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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)

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A case-control study on larynx and hypopharynx cancer was carried out in 6 populations including the city of Turin and the province of Varese (Italy), the provinces of Navarra and Zaragoza (Spain), the canton of Geneva (Switzerland), and the *département* of Calvados (France). This report presents an analysis of the risk associated with alcohol and tobacco consumption based on 1,147 male cases and 3,057 male population controls. Special attention was given to the study of the risk at various sites of larynx and hypopharynx. The effect of tobacco is similar for all sites and the risk associated with ever smoking is on the order of 10. The risks from alcohol drinking depend on site. They are similar for epilarynx and hypopharynx (RR = 4.3, for more than 80 g/day) and lower for endolarynx (RR = 2.1, for more than 80 g/day). For all sites the risk decreases after quitting (RR = 0.3 after 10 years); exclusive use of filter cigarettes is protective (RR = 0.5 relative to smokers of plain cigarettes only) as is exclusive use of blond tobacco (RR = 0.5 relative to smokers of black tobacco only). Inhalation increases the risk of endolaryngeal cancer but not that of hypopharynx or epilarynx. The relative risks for joint exposure to alcohol and tobacco are consistent with a multiplicative model.

Laryngeal cancer is unevenly distributed in Europe. In 1978, when this study was designed, the latest available mortality data were from 1973 (WHO, 1976) and the highest rates for males were over 9 per 100,000 in France, Italy and Spain, while the figures were below 3 in the Scandinavian countries and in the UK. Switzerland had a rate of 4.8, but rates in the French-speaking *cantons* were much higher than in the German-speaking ones (Brooke, 1975). In the same period, incidence rates available from the cancer registries located in the above-mentioned countries were consistent with the high mortality data in the South-Western European populations of Latin origin.

Two other features characterised laryngeal cancer in these countries: the extreme rarity of the disease in females (with an M/F sex ratio above 20) and an increase in mortality rates with time among males in Turin (Terracini *et al.*, 1974) and in France (Tuyns and Audigier, 1976). Such an increase had also been described in Australia and the UK (McMichael, 1978).

All these observations pointed to environmental factors prevailing in males living in this part of Europe. Tobacco smoking was, of course, the first factor to be suspected, but it had been noted that the distribution of lung cancer was in sharp contrast to that of laryngeal cancer (Tuyns, 1982*a*), the Latin countries having rates lower than the UK and the Benelux countries. In 1973, the lung cancer/larynx cancer mortality ratio was 61 in the UK and 3 in France. If tobacco smoking was also responsible for laryngeal cancer, some parameter related to smoking should be specific to Latin countries, as for example "black" as opposed to "blond" tobacco. Another possibility would be that the role of alcohol, in combination with smoking, might be of greater importance than hitherto reported. In fact, the national mortality figures correlated with national alcohol consumption figures but not with tobacco (Tuyns, 1982*a*).

Hitherto, the initial observations of Schwartz *et al.* (1962) in France, studies carried out in the US (Wynder *et al.*, 1976) and in other countries (Jensen, 1979) had demonstrated the importance of alcohol as an aetiologic factor for larynx cancer. The prevailing opinion was that alcohol is not a carcinogen *per se* but rather a potent co-factor for the carcinogens present in tobacco. This was based on the observation that the risk related to alcohol appears clearly in smokers but not in non-smokers (Wynder *et al.*, 1976). Such an effect would thus be different from the multiplicative model described in France for oesophageal cancer (Tuyns *et al.*, 1977*b*).

In addition to tobacco and alcohol, occupational factors have also been described in relation to laryngeal cancer. The suspected agents can be found, for example, in a review article linking suspected chemical carcinogens and risk of cancer at different sites (Merletti *et al.*, 1984).

For all the reasons enumerated above and with the evidence available at that time, it was decided (Tuyns *et al.*, 1980) to set up a population-based case-control study in 6 areas, namely Turin and Varese in Italy, Zaragoza and Navarra in Spain, Geneva in Switzerland and Calvados in France. In the latter area, a research project on oesophageal cancer was already in operation. In each of these regions, incidence data were available at that time as well as qualified personnel for carrying out such a study. The statistical department of the Institut Gustave-Roussy, which was planning a case-control hospital-based study on the subject, joined in.

The major aim of the study was to define the respective role of tobacco and alcohol in laryngeal cancer and to study the combination of their effects. Additional working hypotheses concerned the possible role of occupation, diet, kind of tobacco and kind of alcoholic beverage.

The present paper deals only with the role of tobacco and alcohol.

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MATERIAL AND METHODS

Sources and definition of cases

Cancers occurring at the upper limits of the larynx are not always clearly distinguished from those at the upper hypopharynx. It was therefore decided to incorporate in the study cases of cancer of the hypopharynx, and attempt to define the primary site of origin of tumours at the junction between larynx and hypopharynx. An additional reason for studying hypopharynx as well as larynx was their common exposure to both tobacco and alcohol. In at least one of the study areas (Calvados), there was evidence that the incidence of hypopharyngeal cancer was even greater than that of laryngeal cancer; this was not so in the other areas (Table I).

On the other hand, a first analysis of the anatomical classification into sites and subsites within the larynx and the hypopharynx region indicated the need for singling out those anatomical areas corresponding to epilarynx and forming the borderline between larynx and hypopharynx. According to the ICD, these areas ought to be classified partly under 161 and partly under 146 and 148, even though in terms of potential exposure they were all located at the junction of organs mainly exposed to inhaled (endolarynx) or to ingested (hypopharynx) agents. An *ad hoc* topographical classification was thus elaborated, largely derived from the work of Lehmann (1977) who recoded the presumed subsite of origin for each case. This detailed classification, and its correspondence with the ICD, appears in Table II, and the subsites regrouped under *epilarynx* are represented in Figure 1.

The cases were epidermoid carcinomas, histologically verified. Multiple cancers and cancers which originated in the oesophagus or oropharynx were excluded. The proportion of patients who were successfully interviewed among those entered in the study was high everywhere (>80%). The main reason for failure was death. In contrast, the proportion of cases entered in the study among those identified thereafter through the registries varies from centre to centre. As a consequence, the proportion of cases eventually interviewed was on the order of 75% in Spain and Italy and higher in Geneva (92%); it was lower in Calvados where the recruitment was limited to the Centre Anti-Cancéreux which is the main cancer hospital in Normandy. Cases residing in the neighbouring *département* and treated in this hospital were included in the present study after their smoking and drinking habits had been checked against those of the cases residing in Calvados.

The distribution of the 1,147 male cases included in this study, by site and study centre, appears in Table III. There were, in addition, 58 female cases which will not be examined in this report.

Controls

One of the aims of the study was to define the characteristics of each of the 6 populations under study with regard to the factors to be examined, as had been done previously (Tuyns *et al.*, 1975, 1983; Tuyns and Hu, 1982). The controls were therefore drawn from the general population in the 6 areas considered, and the initial design called for a stratified sample with the same number of individuals in each of 12 age-sex strata for 6 10-year age groups in the range 25+. These controls were drawn from census lists, electoral lists or population registries, depending upon the best available and most reliable source of information in each centre. In Geneva, Turin and Navarra, financial constraints made it necessary to restrict the recruitment of controls to the oldest age groups in order to maintain a sufficient control/case ratio above 2.

The procedures involved have been described (Riboli *et al.*, in press). The response rate was above 75% in 4 centres and lower in Geneva (64%) and Turin (56%). In these 2 highly urbanized centres the persons who could not be interviewed

TABLE I - LARYNX, HYPOPHARYNX AND OROPHARYNX CANCER INCIDENCE IN THE COUNTRIES OF THE STUDY[1]

World age-standardized rate	Larynx ICD-161		Hypopharynx ICD-148		Oropharynx ICD-146	
	M	F	M	F	M	F
Calvados (France) (1978–1980)	10.93	0.13	16.11	0.18	12.76	0.73
Geneva (Switzerland) (1973–1977)	10.10	0.80	4.20	0.10	5.70	0.90
Navarra (Spain) (1973–1977)	15.00	0.20	0.20	0.00	1.00	0.20
Zaragoza (Spain) (1973–1977)	12.00	0.20	0.40	0.00	3.90	0.10
Varese (Italy) (1976–1977)	16.00	0.50	3.20	0.00	4.10	0.10

Source: Cancer in Five Continents, Volume IV, except for Calvados for which the 1978–1980 incidence was obtained directly from the cancer registry.–[1]No data from the same source for Turin.

TABLE II - CODING SCHEME FOR SITES AND SUBSITES

Endolarynx			Epilarynx			Hypopharynx		
Code	Subsites	ICD-9	Code	Subsites	ICD-9	Code	Subsites	ICD-9
11	Supraglottis[1]	161.1	21	Anterior: Epiglottis, free border [2,3] Epiglottis, posterior surface of supra-hyoid portion	146.4 161.1	31	Piriform sinus	148.1
12	Glottis	161.0	22	Lateral:[4] Junctional region of 3 folds Ary-epiglottic fold	146.5 161.1 and[5] 148.2	32	Post-cricoid area	148.0
13	Subglottis	161.2	23	Posterior: Arytenoid and inter-arytenoid incisure	161.1 and[5] 148.2	33	Posterior wall	148.3
14	Endolarynx unspecified	161.8 or 161.9	24	Epilarynx unspecified	149.8 or 195.0	34	Hypopharynx unspecified	149.8

[1]Excludes epilarynx. Includes the infra-hyoid epiglottis, the ventricular bands (false cords) and the ventricular cavities.–[2]See also Figure 1.–[3]161.1 in ICD-0.–[4]Is composed of the junction of the lateral glosso-epiglottic fold, the pharyngo-epiglottic fold and the ary-epiglottic fold. Does not exist in ICD-0 (146.5 = junctional region of oropharynx).–[5]In ICD-0 and ICD-9, there is a separation between laryngeal aspect (161.1) and hypopharyngeal aspect (148.2).

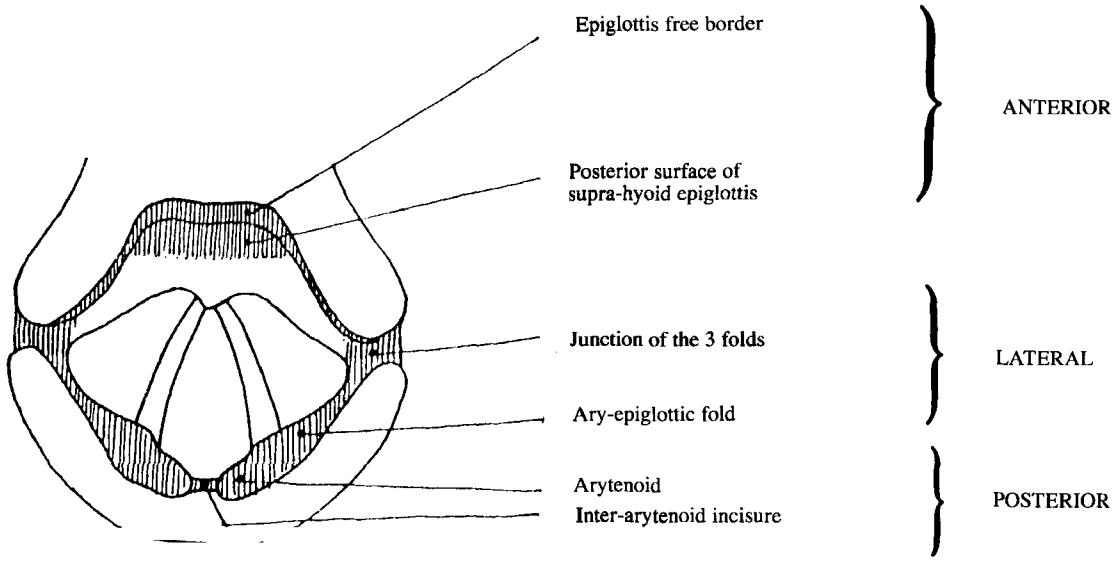

FIGURE 1 - Epilarynx (*margelle laryngée, auditus laryngis*), as defined in the IARC/Latin Cancer Registries Group study (1986), is composed of 3 parts, each of which is to be regarded as 2 sub-parts.

comprised equal numbers of those who could not be traced and those who refused to participate. The number of controls interviewed appears in Tables III and IV.

Definition and ascertainment of exposure

Cases and controls were interviewed on their smoking, drinking and dietary practices and on their occupational career.

A complete smoking history was obtained, noting for each main period of life: type of smoking, amount smoked and brand. Each brand was identified as black or blond by obtaining information on the type of curing from the local tobacco administration or specialized retailers in Geneva. This was unknown for 3% of the brands, and these brands were used by less than 10% of the persons interviewed. As smoking habits tend to change with age (Tuyns and Hu, 1982), an average daily consumption of cigarettes was computed for each individual by dividing the cumulative number of cigarettes by the number of days between beginning and end of smoking; this parameter was used throughout the analyses in conjunction with other characteristics of smoking.

The information on alcohol consumption was collected within the scope of the dietary questionnaire, using a technique previously described (Péquignot and Cubeau, 1973; Cubeau and Péquignot, 1980; Tuyns *et al.*, 1975, 1983). This was complemented by a short questionnaire determining the period of adult life in which important changes in drinking habits had occurred. The average adult life-time daily consumption in grams was computed and used in the analyses, as it was shown to be more relevant than present consumption in this type of investigation (Tuyns and Estève, 1983).

The questionnaires on the other risk factors and the characteristics of the 6 populations with regard to tobacco, alcohol and diet have been described (Berrino *et al.*, in press; Péquignot *et al.*, in press; Ribolo *et al.*, in press).

Methods of analysis

Statistical analysis was performed through logistic regression (Breslow and Day, 1980) using the GLIM package (Baker and Nelder, 1978). All models fitted to the data include terms for age, place and their interaction. This procedure is equivalent to the estimation of odds ratios after separate adjustment for age in each study centre. Confidence intervals for relative risks were obtained by considering that half the length of a 95% confidence interval for the log odds ratio is equal to 1.96 times its standard error and exponentiating the corresponding limits. The adjustment for confounding factors was done by incorporating these in the model equations. The comparison between risk of cancer at different sites was made by fitting a log linear model to the case population and assessing the significance of the interaction between site and exposure (Thomas *et al.*, 1986); for comparison of the risks for smoking among subsites, cigarette consumption was broken down into 3 categories (0, 1-19, 20+). The comparison for drinking was made with only 2 categories (<80 g, >80 g), and the comparison for age distribution with the 6 10-year age groups. When studying factors which modify the risk of smoking, we calculated relative risks, assuming a constant multiplicative effect at each dose of tobacco. Although for some of these factors the relative risk is bound to be dose-dependent, no attempt was made to study the interaction of these factors with the number of cigarettes.

RESULTS

The distribution of cases by site and age is given in Table IV. There is little difference in age distribution between sites ($\chi^2 = 24.3$ for 15 df). The mean age of all cases is 60 years.

Alcohol- and tobacco-related risks by site

The tobacco-related risks, adjusted for alcohol, appear in the upper half of Table V. There is a clear-cut dose-response relationship for all sites. The effect is similar for each of the 3 sites and the 2 endolaryngeal subsites; the differences from one to another are just below the level of significance ($\chi^2 = 12.3$ for 6 df; $p=0.06$).

The alcohol-related risks, adjusted for tobacco, appear in the lower half of Table V. There is a dose-response relationship for each site, but they differ considerably and significantly ($\chi^2=36.4$ for 3 df; $p< 10^{-7}$). The relationship is much

TABLE III - DISTRIBUTION OF CASES AND CONTROLS BY STUDY CENTRE (SITE PERCENTAGES IN BRACKETS)

Centre	Endolarynx		NOS[1]	Epilarynx	Hypopharynx	Other (unspec.)	Total cases	Controls
	Supraglottic	Glottic and subglottic						
Caen	27	24	4	29	138	4	226	922
	(11.9)	(10.6)	(1.8)	(12.8)	(61.1)	(1.8)	(100)	
Geneva	28	32	3	14	27	0	104	389
	(26.9)	(30.8)	(2.9)	(13.5)	(26.0)	—	(100)	
Navarra	69	10	0	15	35	2	131	525
	(52.7)	(7.6)	—	(11.4)	(26.7)	(1.5)	(100)	
Zaragoza	73	40	6	12	15	7	153	349
	(47.7)	(26.1)	(3.9)	(7.8)	(9.8)	(4.6)	(100)	
Turin	122	73	12	28	37	4	276	385
	(44.2)	(26.4)	(4.3)	(10.1)	(13.4)	(1.4)	(100)	
Varese	107	91	6	20	29	4	257	487
	(41.6)	(35.4)	(2.3)	(7.8)	(11.3)	(1.5)	(100)	
Total cases	426	270	31	118	281	21	1,147	3,057
	(37.1)	(23.5)	(2.7)	(10.3)	(24.5)	(1.8)		

[1]Endolarynx not otherwise specified.

TABLE IV - DISTRIBUTION OF CASES BY SITE AND AGE, AND CONTROLS BY AGE (AGE PERCENTAGES IN BRACKETS)

Age	Endolarynx		NOS[1]	Epilarynx	Hypopharynx	Other (unspec.)	All	Controls
	Supraglottic	Glottic and subglottic						
<45	20	17	3	6	14	1	61	902
	(4.7)	(6.3)	(9.7)	(5.1)	(5.0)	(4.8)	(5.3)	(29.5)
45–54	114	67	4	33	87	5	310	557
	(26.8)	(24.8)	(12.9)	(28.0)	(31.0)	(23.8)	(27.0)	(18.2)
55–64	174	79	15	47	87	12	414	670
	(40.8)	(29.3)	(48.4)	(39.8)	(31.0)	(57.1)	(36.1)	(21.9)
65–74	87	85	8	24	76	3	283	574
	(20.4)	(31.5)	(25.8)	(20.3)	(27.0)	(14.3)	(24.7)	(18.8)
75+	31	22	1	8	17	0	79	354
	(7.3)	(8.1)	(3.2)	(6.8)	(6.0)	—	(6.9)	(11.6)
Total	426	270	31	118	281	21	1,147	3,057
	(100)	(100)	(100)	(100)	(100)	(100)	(100)	(100)
Mean age	60	61	60	60	60	58		

[1]Endolarynx not otherwise specified.

stronger for the hypopharynx and for the epilarynx than for the 2 endolaryngeal subsites. This justifies the regrouping of hypopharynx and epilarynx together and of the 2 subsites of the endolarynx together.

The relative risks for each level of consumption of tobacco and alcohol, for the 2 anatomical regions so defined, are shown in Table VI and Figure 2.

Risks related to various parameters concerning smoking practices

These are examined in Table VII. All risks are adjusted for alcohol and for life-time average daily dose of tobacco.

Quitting. Quitting entails a decrease of risk after 5 years' abstention; the benefit seems to appear earlier for hypopharynx/epilarynx than for larynx.

Use of filter cigarettes. Smokers of exclusively filter cigarettes have half the risk of laryngeal or hypopharynx/epilarynx cancer as compared with smokers of only plain cigarettes.

Blond versus *black tobacco.* The risk is twice as high in users of black tobacco cigarettes than in smokers of blond tobacco only. For people using alternatively one or the other kind, risks are increased by about 50%.

Inhalation. Non-inhalers have a lower risk of endolaryngeal cancer but there is no significant effect for hypopharynx/epilarynx.

Age at start and duration. Since very few individuals stopped smoking temporarily, the effects of age at start and duration of smoking are strongly confounded and it is almost impossible to adjust one for the other (Vineis and Estève, 1987). When adding either of these variables in the model equation including alcohol and all the previous smoking variables, the fit was improved and the estimate of effect was in the expected direction. This improvement, however, was significant only for age at start (χ^2 = 7.3 on 2 df); the corresponding relative risks were 0.70 for starting smoking between 15 and 20 and 0.80 for starting at 21 or after, relative to starting before age 15.

Combined effects of alcohol and tobacco

When the study subjects were simultaneously stratified by consumption of alcohol and tobacco according to the categories in Table VI, very few cases remained in the lowest exposure groups. Therefore, in order to have a sufficiently large reference category, the 2 lowest consumption groups were combined (0–7 g for tobacco, 0–40 g for alcohol).

TABLE V - RELATIVE RISK[1] FOR ALCOHOL AND TOBACCO BY SITE (95% CONFIDENCE INTERVAL IN BRACKETS)

	Endolarynx		Epilarynx	Hypopharynx
	Supraglottic	Glottic and subglottic		
Number of cigarettes/day[2]				
0	1	1	1	1
1-7	2.83 (1.19-6.76)	1.92 (0.88-4.21)	2.25 (0.59-8.61)	5.48 (1.98-15.14)
8-15	9.62 (4.75-19.47)	4.38 (2.34-8.20)	6.67 (2.29-19.43)	13.69 (5.43-34.49)
16-25	21.01 (10.61-41.62)	7.64 (4.19-13.81)	10.97 (3.88-31.05)	17.96 (7.20-44.78)
26+	23.98 (11.81-48.70)	10.23 (5.43-19.25)	9.40 (3.16-27.97)	20.01 (7.85-51.03)
Grams of alcohol/day[2]				
0-20	1	1	1	1
21-40	0.88 (0.58-1.35)	0.84 (0.49-1.44)	0.87 (0.29-2.65)	1.57 (0.72-3.42)
41-80	1.08 (0.74-1.58)	1.05 (0.65-1.69)	1.53 (0.60-3.87)	3.15 (1.58-6.24)
81-120	1.68 (1.12-2.51)	1.73 (1.05-2.86)	5.10 (2.09-12.44)	5.59 (2.79-11.21)
121+	2.00 (1.33-3.02)	3.40 (2.07-5.56)	10.64 (4.38-25.84)	12.54 (6.29-25.00)

[1]These risks are adjusted for the other factor and calculated from a logistic regression including an age/place interaction term.-[2]Averaged over the period of consumption.

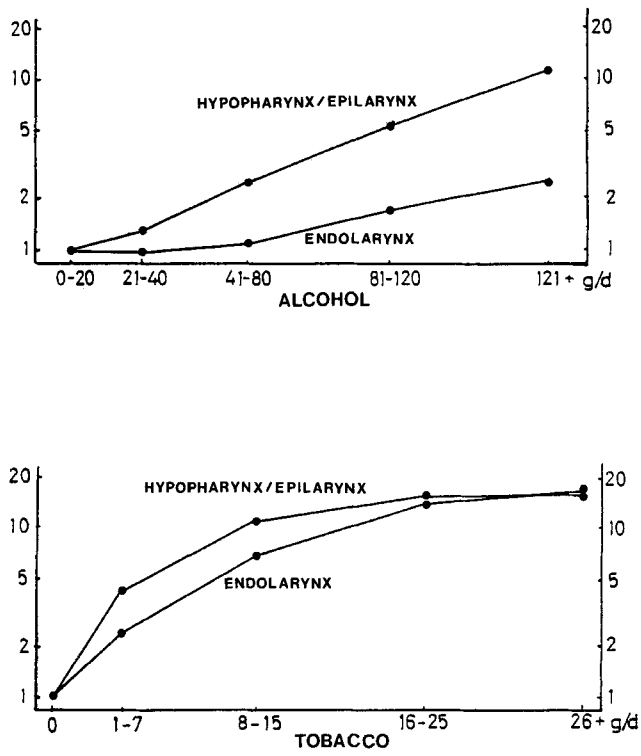

FIGURE 2 - Relative risk of cancer of the endolarynx and hypopharynx/epilarynx according to average alcohol and tobacco consumption.

The multiplicative model provides a good description of the simultaneous effect of alcohol and tobacco for both endolarynx and hypopharynx/epilarynx, the statistical fluctuations being somewhat larger for the latter (χ^2 respectively 5.8 and 14.5 with 9 degrees of freedom). For tumours of the hypopharynx/epilarynx, the role of alcohol predominates; it appears clearly at each level of smoking, while the reverse for smoking is less obvious. In contrast, for endolarynx the effect of tobacco seems to be more important than the effect of alcohol. The latter, however, is already present in the lowest smoking class (Table VIII and Fig. 3).

DISCUSSION

The selection of the 6 study areas was based on the initial observation of very high larynx cancer mortality and incidence rates in the "Latin" countries of South-West Europe, all sharing many cultural characteristics. Some of these were directly relevant to the hypotheses related to cancer of the larynx/hypopharynx.

In all these countries, the consumption of a large amount of alcohol, mainly in the form of wine, is a common feature, in contrast with northern parts of Europe where alcohol consumption is lower and beer drinking is predominant. Another feature concerns the type of tobacco commonly available. Smoking is widespread in all the Latin countries, but cigarettes are (or used to be) made mainly of the so-called "black" tobacco, which the "blond" tobacco smokers in other countries consider as "strong". One might expect black tobacco to have a greater carcinogenic potency since it is richer in aromatic amines and in tobacco-specific nitrosamines than blond tobacco (Patrianakos and Hoffman, 1979; Hoffmann *et al.*, 1984).

Within these common Latin background features, there are, however, regional differences in smoking and drinking habits which justified the inclusion of several subgroups from the countries. The choice of the areas was indeed influenced by availability of incidence data, which was also associated with the epidemiological experience necessary to carry out such a study.

A comparative project of this kind entailed, of course, undeniable difficulties. The standardization of information on diet and beverages required lengthy preparatory work including the construction of a food table adapted to the various countries. A review of the various brands of tobacco was necessary to identify them as being "black" or "blond".

These problems have been extensively discussed in the preliminary studies carried out to describe and compare the 6 areas with respect to their smoking (Berrino *et al.*, in press), drinking (Péquignot *et al.*, in press) and dietary (Riboli *et al.*, in press) practices.

The re-arrangement of subsites into categories slightly different from those of the ICD became clearly justified *a posteriori* in view of the analysis showing the very distinct influence of alcohol on the epilarynx. In the ICD, there are some problems related to the limits between 2 adjacent sites (rectum and sigmoid colon is another example); in this particular instance, the reclassification turned out to be of great epidemiological importance.

The contrast between endolaryngeal cancer, mainly induced by tobacco with an alcohol component, and hypopharynx/epilarynx cancer, more influenced by alcohol than by tobacco, makes sense. It completes our understanding of the major influence of alcohol on the upper digestive pathway, for hypopharynx/epilarynx as for oesophagus (Brugère *et al.*, 1986; Tuyns *et al.*, 1977*b*), in contrast with the predominant influence of tobacco on the upper respiratory tract (endolarynx) and on lung, of course.

The observation of an effect of alcohol even in the lowest tobacco consumption category, noted in Table VIII, contrasts with the observations of Wynder *et al.* (1976) who observed this effect only for higher levels of smoking. These authors, however, used current smoking and current drinking data, which did not take into account the past smoking and drinking habits of the persons studied. On the other hand, that study was carried out in a population which would be considered—

TABLE VI - RELATIVE RISKS FOR TOBACCO AND ALCOHOL CONSUMPTION[1]

	Endolarynx			Hypopharynx/Epilarynx[3]		
	RR	95% CI	Number of cases	RR	95% CI	Number of cases
Average cigarette consumption[2]						
0	1	—	22	1	—	9
1–7	2.37	(1.3–4.3)	28	4.18	(1.9–9.3)	23
8–15	6.68	(4.2–10.7)	147	10.79	(5.3–21.8)	108
16–25	13.69	(8.7–21.6)	357	15.80	(7.9–30.6)	177
26+	16.42	(10.1–26.6)	173	16.11	(7.9–33.0)	92
Ever smoked	9.91	(6.4–15.4)	705	12.37	(6.3–24.4)	400
G alcohol per day[2]						
0–20	1	—	83	1	—	17
21–40	0.94	(0.7–1.3)	106	1.23	(0.7–2.3)	28
41–80	1.06	(0.8–1.5)	191	2.43	(1.4–4.2)	99
81–120	1.71	(1.2–2.4)	164	5.19	(3.0–9.0)	109
121+	2.56	(1.8–3.6)	183	11.37	(6.6–19.6)	156
Drinker of > 80 g[4]	2.05	(1.7–2.5)	347	4.28	(3.4–5.4)	265

[1]These risks are adjusted for the other factor and calculated from a logistic regression including an age/place interaction term.–[2]Averaged over the period of consumption.–[3]Those cancers which were unspecified but originated from hypopharynx or epilarynx were included in this category.–[4]Relative to ⩽80 g.

TABLE VII - MODIFICATION OF THE RISK OF CIGARETTE SMOKING ACCORDING TO VARIOUS BEHAVIOURS[1]

	Endolarynx			Hypopharynx/Epilarynx		
	RR	95% CI	Number of cases	RR	95% CI	Number of cases
A. Years since quitting						
Current smoker	1	—	470	1	—	270
1–4	1.51	(1.2–2.0)	155	1.09	(0.8–1.5)	81
5–9	0.52	(0.3–0.8)	35	0.28	(0.1–0.5)	14
10+	0.28	(0.2–0.4)	45	0.32	(0.2–0.5)	35
B. Use of filter						
Only plain	1	—	218	1	—	193
Plain > filter	0.87	(0.7–1.2)	220	0.68	(0.5–0.9)	81
Plain < filter	1.03	(0.8–1.4)	216	0.60	(0.4–0.9)	56
Only filter	0.49	(0.3–0.8)	33	0.47	(0.3–0.8)	20
Unclassifiable[2]	0.63	(0.3–1.3)	18	0.60	(0.4–1.1)	50
C. Colour of tobacco						
Only blond	1	—	32	1	—	12
Blond > black	1.58	(0.9–2.7)	79	1.31	(0.5–3.2)	15
Blond < black	1.66	(1.0–2.7)	149	1.71	(0.8–3.6)	45
Only black	1.98	(1.2–3.2)	417	2.16	(1.1–4.2)	316
Unclassifiable[2]	1.06	(0.6–2.0)	28	0.79	(0.3–2.0)	12
D. Inhalation						
Inhaler	1	—	614	1	—	242
Non-inhaler	0.66	(0.5–0.9)	69	0.87	(0.6–1.3)	82
No information	0.60	(0.3–1.2)	22	0.90	(0.5–1.6)	76

[1]Adjusted for each other and for consumption of cigarettes and alcohol.–[2]This category includes those for whom more than 10% of the cigarettes smoked could not be classified.

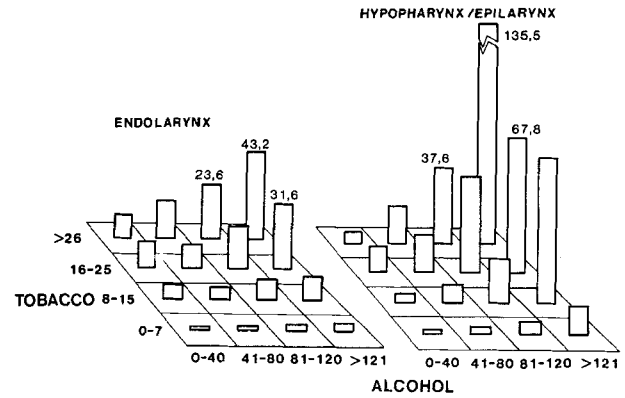

FIGURE 3 - Relative risks according to daily consumption of tobacco and alcohol (g/day).

TABLE VIII - COMBINED EFFECT OF ALCOHOL AND TOBACCO. RELATIVE RISK AND NUMBER OF CASES

Alcohol, g per day	Cigarettes per day 0-7	8-15	16-25	26+	Total (RR for alcohol)
Endolarynx					
0-40	1.0 (13)	6.68 (44)	12.72 (95)	11.47 (37)	1.0 (189)
41-80	1.65 (18)	5.94 (39)	12.23 (94)	18.51 (40)	1.10 (191)
81-120	2.31 (9)	10.70 (38)	21.01 (82)	23.55 (35)	1.78 (164)
121+	3.78 (10)	12.20 (26)	31.55 (86)	43.21 (61)	2.66 (183)
Total (RR for tobacco)	1.0 (50)	4.51 (147)	9.26 (357)	11.14 (173)	(727)
Hypopharynx/ epilarynx					
0-40	1.0 (4)	4.65 (9)	13.91 (27)	4.90 (5)	1.0 (45)
41-80	2.99 (10)	14.58 (32)	19.54 (42)	18.43 (15)	2.18 (99)
81-120	5.52 (7)	27.47 (28)	48.25 (52)	37.62 (22)	4.63 (109)
121+	14.67 (11)	71.59 (39)	67.81 (56)	135.46 (50)	10.18 (156)
Total (RR for tobacco)	1 (32)	4.89 (108)	7.20 (177)	7.32 (92)	(409)

by South-West European standards anyway—as moderate drinkers. Among the 650 male controls in Wynder's study, there were 236 non-drinkers (36%), a much higher figure than the 10% found in our controls (Péquignot *et al.*, in press). These differences probably explain why the effects of alcohol appeared more clearly at all levels of smoking in the present study.

In fact, more recent studies of Burch *et al.* (1981) in Canada and of Elwood *et al.* (1984) confirmed the effect of alcohol even in non-smokers. These authors concluded that alcohol plays a more important role than previously indicated, a conclusion which is fully supported by our analyses. In our series

TABLE IX - ALCOHOL CONSUMPTION OF NON-SMOKING CASES

Daily alcohol g/day	Endolarynx cases Observed	Endolarynx cases Expected[1]	Hypopharynx/Epilarynx cases Observed	Hypopharynx/Epilarynx cases Expected[1]
0-40	7	9.4	1	4.1
40-80	9	7.8	0	3.1
80+	6	4.8	8	1.8
Total	22	22	9	9

[1]Computed from control distribution by an indirect method taking into account age, centre and smoking habit.

of more than 1,000 cases, there were only 34 non-drinkers—all of whom were smokers, and 31 lifetime non-smokers—all of whom drank and had a higher alcohol consumption than controls (Table IX).

There is no indication of a strong departure from a multiplicative joint effect of alcohol and tobacco; however, the formal testing of various models of interaction would require a more precise approach (Breslow and Storer, 1985; Estève and Tuyns, in press). It was seen in Table VIII that the adequacy of the multiplicative model is good with slightly larger discrepancies at lower levels of alcohol consumption. Defining light smokers as those who have smoked less than 7 cigarettes a day for less than 10 years, a reliable risk of cancer could be computed for those drinking more than 40 g/day: for endolarynx cancer this risk is 2.14 among light smokers and 1.55 among other smokers. The figures are 5.88 and 4.06 respectively for hypopharynx/epilarynx cancer. These differences are not significant. There is therefore no evidence that relative risk due to alcohol would be different at low level of tobacco consumption.

Given that the multiplicative model is correct, the average proportion of larynx/hypopharynx cancer attributable to drinking more than 40 g/day in these populations may be calculated easily from the corresponding relative risk adjusted for tobacco and the proportion of cases who are in this category of alcohol consumption (Miettinen, 1974). The figures are respectively 28% for larynx cancer and 68% for hypopharynx/epilarynx cancer. Although these figures do not account completely for the difference in rates between the United Kingdom and the south of Europe, they might help to explain part of it. Further analysis of this set of data in relation to nutrition and occupational exposure in each study area may provide a better understanding of the distribution of these cancers in the European countries.

The finding of a slightly lower risk for filter cigarettes confirms the observations of Wynder *et al.* (1976) and of others.

The aggravating role of inhalation has long been identified (Schwartz *et al.*, 1962) in relation to lung cancer; it holds true for endolaryngeal cancer as well but not for the hypopharynx/epilarynx.

The distinction between black and blond tobacco confers a new dimension to the smoking-cancer problem. It has already been described (Estève *et al.*, 1984) and found to be of importance too for bladder cancer (Vineis *et al.*, 1984) and lung cancer (Benhamou *et al.*, 1985).

The chemical carcinogens present in tobacco smoke have been extensively investigated for more than 40 years and some coherent picture seems to emerge (IARC, 1986). Our understanding of the role of alcohol is far from having reached that stage (Tuyns, 1982*b*; Lieber *et al.*, 1986). Alcohol is usually

considered as a vector or a co-carcinogen rather than as a carcinogen *per se*; for most cancer sites of the upper aerodigestive tract the effect of alcohol is indeed combined with that of tobacco, providing support for that opinion. There is evidence, however, that for oesophageal cancer there is a strong effect of alcohol even in the absence of smoking (Tuyns, 1983), and the data presented here point in the same direction since, for larynx and hypopharynx/epilarynx cancer as well, the effect of alcohol is present even at the lowest level of tobacco consumption.

Our study shows the importance of alcohol consumption in the aetiology of laryngeal and hypopharyngeal cancer, even among non-smokers. A vast amount of research has been invested in understanding the mechanisms of tobacco carcinogenesis, and in public health strategies aimed at reduction of smoking. There is a clear need for a similar effort in relation to alcohol.

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REFERENCES

BAKER, R.J., and NELDER, J.A., *The GLIM System, Release 3. Generalised linear interactive modelling*. Numerical Algorithms Group, Oxford (1978).

BENHAMOU, S., BENHAMOU, E., TIRMARCHE, M., and FLAMANT, R., Lung cancer and use of cigarettes: a French case-control study. *J. nat. Cancer Inst.*, **74,** 1169–1175 (1985).

BERRINO, F., MERLETTI, F., ZUBIRI, A., DEL MORAL, A., RAYMOND, L., ESTÈVE, J., and TUYNS, A., A comparative study of smoking, drinking and dietary habits in population samples in France, Italy, Spain and Switzerland. II. Tobacco smoking. *Rev. Epidemiol. Santé Publ.* (in press).

BRESLOW, N.E., and DAY, N.E., Statistical methods in cancer research. Vol. **I,** *The analysis of case-control studies,* IARC Scientific Publication **32,** IARC, Lyon (1980).

BRESLOW, N.E., and STORER, B.E., General relative risk functions for case-control studies. *Amer. J. Epidemiol.*, **122,** 149–162 (1985).

BROOKE, E.M., Géographie de la mortalité due au cancer en Suisse, 1969–1971. Institut Universitaire de Médecine Sociale et Préventive, Lausanne (1975).

BRUGÈRE, J., GUÉNEL, P., LECLERC, A., and RODRIGUEZ, J., Differential effects of tobacco and alcohol in cancer of the larynx, pharynx and mouth. *Cancer,* **57,** 391–395 (1986).

BURCH, J.D., HOWE, G.R., MILLER, A.B., and SEMENCIW, R., Tobacco, alcohol, asbestos and nickel in the etiology of cancer of the larynx: a case-control study. *J. nat. Cancer Inst.*, **67,** 1219–1224 (1981).

CUBEAU, J., and PÉQUIGNOT, G., La technique du questionnaire alimentaire quantitatif utilisé par la section Nutrition de l'INSERM. *Rev. Epidémiol. Santé publ.*, **28,** 367–372 (1980).

ELWOOD, J.M., PEARSON, J.C.G., SKIPPEN, D.H., and JACKSON, S.M., Alcohol, smoking, social and occupational factors in the aetiology of cancer of the oral cavity, pharynx and larynx. *Int. J. Cancer,* **34,** 603–612 (1984).

ESTÈVE, J., TUYNS, A.J., RAYMOND, L., and VINEIS, P., Tobacco and the risk of cancer. Importance of kinds of tobacco. *In:* I.K. O'Neill, R.C. von Borstel, C.T. Miller, J. Long and H. Bartsch (eds.), *N-nitroso compounds: occurrence, biological effects and relevance to human cancer,* pp. 867–876. IARC Scientific Publication **57,** IARC, Lyon (1984).

ESTÈVE, J., TUYNS, A.J., Models for combined action of alcohol and tobacco on risk of cancer: what do we really know from epidemiological studies? Proceedings of the Fourth Sardinian International Meeting on Models and Mechanisms in Chemical Carcinogenesis (in press).

HOFFMANN, D., BRUNNEMANN, K.D., ADAMS, J.D., and HECHT, S.S., Formation and analysis of N-nitrosamines in tobacco products and their endogenous formation in consumers. *In:* I.K. O'Neill, R.C. von Borstel, C.T. Miller, J. Long and H. Bartsch (eds.), *N-nitroso compounds: occurrence, biological effects and relevance to human cancer,* pp. 743–762, IARC Scientific Publication **57,** IARC, Lyon (1984).

INTERNATIONAL AGENCY FOR RESEARCH ON CANCER, Tobacco smoking. *IARC Monographs on the evaluation of the carcinogenic risk of chemicals,* Vol. **37,** IARC, Lyon (1986).

JENSEN, O.M., Cancer morbidity and causes of death among Danish brewery workers. *Int. J. Cancer,* **23,** 454–463 (1979).

LEHMANN, W., *Les cancers de l'endolarynx. Bilan clinique et résultats thérapeutiques de 417 cas traités à l'Institut Gustave-Roussy entre 1968 et 1972. Mémoire.* Faculté de Médecine, Paris (1977).

LIEBER, C.S., GARRO, A., LEO, M.A., MAK, K.M., and WORNER, T., Alcohol and cancer. *Hepatology,* **6,** 1005–1019 (1986).

MCMICHAEL, A.J., Increases in laryngeal cancer in Britain and Australia in relation to alcohol and tobacco consumption trends. *Lancet,* **I,** 1244–1247 (1978).

MERLETTI, F., HESELTINE, E., SARACCI, R., SIMONATO, L., VAINIO, H., and WILBOURN, J., Target organs for carcinogenicity of chemicals and industrial exposures in humans: a review of results in the IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans. *Cancer Res.*, **44,** 2244–2250 (1984).

MIETTINEN, O.S., Proportion of disease caused or prevented by a given exposure, trait or intervention. *Amer. J. Epidemiol.*, **99,** 325–332 (1974).

PATRIANAKOS, C., and HOFFMANN, D., Chemical studies of tobacco smoke. LXIV. On the analysis of aromatic amines in cigarette smoke. *J. anal. Chem.*, **3,** 150–154 (1979).

PÉQUIGNOT, G., and CUBEAU, J., Enquêtes méthodologiques comparant chez les mêmes sujets la consommation alimentaire appréciée par interrogatoire à la consommation mesurée par pesée. *Rev. Epidémiol. Méd. soc. Santé publ.*, **21,** 585–608 (1973).

PÉQUIGNOT, G., CROSIGNANI, P., TERRACINI, B., ASCUNCE, N., ZUBIRI, A., RAYMOND, L., ESTÈVE, J., and TUYNS, A., A comparative study of smoking, drinking and dietary habits in population samples in France, Italy, Spain and Switzerland. III. Consumption of alcohol. *Rev. Epidémiol. Santé publ.* (in press.)

RIBOLI, E., PÉQUIGNOT, G., REPETTO, F., AXERIO, M., RAYMOND, L., BOFFETTA, P., ZUBIRI, A., DEL MORAL, A., ESTÈVE, J., and TUYNS, A.J., A comparative study of smoking, drinking and dietary habits in population samples in France, Italy, Spain and Switzerland, I. Study design and dietary habits. *Rev. Epidémiol. Santé publ.* (in press.)

SCHWARTZ, D., LELLOUCH, J., FLAMANT, R., and DENOIX, P.F., Alcool et cancer. Résultats d'une enquête retrospective. *Rev. franç. Etud. clin. biol.*, **7**, 590–604 (1962).

TERRACINI, B., PASTORE, G.E., and COVERLIZZA, S., Aumento della mortalità per tumori maligni della laringe successivo al 1951 nel comune di Torino e in Italia. *Tumori*, **60**, 221–230 (1974).

THOMAS, D.C., GOLDBERG, M., DEWAR, R., and SIEMIATYCKI, J., Statistical methods for relating several exposure factors to several diseases in case-heterogeneity studies. *Statist. Med.*, **5**, 49–60 (1986).

TUYNS, A.J., Incidence trends of laryngeal cancer in relation to national alcohol and tobacco consumption. *In:* K. Magnus (ed.), *Trends in cancer incidence*, pp. 199–214, Hemisphere, Washington (1982*a*).

TUYNS, A.J., SCHOTTENFELD, D., and FRAUMENI, J.F. (eds.), *Alcohol in cancer epidemiology and prevention.* Saunders, Philadelphia (1982*b*).

TUYNS, A.J., Oesophageal cancer in non-smoking drinkers and in non-drinking smokers. *Int. J. Cancer*, **32**, 443–444 (1983).

TUYNS, A.J., and AUDIGIER, J.C., Double wave cohort increase for oesophageal and laryngeal cancer in France in relation to reduced alcohol consumption during the Second World War. *Digestion*, **14**, 197–208 (1976).

TUYNS, A.J., BERRINO, F., DEL MORAL, A., RAYMOND, L., REPETTO, F., TERRACINI, B., ZUBIRI, A., BLANCHET, F., ESTÈVE, J., LEHMANN, W., PÉQUIGNOT, G., and SANCHO-GARNIER, H., Cancer du larynx. Enquête internationale épidémiologique sous l'égide du CIRC. *Ouest med.*, **33**, 1143–1147 (1980).

TUYNS, A.J., and ESTÈVE, J., Present and past alcohol consumption in Calvados (France). *Rev. Epidémiol. Santé publ.*, **31**, 487–488 (1983).

TUYNS, A.J., and HU, M.X., Changing smoking patterns in the *département* of Calvados (France). *Brit. J. Addict.*, **77**, 167–183 (1982).

TUYNS, A.J., JENSEN, O.M., and PÉQUIGNOT, G., Le choix difficile d'un bon groupe de témoins dans une enquête retrospective. *Rev. Epidémiol. Santé publ.*, **25**, 67–84 (1977*a*).

TUYNS, A.J., PÉQUIGNOT, G., and HU, M.X., Alcohol consumption patterns in the *département* of Calvados (France). *Rev. Epidémiol. Santé publ.*, **31**, 179–197 (1983).

TUYNS, A.J., PÉQUIGNOT, G., and JENSEN, O.M., Le cancer de l'oesophage en Ille-et-Vilaine en fonction des niveaux de consommation d'alcool et de tabac. Des risques qui se multiplient. *Bull. Cancer*, **64**, 45–60 (1977*b*).

TUYNS, A.J., PÉQUIGNOT, G., JENSEN, O.M., and POMEAU, Y., La consommation individuelle de boissons alcoolisées et de tabac dans un échantillon de la population en Ille-et-Vilaine. *Rev. Alcool*, **21**, 105–150 (1975).

VINEIS, P., ESTÈVE, J., and TERRACINI, B., Bladder cancer and smoking in males: types of cigarettes, age at start, effect of stopping and interaction with occupation. *Int. J. Cancer*, **34**, 165–170 (1984).

VINEIS, P., and ESTÈVE, J., Temporal aspects of bladder carcinogenesis. *Toxicol. Pathol.*, **15**, 234–237 (1987).

WORLD HEALTH ORGANIZATION, *Annuaire de statistiques sanitaires mondiales, 1973–1976.* WHO, Geneva (1976).

WYNDER, E.L., COVEY, L.S., MABUCHI, K., and MUSHINSKI, M., Environmental factors in cancer of the larynx. A second look. *Cancer*, **38**, 1591–1601 (1976).