohol being aspirated) that increases the risk of laryngeal cancer; or that alcoholism may be a marker for host susceptibility to the carcinogenic effects of alcohol.

A different study which examined the relationship between alcoholism and cancer risk in a population-based cohort of 9353 individuals who were discharged with a diagnosis of alcoholism between 1965 and 1983 found an excess risk for larynx cancer (SIR = 3.3, 95% CI 1.7–6.0) [54].

Joint effects of tobacco smoking and alcohol consumption

Tobacco smoking [34] and alcohol consumption [50] are the major established risk factors for laryngeal cancer, as for other neoplasms of the upper aerodigestive tract. That the relationship between cigarette smoking and laryngeal cancer risk is causal is strongly suggested by the magnitude of the relative risk estimates derived from comparisons between smokers and non-smokers, by the positive trend in these estimates with increasing cigarette usage, by the relatively reduced risk incurred by groups such as Seventh Day Adventists who do not smoke, by the decrease in risk among ex-smokers relative to those who continue to smoke and by the consistency of these findings in epidemiological studies of a variety of different designs [34, 55]. There are, however, some quantitative differences in the association with other upper digestive tract cancers, since cancer of the larynx, and particularly the endolarynx, is less strongly associated to alcohol and more strongly to tobacco than cancer of the oral cavity or of the oesophagus [1]. This difference is biologically plausible since the endolarynx is not in direct contact with alcohol. There is still some debate on the nature of the biological and statistical interaction between alcohol and tobacco on risk of laryngeal cancer [50], although most investigations have concluded that the combined risk is multiplicative, or at least greater than additive [56]. This further indicates the importance of intervention on at least one factor for subjects exposed to both habits. The recent study from Poland estimated that cigarette smoking alone accounted for an estimated 95 per cent of laryngeal cancer in that high-risk area [43].

There is little evidence that different types of alcohol have appreciably different effects on laryngeal cancer risk. Rothman *et al.* [53] reported that consumption of 'dark' liquor and 'light' liquor had essentially similar effects on laryngeal cancer risk. Pipe and cigar smoking is strongly related to laryngeal cancer, although the risk is lower for filter, low-tar cigarettes.

In Heidelberg (Germany), combined alcohol and tobacco consumption showed a synergistic effect; the risk ratio being increased in a multiplicative manner rather than in an additive manner [47]. The same conclusion was reached by a large population-based case-control study in Southern Europe [1] and by a Polish case-control study [43] where exposure to both tobacco and alcohol showed a clear multiplicative effect in all categories of exposure. The presence of this kind of interaction stresses the importance to intervene on at least one factor for subjects exposed to both habits.

Dietary and nutritional factors

Other factors may play some independent role in laryngeal carcinogenesis such as diet. The latter is indirectly suggested by the observation that social class indicators are strongly and inversely related to laryngeal cancer rates, and more directly by a few case-control studies showing that a poor diet in general terms [43] and specifically a diet poorer in fresh fruit, vegetables and vitamin A and C is associated with the risk of laryngeal cancer [57–59]. Diet is being increasingly studied as an aetiologic factor and its role, in the causal pathway, has gained a lot of importance [60].

Evidence is accumulating both in the sense that a diet deficient in fruits and vegetables may increase the risk of laryngeal cancer [16, 40] and that a diet rich of fruits and vegetables may be protective [27].

Beta-carotene intake has been investigated in a case-control study in Northern Italy: people in the intermediate tertile of intake had an OR of 1.4 (95% CI 1.0–2.0) and people in the lowest tertile had an OR of 1.8 (95% CI 1.3–2.5) as compared to the highest tertile. It has been estimated that carotene intake explained 18% of cases [46].

A Chinese population-based case-control study conducted in Shanghai between 1988 and 1990 demonstrated a protective effect associated with the intake of fruits (particularly oranges and tangerines), certain dark green/yellow vegetables (other than bok choy) and garlic. An increased risk of laryngeal carcinomas instead was associated with salt-preserved meat and fish, but not with salt-preserved vegetables; a dose-response relationship for salted meat/fish was also found and it remained significant after additional adjustment. Moreover, the risk was elevated for frequent consumption of deep-fried foods even if a no clear dose-response relationship was observed. Red meat, white meat and fresh fish were not related to cancer risk [41].

A case-control study conducted in Beograd found a statistically significant risk for a diet containing tinned food and meat products (OR 2.65, 95% CI 1.02–6.88) while, spiced food, consumed over an extended period of time, and a mostly sandwich-based diet (uncooked food) were found not to have a statistically significant effect related to laryngeal cancer, respectively: OR 1.77, 95% CI 0.80–3.93 and OR 3.03, 95% CI 0.92–10.01 [44].

A population-based case-control study conducted in Western Washington State investigated the role of past dietary intake of iron and zinc. People who reported dietary intake of these minerals in the upper quartile were less likely to develop cancer of the larynx when compared to those in the lowest quartile; the ORs were 0.5 for iron and 0.1 for zinc. However, there was no significant difference in zinc concentration in nail tissue between cases and controls [61].

The same study also investigated the role of nitrate intake from food and beverages in a population-based case-control study conducted in the same state. Individuals who consumed higher amounts of nitrate (upper tertile) had less than one-half of the risk of laryngeal cancer compared with the lowest tertile [62].

Poor nutrition was identified as a strong independent risk factor in a Polish study [43]. A significant inverse trend with body mass was observed for cancer of the supraglottis [49].

Maté drinking, a tea-like infusion of the herb *Ilex paraguariensis*, common in South America, was investigated by a case-control study. Some excess risk was found for laryngeal cancer even after having controlled for confounders (age, sex, admission period, smoking, alcohol, income, rural residency, consumption of 10 dietary variables, non-alcoholic beverages), indeed an adjusted OR of 2.24 (95% CI (1.1, 4.5)) was obtained. Moreover, the same study demonstrated no association with coffee and tea drinking [63].

OCCUPATIONAL EXPOSURES

Asbestos

The available evidence supports an association between occupational exposure to asbestos and an increased risk of laryngeal cancer [16, 64, 65].

Results from a Chinese population-based case–control study conducted in Shanghai between 1988 and 1990 revealed an elevated OR associated with asbestos exposure (OR 2.0, 95% CI 1.0–4.3) although no dose–response relationship with frequency or duration of exposure was observed [41].

From data recorded during a hospital-based case–control study in New York between 1985 and 1990, a slightly elevated but not statistically significant association was seen for glottic cancer and asbestos exposure (OR 1.3). Moreover, the risk did not show any linear trend with the number of years employed in asbestos-related occupation. Neither a relationship between asbestos and supraglottic cancer nor a synergistic effect between cigarette smoking and asbestos exposure was observed [49].

Data derived from personnel working in a plant that manufactures brake linings and disks where asbestos is a major component, did not support the hypothesis that asbestos is an aetiological factor for laryngeal cancer, but they implied that asbestos may act as an irritant [66].

Exposure to chrysotile (a mineralogical division of asbestos), assessed in a cohort study of over 10 000 chrysotile miners and millers, showed no evidence of an adverse effect on larynx cancer [67].

Diesel exhaust fumes

There has been recent examination of the potential role of diesel exhaust fumes in the pathogenesis of respiratory tract neoplasms. A significantly elevated risk was found for men exposed to diesel fumes (OR 5.2) in a case–control study conducted in New York between 1985 and 1990 [49].

The same authors conducted another hospital-based case–control study a few years later with the purpose of better investigating this finding. Their results implied that diesel engine exhaust is unrelated to laryngeal cancer risk due to the different estimates obtained from self-reported and occupation-based exposures. They found an OR of 0.96 (95% CI 0.5–1.8) for occupations that involve substantial exposure to diesel engine exhaust (truck drivers, mine workers, firefighters, railroad workers) and an OR of 1.47 (95% CI 0.5–4.1) for self-reported exposure to diesel exhaust. However, an OR of 6.4 (95% CI 1.8–22.6) was found for self-reported exposure to diesel fumes. The authors concluded that these results may reflect recall bias and were not convinced that diesel fumes play a role in the aetiology of larynx cancer [68].

Another study conducted in Shanghai between 1988 and 1990 found no association between diesel, gasoline and kerosene fumes and an increased risk of laryngeal cancer [41].

In a study conducted in New Caledonia (South Pacific) among workers in the nickel mining and refining industry, an association was found between exposure to diesel engine exhaust fumes on mining sites and larynx cancer; the age-adjusted OR was 5.1 (95% CI 1.1–22.3). Confounding from tobacco and alcohol was not present according to the authors [69].

Other professional exposures

Exposure to mustard gas and sulphuric acid have been implicated as risk factors for laryngeal cancer [16].

Elevated but not statistically significant (at the 5% level) effects were seen for men chronically exposed to rubber (OR 6.4) and wood dust or employed as construction labourers and auto mechanics [49].

A Chinese population-based case–control study conducted in Shanghai between 1988 and 1990 investigated the risk associated with job exposure. Using as the reference group the professional and administrative workers, and adjusting for smoking, this study failed to demonstrate any increase in risk for the following occupational categories: commercial workers, service workers, farmers, metal refining and processing workers, chemical, rubber and leather workers, textile workers, blacksmiths, machine-tool operators, electricians and other related workers, material handling and construction workers, drivers and other transportation workers [41].

The same study also failed to demonstrate any association with the exposure to the following substances: silica, wood dust, metal dust, benzene, paint, pitch, lubricant fumes, hydrochloric acid. Exposure to coal dust, on the contrary, was found to be significantly associated to an increased risk of laryngeal cancer with an OR of 2.6 (95% CI 1.4–4.8) adjusted for age, education and smoking. Moreover, the risk increased with frequency and duration of exposure [41].

A population-based case–control study conducted in Western Washington State between 1983 and 1987 found, after controlling for alcohol, tobacco, age and education, a significantly increased risk for painters in construction (OR 2.8; 95% CI 1.1–6.9), supervisors and miscellaneous mechanics (OR 2.3; 95% CI 1.1–4.8), construction workers (OR 3.4; 95% CI 1.4–8.1), metal working and plastic working machine operators (OR 2.6; 95% CI 1.3–4.9), and handlers and equipment cleaners and labourers (OR 1.5; 95% CI 1.0–2.2). Allowing for a 10 year induction and latent period did not have a consistent effect on the associations observed [70].

Being exposed to poor working conditions over an extended period of time and to be simultaneously exposed to low temperatures and dust, like people in the building material industry, textiles and metal working, resulted in an OR of 4.5 (95% CI 1.8–11.4) [44].

Exposure to nickel or nickel compounds has shown no increase in risk of larynx cancer among workers in the nickel mining and refining industry in a study conducted in New Caledonia (South Pacific). However, exposure to dust on mining sites resulted in statistically significant OR; specifically exposure to road and site dust (mine) had an age-adjusted OR of 5.1 (95% CI 1.1–22.3) and exposure to perforation dust had an age-adjusted OR of 5.4 (95% CI 1.2–23.9), confounding from tobacco and alcohol not being present according to the authors [69].

No association was observed between potential carcinogens in a metallurgy plant and risk of laryngeal cancer, in a study conducted in Montreal (Canada) [71].

Within a cohort of automobile workers, exposure to metal working fluids, commonly referred to as machining fluids was assessed in relation to risk of laryngeal cancer. This was the first study that distinguished straight mineral oils from other types of machining fluids. The results suggested that straight mineral oils are associated with an almost two-fold excess risk. There was also an association with elemental sulphur (commonly added to machining fluids to improve the integrity of the material under extreme pressure and heat) but confounding by other contaminant or process features could not be excluded [72].

A suspicion of the involvement of incinerators of waste solvents and oils in the risk of larynx cancer was investigated in the U.K. due to a cluster of cases near Charnock Richard, Coppull, Lancashire. A study was conducted around ten incinerators in the U.K. but no evidence of decreasing risk with distance was found and so the suspicion was not proved [73].

POLLUTION (INDOOR AND OF THE WORK PLACE)

Air pollution in a room and in the working environment was found to be strongly associated with occurrence of laryngeal cancer in a Chinese study [40].

A Polish study, confirmed that air pollution in the work place was associated with an increase in risk among natives and immigrants, but failed to demonstrate an association between air pollution in the living place and a greater risk among natives [42].

A more detailed study conducted in Heidelberg (Germany) to assess the risk of laryngeal cancer in indoor air, polluted by emission of fossil fuel, found that the exposure for more than 40 years to fossil fuel due to stove-heating with oil, coal, gas and wood was associated with an OR of 2.5 (95% CI 1.51–4.05). The association was still significant after adjustment for tobacco and alcohol (OR = 2.0 95% CI 1.10–3.46) [74].

HUMAN PAPILLOMAVIRUS (HPV) AND P53

Detection of HPV in laryngeal carcinomas has recently been assessed to investigate the hypothesis that HPV may be associated with larger or more aggressive tumours. Evidence that the presence of HPV was significantly related to decreased survival, independent of disease stage, was presented by Clayman, who also suggested that laryngeal carcinomas with detectable HPV may represent a biologically distinct subset of tumours [75]. Brandwein *et al.* [76] reached the same conclusions, even if he analysed only a very small sample of patients.

Moreover, it has been suggested that HPV transmission could account in part for the paired occurrence of cervix and laryngeal cancer (see specific paragraph) and that cigarette smoking could act as a synergistic cofactor in the malignant transformation of viral genome-harbouring tissue [77].

A different effect of smoking in relation to a possible aetiologic role of HPV was proposed by a German study. The authors suggested that the integration of virus DNA into host cell DNA may be the result of action of nicotine and/or alcohol. They also assessed the presence of specific subtypes of HPV in positive laryngeal cancer and found HPV 16 and HPV 18 subtypes, the same subtypes regularly found in cervical cancers, thus suggesting the possibility of the virus as an aetiological factor in oral carcinogenesis [78].

The same conclusion was drawn by a Chinese study which suggested that HPV-16 may induce laryngeal carcinoma [79]. A different conclusion was drawn for verrucous carcinomas, which according to the authors, do not seem to be related to HPV [80].

A Japanese study, which investigated the relationship between p53 abnormality and HPV infection, reported that p53 abnormality is related to smoking history and that correlation might be better for smoking and chemical mutagenesis than for HPV [81]. A Swedish study found that the typical p53 mutations associated with smoking and usually found in lung cancer, accounted for 46% of the mutations detected in laryngeal cancer [82]. However, an Italian study reached the opposite conclusion, reporting that their molecular biology study did not support an association between elevated p53 expression and tobacco smoking or alcohol intake [83].

HORMONAL FACTORS

The observation that women, in the same state of clinical advancement of the disease as men, had better 5-year survival, caused some researchers to put forward the hypothesis that an unknown phenomena, perhaps hormone-immune, explained their better survival [30].

A Chinese study investigated the effect of sexual hormones on proliferation of laryngeal carcinoma cells in *in vitro* and found that testosterone may stimulate the proliferation, while beta-estradiol and progesterone have no such effect. The authors said that this study offers evidence of endocrine therapy for laryngeal carcinoma [85].

In order to verify the hypothesised hormone sensitivity of laryngeal carcinoma, an Italian study evaluated the level of receptors for oestrogen, progesterone, androgens and glucocorticoids. No statistical difference with regard to grading, site and extension of the cancer, extra-laryngeal tissue involvement or node metastasis was noted between the groups of patients with and without steroid receptors [86].

Finally, difference in detecting a marker related to carcinogenesis was observed between male and female populations and discussion on hormonal carcinogenesis was faced [87].

ASSOCIATION AND SIMILARITIES WITH OTHER CANCERS

Some associations among anatomically distinct cancer sites have been noted. Laryngeal cancer has been noted to be associated with cervical cancer either as the primary or the second primary neoplasm. It has been suggested that HPV transmission could account in part for the paired occurrence of cervix and laryngeal cancer [77]. Moreover, the fact that the same subtypes, HPV 16 and HPV 18, have been detected in cervix and laryngeal cancer, stressed the possibility that the two tumours may have the same virus and the same aetiologic factor [78].

The risk of developing a second primary cancer after a laryngeal neoplasm has been reported to be greater than that for other neoplasms and the hypothesis of clonality of multiple primary cancers has been proposed. The analysis of genetic lesions in multiple primary cancer, however, supported the independence of these cancers [88].

The most frequent localisation of second primary cancers after laryngeal neoplasms was reported to be pulmonary (70%) [89]. An Italian study based on autopsies, confirmed a high relative risk of a second pulmonary cancer in patients affected by laryngeal cancer; in detail, the relative risk for supraglottic cancer during the first 2 years of follow up was 32.6, while for glottic cancer it was 5.5. The authors stressed the importance following strict preventive and follow up protocols [90].

Two Japanese studies evaluated the same issues and found that the cumulative risk of developing a second primary cancer was more than 30% at 15 years after laryngeal cancer. The risk was significantly increased for tobacco-related cancers (RR = 24.5 for oral cavity and pharynx, RR = 6.1 for oesophagus and RR = 2.3 for lung). Radiotherapy for laryngeal cancer did not seem to have an adverse effect on the development of thyroid cancer, lymphoma and leukemia [91, 92].

A Polish study estimated that more than 10% of patients with laryngeal cancer every year get a second primary malignant neoplasm which is also a tobacco-related neoplasm [93]. In a retrospective Spanish study, a second neoplasm was found in about 8% of 428 cases who underwent pharyngectomy for cancer of the larynx [94].

In a New Zealand [95] and a Spanish [96] study, lung or oesophageal cancers usually developed as second primary cancers in patients with larynx cancer.

The risk of developing a subsequent primary larynx cancer following other cancers has also been evaluated. The risk was evaluated in Finland for bladder cancer, where an increased SIR for laryngeal cancer was observed (SIR 1.7, 95% CI from 0.9 to 2.8) [97]. The risk of second aerodigestive cancers in patients who survive free of small-cell lung cancer for more than 2 years was evaluated at the National Cancer Institute of Bethesda. The results showed that there is an increasing risk of second aerodigestive cancers (including cancer of the larynx) with the passage of time (from 2% per patient per year to more than 14% after more than 10 years) [98].

Finally, epidemiological peculiarities of gall-bladder and larynx cancer have been investigated in a Japanese study. The authors conclude that the epidemiological trait of gall-bladder cancer is a "mirror image of that of laryngeal cancer in many respects including sex-discrimination of cancer risk and geographical distribution of both high-risk and low-risk populations" [87]: the aetiological significance of this observation remains unclear at the present time.

CONCLUDING DISCUSSION

In this review the major epidemiological aspects of laryngeal cancer have been taken into consideration. Principal risk factors have been considered in some detail and also new hints for therapy, like endocrine therapy, have been mentioned as the secondary target of some studies. These new perspectives are very important due to the poor quality of life of patients treated with surgery. After total laryngectomy, indeed, some functional changes occur, such as: hyposmia, dysgeusia, nasal discharge, problems in swallowing, which often induce changes in diet, and problems in speaking, which may be only partially overcome with rehabilitation [94, 99, 100].

Evidence from epidemiological studies which supports the involvement of new risk factor in the aetiology of larynx cancer as well as new perspectives in therapy must be taken into great consideration in order to realise primary and tertiary prevention. However, it remains clear that, even as new evidence continues to amass about a wide range of risk factors, primary prevention of the great majority of laryngeal cancers could be achieved by elimination of tobacco smoking and reduction of consumption of alcoholic beverages. There could also be an additional benefit from increased consumption of fruits and vegetables although this is likely to be a much lesser effect than that obtained by reducing smoking or alcohol consumption.

1. Tuyns AJ, Esteve J, Raymond L, *et al.* Cancer of the larynx/hypopharynx, tobacco and alcohol. IARC International Case-Control Study in Turin and Varese (Italy), Zaragoza and Navarra (Spain), Geneva (Switzerland) and Calvados (France). *Int J Cancer* 1988, **41**, 483–491.
2. Lehman W, Raymond L, Faggiano F, *et al.* Cancer of the endolarynx, epilarynx and hypopharynx in South-Western Europe: assessment of tumoral origin and risk factors. *Adv Otorhinolaryngol* 1991, **46**, 145–156.
3. Sikand A, Flores AD, Morrison MD, Durham JS. Design and evaluation of a subclassification system for supraglottic laryngeal cancer [see comments]. *J Otolaryngol* 1992, **21**(4), 270–275.
4. Silvestri F, Bussani R, Stanta G, Cosatti C, Ferlito A. Supraglottic versus glottic laryngeal cancer: epidemiological and pathological aspects. *ORL J Otorhinolaryngol Relat Spec* 1992, **54**, 43–48.
5. Merino E, Hellin D, Amoros LM, Pernas J, Jimenez-Cervanates J. Cancer of the larynx and 5 years survival. *An Otorrinolaringol Ibero Am* 1994, **21**, 357–368.
6. Tuyns AI. Laryngeal cancer. *Cancer Surv* 1994, **19-20**, 159–173.
7. Parkin DM, Ferlay J, Pisani P. Estimates of the worldwide-incidence of eighteen major cancers in 1985. *Int J Cancer* 1993, **54**, 594–606.
8. Boyle P, Macfarlane GJ, McGinn R, *et al.* International epidemiology of head and neck cancer. In de Vries N, Gluckman JL, eds. *Multiple Primary Tumors of the Head and Neck.* George Thielme Verlag, 1990, 80–138.
9. Hedberg K, Vaughan TL, White E, Davis S, Thomas DB. Alcoholism and cancer of the larynx: a case–control study in western Washington (United States). *Cancer Causes Control* 1994, **5**, 3–8.
10. Van Cauwenberge P, Dhooge I, Ingels K. Epidemiology and etiological factors of laryngeal cancer. *Acta Otorhinolaryngol Belg* 1992, **46**, 99–102.
11. Ronda-Marisy H, Pila-Perez R, Castillo-Toledo L, Pila-Pelaez R. Laryngeal cancer in Camaguey (Cuba). Study of 168 cases. *Acta Otorrinolaringol Esp* 1994a, **45**, 191–194.
12. Benhamou CA, Laraqui N, Touhami M, Chekkoury A, Benchakroun Y, Samlali R. Tobacco and cancer of the larynx: a prospective survey of 58 patients. *Rev Laryngol Otol Rhinol* 1992, **113**, 285–288.
13. Ohlms LA, McGill T, Healy GB. Malignant laryngeal tumors in children: a 15-year experience with four patients. *Ann Otol Rhinol Laryngol* 1994, **103**, 686–692.
14. DeRienzo DP, Greenberg SD, Fraire AE. Carcinoma of the larynx. Changing incidence in women. *Arch Otolaryngol Head Neck Surg* 1991, **117**(6), 681–684.
15. Boyle P, La Vecchia C, Maissoneuve P, Zheng T, Macfarlane GJ. Cancer epidemiology and prevention. In Peckam MJ, Pinedo H, Veronesi U, eds. *Oxford Textbook of Oncology.* Oxford, Oxford Medical Publications, 1995, 199–273.
16. Boyle P, Macfarlane GJ, Zheng T, Maissoneuve P, Evstifeeva T, Scully C. Recent advances in epidemiology of head and neck cancer. *Curr Opin Oncol* 1992, **4**, 471–477.
17. Espinosa J, Bravo P, Baron MG. Influence of tobacco on laryngeal carcinoma in Spain. *Neoplasma* 1992, **39**(5), 319–322.
18. Morales Suarez Varela MM, Llopis Gonzalez A, Moreno Guillen E, Megia Sanz MJ. An epidemiological analysis of the trends in laryngeal cancer mortality and morbidity in Spain and the Commune of Valencia (1977–1985). *Acta Otorrinolaringol Esp* 1992, **43**(2), 83–88.

19. Kaiser C, Riva B, Fernandez Quintana G. Incidence of laryngeal cancer in Segovial (1975–1991). *Acta Otorrinolaringol Esp* 1994, **45**, 99–102.
20. Merino E, Hellin D, Girona JC, Arregui M, Jimenez-Cervantes J. Laryngeal cancer in Murcia. *Acta Otorrinolaringol Esp* 1994, **45**, 37–40.
21. Zatonski W, Becker N. *Atlas of Cancer Mortality in Poland* 1975–79. Heidelberg, Springer-Verlag, 1988.
22. Capocaccia R, Micheli A, Berrino F, *et al.* Time trends of lung and larynx cancers in Italy. *Int J Cancer* 1994, **57**, 154–161.
23. Ferrario F, Maffioli M, Piantanida R, Boschini P, Spriano G. Prospective, cohort, epidemiologic studies of laryngeal neoplasms in Italy. *Acta Otorhinolaryngol Ital* 1992, **12**, 355–361.
24. Cislaghi C, Decarli A, La Vecchia C, Mezzanotte G, Smans M. *Dati, Indicatori e Mappe di mortalita' tumorale, Italia* 1975–77. Bologna, Pitagora Editrice, 1986.
25. Benasso M, Merlano M, Toma S. Epidemiology and natural history of cancer of the upper respiratory-digestive tract. *Acta Otorhinolaryngol Ital* 1992, **10**(Suppl 27), 5–10.
26. La Vecchia C, Negri E, Decarli A, Fasoli M, Cislaghi C. Cancer mortality in Italy: an overview of age-specific and age-standardised trends from 1955 to 1984. *Tumori* 1990, **76**, 87–166.
27. Berrino F, Crosignani P. Epidemiology of malignant tumors of the larynx and lung. *Ann Ist Super Sanitá* 1992, **28**, 107–120.
28. Hansen J, Olsen JH. Survival of Danish cancer patients 1943–1987. Respiratory system. *APMIS Suppl* 1993, **33**, 77–98.
29. Harris JA, Meyers AD, Smith C. Laryngeal cancer in Colorado. *Head Neck* 1993, **15**, 398–404.
30. Osmolski A, Kus JJ. Clinical course of laryngeal cancer in relation to sex. *Otolaryngol Pol* 1992, **46**(2), 117–126.
31. Swoboda H, Friedl HP. Mortality from cancer of the head and neck, lung and esophagus in eastern Austria between 1960 and 1989. *Eur Arch Otorhinolaryngol* 1994, **251**(1), 52–56.
32. Sani A, Said H, Lokman S. Carcinoma of the larynx in Malaysia. *Med J Malaysia* 1992, **47**, 297–302.
33. Ronda-Marisy H, Pila-Perez R, Castillo-Toledo L, Pila-Pelaez R. Laryngeal cancer in females in Camaguey (Cuba). *Acta Otorrinolaringol Esp* 1994, **45**, 61–63.
34. IARC Monographs on the Evaluation of Carcinogenic Risk to Humans. Tobacco smoking, Vol. 38. International Agency for Research on Cancer, Lyon, 1986.
35. Farchi G. Estimation of the impact of cigarette smoking reduction on mortality from tumors of the lung and larynx. *Ann Ist super Sanita* 1992, **28**(1), 147–153.
36. Tomatis L. Cancer: causes, occurrence and control. IARC Scientific Publication n. 100. International Agency for Research on Cancer, Lyon, 1990.
37. Parkin DM, Pisani P, Lopez AD, Masuyer E. At least one in seven cases of cancer is caused by smoking. Global estimates for 1985. *Int J Cancer* 1994, **59**(4), 494–504.
38. Franceschi S, Talamini R, Barra S, *et al.* Smoking and drinking in relation to cancers of the oral cavity, pharynx, larynx, and esophagus in Northern Italy. *Cancer Res* 1990, **50**, 6502–6507.
39. La Vecchia C, Bidoli E, Barra S, *et al.* Type of cigarettes and cancers of the upper digestive and respiratory tract. *Cancer Causes Control* 1990, **1**, 69–74.
40. Guo X. A case–control study of the etiology of laryngeal cancer in Liaoning Province. *Chung Hua Erh Pi Yen Hou Ko Tsa Chih* 1993, **28**(4), 219–221.
41. Zheng W, Blot WJ, Shu XO, *et al.* Diet and other risk factors for laryngeal cancer in Shanghai, China. *Am J Epidemiol* 1992, **136**, 178–191.
42. Zemla B, Swiatnicka J, Kolosza Z, Banasik R. Epidemiological risk factors of larynx cancer among natives and immigrants in the Upper Silesian region. *Otolaryngol Pol* 1993, **47**(4), 330–337.
43. Zatonski W, Becker H, Lissowska J, Wahrendorf J. Tobacco, alcohol and diet in the aetiology of laryngeal cancer: a population-based case–control study. *Cancer Causes Control* 1991, **2**, 3–11.
44. Sokic SI, Adanja BJ, Marinkovic JP, Vlajinac HD. Case–control study of risk factors in laryngeal cancer. *Neoplasma* 1994, **41**(1), 43–47.
45. De Stefani E, Oreggia F, Rivero S, Fierro L. Hand-rolled cigarette smoking and risk of cancer of the mouth, pharynx, and larynx. *Cancer* 1992, **70**(3), 679–682.
46. Tavani A, Negri E, Franceschi S, Barbone F, La Vecchia C. Attributable risk for laryngeal cancer in northern Italy. *Cancer Epidemiol Biomarkers Prev* 1994, **3**(2), 121–125.
47. Maier H, Dietz A, Gewelke U, Heller WD, Weidauer H. Tobacco and alcohol and the risk of head and neck cancer. *Clin Investig* 1992, **70**(3–4), 320–327.
48. Maier H, Gewelke U, Dietz A, Heller WD. Risk factors of cancer of the larynx: results of the Heidelberg case–control study. *Otolaryngol Head Neck Surg* 1992, **107**(4), 577–582.
49. Muscat JE, Wynder EL. Tobacco, alcohol, asbestos and occupational risk factors for laryngeal cancer. *Cancer* 1992, **69**, 2244–2251.
50. IARC Monographs on the evaluation of carcinogenic risk to human alcohol drinking, Vol. 44. International Agency for Research on Cancer, Lyon, 1988.
51. Franceschi S, Bidoli E, Negri E, Barbone F, La Vecchia C. Alcohol and cancers of the upper aerodigestive tract in men and women. *Cancer Epidemiol Biomarkers Prev* 1994, **3**(4), 299–304.
52. Blot WJ. Alcohol and cancer. *Cancer Res* 1992, **52**(7 Suppl), 2119s–2123s.
53. Rothman KJ, Cann CI, Fried MP. Carcinogenicity of dark liquor. *Am J Public Hlth* 1989, **79**, 1516–1520.
54. Adami HO, McLaughlin JK, Hsing AW, *et al.* Alcoholism and cancer risk: a population-based cohort study. *Cancer Causes Control* 1992, **3**(5), 419–425.
55. Wynder EL, Covey LS, Mabuchi K, Mushinski M. Environmental factors in cancer of the larynx: a second look. *Cancer* 1976, **38**, 1591–1601.
56. Flanders WD, Rothman KJ. Interaction of alcohol and tobacco in laryngeal cancer risk. *Am J Epidemiol* 1982, **115**, 371–379.
57. Graham S, Mettlin C, Marshall JR, Priore R, Rzepka T, Shedd D. Dietary factors in the epidemiology of cancer of the larynx. *Am J Epidemiol* 1981, **113**, 675–680.
58. De Stefani E, Correa P, Orregia F, *et al.* Risk factors for laryngeal cancer. *Cancer* 1987, **60**, 3087–3091.
59. La Vecchia C, Negri E, D'Avanzo B, Franceschi S, Decarli A, Boyle P. Dietary indicators of laryngeal cancer risk. *Cancer Res* 1990, **50**, 4497–4500.
60. Steinmetz KA, Potter JD. Vegetable, fruit, and cancer I. Epidemiology:. *Cancer Causes Control* 1991, **2**, 325–358.
61. Rogers MA, Thomas DB, Davis S, Vaughan TL, Nevissi AE. A case–control study of element levels and cancer of the upper aerodigestive tract. *Cancer Epidemiol Biomarkers Prev* 1993, **2**, 305–312.
62. Rogers MA, Vaughan TL, Davis S, Thomas DB. Consumption of nitrate, nitrite and nitrosodimethylamine and risk of upper aerodigestive tract cancer. *Cancer Epidemiol Biomarkers Prev* 1995, **4**(1), 29–36.
63. Pintos J, Franco EL, Oliveira BV, Kowalski LP, Curado MP, Dewar R. Mate, coffee and tea consumption and risk of cancer of the upper aerodigestive tract in southern Brazil. *Epidemiology* 1994, **5**, 583–590.
64. Doll R, Peto J. *Asbestos. Effects on Health of Exposure to Asbestos.* Health and Safety Commission Her Majesty's Stationary Office, London, 1985.
65. Sturm W, Menze B, Krause J, Thriene B. Use of asbestos, health risks and induced occupational diseases in the former East Germany. *Toxicol Lett* 1994, **72**, 317–324.
66. Parnes SM. Asbestos and cancer of the larynx: is there a relationship. *Laryngoscope* 1990, **100**(3), 254–261.
67. Liddell D. Cancer mortality in chrysotile mining and milling: exposure–response. *Ann Occup Hyg* 1994, **38**(4), 519–523, 412.
68. Muscat JE, Wynder EL. Diesel exhaust, diesel fumes, and laryngeal cancer. *Otolaryngol Head Neck Surg* 1995, **112**(3), 437–440.
69. Goldberg M, Goldberg P, Leclerc A, Chastang JF, Marne MJ, Dubourdieu D. A 10-year incidence survey of respiratory cancer and a case–control study within a cohort of nickel

mining and refining workers in New Caledonia. *Cancer Causes Control* 1994, 5(1), 15–25.
70. Wortley P, Vaughan TL, Davis S, Morgan MS, Thomas DB. A case–control study of occupational risk factors for laryngeal cancer. *Br J Ind Med* 1992, **49**(12), 837–844.
71. Provencher S, Labreche A. Study of a cancer aggregate in a metallurgy plant—practical implications for public health. *Can J Public Health* 1994, **85**(5), 330–333.
72. Eisen EA, Tolbert PE, Hallock MF, Monson RR, Smith TJ, Woskie SR. Mortality studies of machining fluid exposure in the automobile industry. III: a case–control study of larynx cancer. *Am J Ind Med* 1994, **26**(2), 185–202.
73. Elliott P, Hills M, Beresford J, *et al.* Incidence of cancer of the larynx near incinerators of waste solvents and oils in Great Britain. *Lancet* 1992, **339**, 854–858.
74. Dietz A, Senneweld E, Maier H. Indoor air pollution by emissions of fossil fuel single stoves: possibly a hitherto underrated risk factor in the development of carcinomas in the head and neck. *Otolaryngol Head Neck Surg* 1995, **112**(2), 308–315.
75. Clayman GL, Stewart MG, Weber RS, el Naggar AK, Grimm EA. Human papillomavirus in laryngeal and hypopharyngeal carcinomas. Relationship to survival. *Arch Otolaryngol Head Neck Surg* 1994, **120**, 743–748.
76. Brandwein MS, Nuovo GJ, Biller H. Analysis of prevalence of human papillomavirus in laryngeal carcinomas. Study of 40 cases using polymerase chain reaction and consensus primers. *Ann Otol Rhinol Laryngol* 1993, **102**, 309–313.
77. Spitz MR, Sider JG, Schantz SP, Newell GR. Association between malignancies of the upper aerodigestive tract and uterine cervix. *Head Neck* 1992, **14**, 347–351.
78. Arndt O, Brock J, Kundt G, Mullender A. Detection of human papillomavirus DNA in formalin fixed invasive squamous cell carcinoma of the larynx with polymerase chain reaction (PCR). *Laryngorhinootologie* 1994, **73**, 527–532.
79. Cui H, Yang X, He Q. Studies on the relationship between HPV and respiratory tract tumors. I. Correlation between HPV and laryngeal carcinoma. *Chung Kuo I Hsueh Ko Hsueh Yuan Hsueh Pao* 1994, **16**(2), 109–115.
80. Multhaupt HA, Fessler Jn, Warhol MJ. Detection of human papillomavirus in laryngeal lesions by *in situ* hybridization. *Hum Pathol* 1994, **25**(12), 1302–1305.
81. Suzuki T, Shidara K, Hara F, Nakajima T. High frequency of p53 abnormality in laryngeal cancers of heavy smokers and its relation to human papillomavirus infection. *Jpn J Cancer Res* 1994, **85**(11), 1087–1093.
82. Zhang LF, Hemminki K, Szyfter W, Soderkvist P. p53 mutations in larynx cancer. *Carcinogenesis* 1994, **15**, 2949–2951.
83. Franceschi S, Gloghini A, Maestro R, *et al.* Analysis of the p53 gene in relation to tobacco and alcohol in cancers of the upper aerodigestive tract. *Int J Cancer* 1995, **60**(6), 872–880.
84. Munck Wikland E, Edstrom S, Jungmark E, Kuylenstierna R, Lindholm J, Auer G. Nuclear DNA content, proliferating-cell nuclear antigen (PCNA) and p53 immunostaining in predicting progression of laryngeal cancer *in situ* lesions. *Int J Cancer* 1994, **56**(1), 95–99.
85. Zhao X, Xiao X, Liu J. Effect of sexual hormones on proliferation of laryngeal carcinoma cell line Hep-2 *in vitro*. *Chung Hua Erh Pi Yen Hou Ko Tsa Chih* 1994, **29**(3), 149–151.
86. Resta L, Fiorella R, Marsigliante S, *et al.* The status of receptors in laryngeal carcinoma: a study of receptors for estrogen, progesterone, androgens and glucocorticoids. *Acta Otorhinolaryngol Ital* 1994, **14**(4), 358–392.
87. Kodama M, Kodama T. Epidemiological peculiaritis of cancer of the gall-bladder and larynx that distinguish them from other human neoplasias. *Anticancer Res* 1994, **14**, 2205–2214.
88. Yang HK, Kelley MJ, Linnoila R, *et al.* p-53 mutations in multiple primary upper aerodigestive cancers. *Proc Annu Meet Am Assoc Cancer Res* 1994, **35**, A3623.
89. Rovirosa A, Bellmunt J, Lopez A, Fernandez M, Guerra M, Montagut J. The incidence of second neoplasm in advanced laryngeal cancer. Impact on survival. *Med Clin Barc* 1994, **102**(4), 121–124.
90. Silvestri F, Bussani R, Cosatti C, Bosatra A. High relative risk of a second pulmonary cancer in patients affected by laryngeal cancer: differences by specific site of occurrence and lung cancer histotype. *Laryngoscope* 1994, **104**, 222–225.
91. Hiyama T, Sato T, Yoshino K, Tsukuma H, Hanai A, Fujimoto I. Second primary cancer following laryngeal cancer with special reference to smoking habits. *Jpn J Cancer Res* 1992, **83**(4), 334–339.
92. Teshima T, Inoue T, Chatani M, Hata K, Hiyama T, Ikeda H, Murayama S. Incidence of other primary cancers in 1,569 patients with pharyngolaryngeal cancer and treated with radiation therapy. *Strahlenther Onkol* 1992, **168**(4), 213–218.
93. Pawlega J, Geleta M, Dyba T, Rachtan J. Second primary malignant neoplasms in patients treated radically for carcinoma of oral cavity, larynx and lungs. *Otolaryngol Pol* 1994, **48**(3), 239–245.
94. Merino E, Hellin D, Rosique M, Amoros LM, Jimenez-Cervantes J. Laryngeal cancer and secondary neoplasms in Murcia. *Acta Otorrinolaringol Esp* 1994, **45**, 93–97.
95. Allison RS, Wynne CJ, Stevenson DS, Tichener G. Carcinoma of the glottic larynx: the Christchurch Hospital. *NZ Med J* 1992, **105**, 256–257.
96. Esteller More E, Quer Agusti M, Burgues Vila J, Viladot Castells J, Lopez Pousa A, Vega M. Synchronous carcinomas of the upper aerodigestive tract: a diagnostic and therapeutic problem. *Acta Otorrinolaringol Esp* 1992, **43**(5), 329–334.
97. Salminen E, Pukkala E, Teppo L, Pyrhonen S. Subsequent primary cancers following bladder cancer. *Eur J Cancer* 1994, **30A**(3), 303–307.
98. Johnson BE, Linnoila RI, Williams JP, *et al.* Risk of second aerodigestive cancers increases in patients who survive free of small-cell lung cancer for more than 2 years. *J Clin Oncol* 1995, **13**(1), 101–111.
99. Ackerstaff AH, Hilgers FJ, Aaronson NK, Balm AJ. Communication, functional disorders and lifestyle changes after total laryngectomy. *Clin Otolaryngol* 1994, **19**(4), 295–300.
100. Zanaret M, Giovanni A, Gras R, Cannoni M. Near total laryngectomy with epiglottic reconstruction: long-term results in 57 patients. *Am J Otolaryngol* 1993, **14**(6), 419–425.

Acknowledgements—This work was undertaken within the framework of support from the Italian Association for Cancer Research (Associazone Italiana per la Ricerca sul Cancro (AICR)).