Pergamon

Oral Oncol, Eur J Cancer, Vol. 31B, No. 5, pp. 301–309, 1995
Elsevier Science Ltd
Printed in Great Britain
0964–1955/95 $9.50 + 0.00

0964–1955(95)00041–0

Role of Alcohol and Tobacco in the Aetiology of Head and Neck Cancer: a Case–Control Study in the Doubs Region of France

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A case–control study conducted from 1986 to 1989 using the Doubs Cancer Registry included 299 cases of head and neck cancer and 645 controls from the general population. The results provide an indicator of the respective roles of alcohol and tobacco in all these cancers and on the tumour site. The people who smoked more than one packet of cigarettes a day have a risk that is 13 times higher than that of non-smokers and those who drink more than one and a half litres of wine per day have a risk that is 34 times higher of developing head and neck cancer. The combined exposure of alcohol and tobacco is characterised by a high risk and can be described by a multiplicative model without interaction. The age at onset (below 18 years of age) and the duration of smoking (over 35 years) are high risk factors. The risk decreases after stopping smoking, but only casual smokers (less than 7 cigarettes per day) can hope to have the same risk as non-smokers within a period of 15 years. Subjects smoking only non-filter cigarettes have a higher risk (OR = 1.98) than those who smoke filter cigarettes. The same applies to those who roll their own cigarettes (OR = 1.93) or inhale the smoke (OR = 1.51).

Keywords: head and neck cancer, alcohol, tobacco, case–control study, risk factor

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INTRODUCTION

CANCER OF the head and neck in males over the age of 35 years is one of the major problems of French public health due to the bad prognosis that is associated with it (11.5% of deaths from cancer) [1], the onset at an early age (50% before the age of 60 years) [2] and the high incidence rate, giving France one of the highest incidence rates in the world [3]. These incidence rates in males in the Doubs region, standardised on the European population, are 53.8 per 100 000 males for cancer of the mouth and pharynx and 18.1 per 100 000 for cancer of the larynx.

In France, there are geographical variations in mortality of head and neck cancer which are closely linked to those for alcohol mortality. These variations were the origin of the hypothesis of the aetiological role of alcohol half a century ago [4], which had been largely confirmed by numerous studies such as that of the role of tobacco [5–11]. These geographical differences also relate to the incidence rates of these cancers with demographical, socio-educational and occupational differences or food and alcohol–tobacco consumption habits. A cancer registry of the population, such as that in the Doubs region, provides an evaluation of the risks attributed to these factors.

With the aim of evaluating these risks, a case–control study was set up in the Doubs between 1986 and 1989 with the help of the International Center for Cancer Research (IARC) in Lyon. This study concentrates on the risks linked to the consumption of tobacco and alcohol and their association from a quantitative and qualitative point of view. The results concerning food [12], occupational exposure and oral–dental hygiene are, or will be, the subject of other publications. The effect of these two cancer agents differ according to the anatomical site of the cancer or more succinctly, according to where the cancer is located in the digestive tract (oral cavity, hypopharynx), respiratory tract (larynx) or at the aerodigestive junction (oropharynx). Moreover, in the case of larynx cancers, the inclusion or rejection of the auditus laryngis (epilarynx), through which the supraglottis opens into the pharynx, modifies the effect of both alcohol and tobacco. Thus, one part of the analysis will deal with the head and neck as a whole and the other part with a study of the risks specific to each site (oral cavity, oropharynx, hypopharynx, epilarynx and endolarynx). The results of the study will help to define priority preventive measures that need to be implemented in order to reduce the extent and the gravity of these cancers.

PATIENTS AND METHODS

This case–control study was carried out using a methodology that has already been applied to an international analysis

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Received 11 Oct. 1994; accepted 14 June 1995.

of cancer of the larynx and hypopharynx by Tuyns *et al.* in 1988 [13–15].

The population

The cases of head and neck cancer include all the cancers of the oral cavity (Nos 141, 143, 144, 145 of the CIM-O, 1980), oropharynx (No. 146), hypopharynx (No. 148) and larynx (No. 161) recorded between 1986 and 1989 in the Doubs Cancer Registry. Their topographical distribution is detailed in Table 1. All the cases were male and aged over 35 years with an epidermoid carcinoma which was histologically confirmed. Of the 337 patients with these characteristics, only 299 could be interviewed: 38 patients (11%) could not be included in this study, due to death, a critical state of health or refusal to participate in the study. The control group is taken from a random sample of the general population of males aged over 35 years and residing in the Doubs region. This sample was compiled with the help of the Institut National de la Statistique et des Etudes Economiques (INSEE). A stratification of the cases reported during the 10 years prior to the study into five age groups of 10 years each, from the age of over 35 years including the place of residence (urban or rural), was carried out to determine the distribution of the controls during the random selection. Two controls for each case were chosen to cover any possible withdrawals. The two tier selection was carried out as follows: firstly, the rural counties (less than 2000 inhabitants) and the urban regions (more than 2000 inhabitants) were classified by increasing order of population and randomly selected; secondly, 1270 controls (including the replacements) were selected from the electoral rolls of each county in accordance with the different age groups.

Survey

Two specially trained dieticians interviewed both the cases and the controls in their own home using a questionnaire. The cases were interviewed as they were recorded in the Cancer Registry. 645 controls (51%) took part in the survey after they had been contacted by phone or letter: 18.9% of the selected controls refused to take part in the survey, 13% had moved, 12.9% were absent from the region, 1.9% had died and 3% did not take part for other reasons. Among the 164 controls who were absent, 61.6% had replied to a letter which provided information showing that there was no difference in the sociocultural categories or their alcohol–tobacco consumption habits in relation to the 645 controls included in the study.

The two interviewers were able to establish a climate of trust by visiting the homes of subjects who were particularly conscientious and co-operative in relation to the memory

Table 1. Distribution of the cases and controls according to variables

	Cases		Controls		
	n	(%)	*n*	(%)	*P*
Age					
<45	19	(6.4)	58	(9.0)	0.12
45–54	69	(23.1)	137	(21.2)	
55–64	18	(39.5)	209	(32.4)	
65–74	57	(19.1)	147	(22.8)	
75+	36	(12.0)	94	(14.6)	
Environment					
Rural	95	(31.8)	183	(28.4)	0.28
Urban	204	(68.2)	462	(71.6)	
Marital status					
Married	210	(70.2)	535	(82.9)	<0.00001
Single	29	(9.7)	43	(6.7)	
Widowed	34	(11.4)	47	(7.3)	
Separated/divorced	26	(8.7)	20	(3.1)	
Occupation					
White collar worker	29	(9.7)	144	(22.3)	<0.00001
Agricultural worker, craftsman, retailer	19	(6.4)	62	(9.6)	
Worker	70	(23.4)	71	(11.0)	
Retired	173	(57.9)	362	(56.1)	
No occupation	8	(2.7)	6	(0.9)	
Educational level					
University entrance or higher	14	(4.7)	124	(19.2)	<0.00001
Secondary diploma	188	(62.9)	282	(43.7)	
No diploma	97	(32.4)	239	(37.1)	
Cancer site					
Oral cavity	62	(20.7)			
Endolarynx	62	(20.7)			
Epilarynx	13	(4.3)			
Hypopharynx	79	(26.4)			
Oropharynx	83	(27.7)			

effort that was required of them. This enabled the interviewers to obtain all the data required to complete the questionnaire.

Questionnaire

The questionnaire was the same as that used by the Tuyns teams. Apart from the classical sociodemographical details, the questionnaire focused on four aspects: (i) the consumption of alcohol and tobacco; (ii) diet habits; (iii) occupational exposure; and (iv) oral–dental condition. The section devoted to alcohol and tobacco described the complete history of the subjects' consumption; the section dealing with tobacco covered the type of tobacco smoked (blond or black cigarettes, cigars or pipe), the brand name of the tobacco, a description of the dates of beginning and end of each of the n periods (P_i) of consumption, as well as the periodic daily consumption ($C\mathcal{J}P_i$). The lifetime average daily consumption (CMV) for each type of tobacco consumption was estimated as follows by:

$$CMV = \frac{\sum_{i=1}^{n} [C\mathcal{J}P_i \times (\text{age end period } P_i - \text{age beginning period } P_i) \times 365]}{(\text{Age end tobacco consumption} - \text{age beginning tobacco consumption}) \times 365}.$$

Equivalence tables converted data on the daily consumption of different types of tobacco expressed in grams of tobacco per day: 1 cigarette corresponded to 1 g of tobacco, the weight of cigars was obtained by the interviewer presenting the different types of cigars. For pipe smokers, the answers were expressed in packets of tobacco used per week and weight of the packet [14]. The lifetime average daily tobacco consumption was obtained by totalling the lifetime average daily tobacco consumption of each type of tobacco consumption. The duration and the age at the beginning of tobacco consumption and the duration of the period after stopping smoking at the time of the survey provided a definition of a smoker as a subject who had smoked more than 1 g of tobacco per day for at least 6 months.

Ex-smokers were considered to be subjects who had stopped smoking for more than 1 year on the date of interview. Other qualitative information on the method of consuming cigarettes was also collected, i.e. the use or not of filter cigarettes, the consumption of hand-rolled or manufactured cigarettes and whether or not the smoker inhaled the smoke. Data concerning the consumption of alcohol were collected with the food questionnaire so as to reduce the pejorative aspect associated with the consumption of alcohol. The reliability of replies was thus improved by the convivial aspect and socially acceptable notion of alcoholic beverages associated with food.

The history of alcohol consumption after 18 years of age was recorded in the same way as that of tobacco. The quantities of alcohol of each type drunk each day was expressed in grams of pure alcohol using the following conversion table:

100 ml of wine = 9.4 g of pure alcohol
100 ml of beer = 4 g of pure alcohol
100 ml of cider = 4 g of pure alcohol
100 ml of aperitif = 14.5 g of pure alcohol
100 ml of digestive = 31.7 g of pure alcohol.

The mean daily alcohol consumption over the adult lifetime of each subject and the mean lifetime daily consumption of each type of alcohol were calculated in the same way as for tobacco consumption.

Statistical analysis

The calculation of the odds ratio (OR) and their confidence intervals (CI) at 95% was carried out with a BMDP programme [16] using logistic regression models [17] including confounding factors determined in the preliminary analysis and treated as category variables with the two stratification variables of age and rural or urban environment. The dose–response and the duration–response relations were analysed using the χ^2 test of trend.

The risk of head and neck cancer associated with the daily consumption of tobacco (in grams per day) was broken down into four categories (0, 1–7, 8–19, >20) which correspond to the quantities found in the controls. The daily consumption of alcohol (in grams per day) was broken down into five categories (0–20, 21–40, 41–80, 81–120, >120) corresponding to those used by Tuyns *et al.* [13] as the numbers in the control groups did not give the regular and coherent categories required for a quantile breakdown. The small number of non-drinkers (4 cases and 17 controls) was the reason for the inclusion of the casual drinker category (1–20 g/day) in the first category. However, due to the decrease in population for the specific studies of each cancer site, alcohol and tobacco consumption was broken down into three categories 0–7, 8–19, >20 for tobacco and 0–40, 41–100, >100 for alcohol. This same breakdown was also used during the adjustments for the variables and the risk study corresponding to the tobacco–alcohol association and all the head and neck cancer cases. The combination of non-smokers with the casual smokers (1–7 g/day) was justified by the equivalence of the risk.

A more homogeneous distribution of the population was required when the tobacco–alcohol association study was carried out in relation to tumour site. This led to three categories for alcohol (0–40, 41–80, >80) and only two categories for tobacco, with a threshold of 20 g/day corresponding to one packet of cigarettes per day. The different analyses were carried out for the whole population in the study, as well as for the smokers and drinkers separately. Only the pertinent statistical results are presented.

RESULTS

The distribution of the cases and the controls according to age and environment and other sociodemographical characteristics is given in Table 1. There was no significant difference between the cases and the controls concerning age ($P = 0.12$) and environment, indicating that the stratification was of good quality.

Marital status

Subjects who were separated or divorced had a significantly greater risk of developing head and neck cancer (OR = 2.34) in relation to married subjects (Table 2).

Educational level

Subjects with a level of university entrance or higher were taken as the reference category (OR = 1). The risk associated with subjects who had a diploma, but which was below university entrance was twice as great (OR = 2.22) and those

Table 2. Risk associated with sociodemographical characteristics and confidence levels at 95%

	OR*	CI (95%)
Marital status		
Married[R]	1	
Single	1.34	(0.69–2.60)
Widowed	1.61	(0.87–2.97)
Separated/divorced	2.34	(1.11–4.92)
Educational level		
University entrance or higher[R]	1	
Secondary diploma	2.22	(1.10–4.50)
No diploma	3.02	(1.50–6.08)
Occupation		
White collar[R]	1	
Agricultural worker, craftsman, retailer	0.80	(0.35–1.80)
Retired	1.14	(0.57–2.26)
Worker	2.20	(1.16–4.18)
No occupation	4.70	(1.11–19.9)

*Risks adjusted for the other two risks as well as age, environment and lifetime mean daily consumption of alcohol and tobacco. [R]: Reference category.

with no diploma at all had a risk that was three times higher of developing a tumour in the oral–pharyngeal–laryngeal region.

Socio-occupational categories

These were grouped into five logical categories of risk with white collar employees being used as the reference. Workers and subjects without an occupational activity had a significantly higher risk of developing a cancer of the head and neck (2.2 and 4.7 times greater). As none of these factors had a pertinent confounding effect on tobacco–alcohol consumption, they were not taken into account for the analysis.

The risks linked to tobacco adjusted for the consumption of alcohol as well as the risks linked to alcohol adjusted for the consumption of tobacco are detailed in Table 3. There is a dose–response relationship ($P<0.0001$). The same dose–response relationships were observed for each cancer site (Table 4), but there were variations: it was difficult to regroup certain sites because when the sites showed a similar behaviour in relation to increasing doses of tobacco, they differed for increasing doses of alcohol. Only the hypopharynx and the epilarynx were grouped together due to the small number of cases with epilarynx cancer ($n=13$) and the results of the international survey of Tuyns. It was confirmed that the 13 cases of epilarynx cancer added to the 79 cases of hypopharynx cancer did not significantly alter the risk calculated for hypopharynx cancers. The effect of tobacco was more marked for the hypopharynx–epilarynx and the oral cavity than for the endolarynx and oropharynx (Fig. 1). Alcohol had an effect with comparable intensities on the oropharynx and oral cavity, and to a lesser extent on the hypopharynx–epilarynx and endopharynx (Fig. 2).

The combined effect of alcohol and tobacco appeared to follow a multiplicative model without interaction with a risk that was 200 times greater for heavy smokers (+20 g/day) and drinkers (Fig. 3, Table 5).

A pertinent alcohol effect (OR = 62 for a daily consumption of more than 100 g of pure alcohol) was observed for both non-smokers and casual smokers (1–7 g/day). The combined synergistic action of alcohol and tobacco varied in intensity according to the tumour site (Table 6). The combination of the effects was similar for the hypopharynx–epilarynx and the oropharynx. The risk of developing a cancer of the oral cavity in a subject drinking more than 1 litre of wine at 11% per day (>80 g/day) and smoking more than one packet of cigarettes was approximatively five times greater (OR = 75) than the risk of developing an endolarynx cancer (OR = 14.5).

The statistical models used to study these variables are relatively complete as each of the variables was adjusted in accordance with the others as well as the duration and the period of time the subject had stopped smoking cigarettes.

Type of tobacco

Smokers of blond cigarettes and smokers of black cigarettes were defined as subjects who smoked more than 90% of blond or black cigarettes during their life. The other smokers were classed as mixed smokers.

Cigarette smokers consuming more than 10% of cigarettes of an unknown brand name (9 subjects) were placed in the intermediate category (mixed). It was confirmed that this figure did not bias the reference category (smokers of blond cigarettes) because their consumption did not reach 90% of the total consumption. Thus, only the category of black

Table 3. Risk associated with the consumption of alcohol and tobacco

	Controls		Cases				
	n	(%)	*n*	(%)	OR*	CI (95%)	*P* of linear trend
Tobacco (g/day)							
0	135	(20.9)	6	(2.0)	1		
1–7	115	(17.8)	14	(4.7)	2.46	(0.86–6.98)	<0.0001
8–19	222	(34.4)	110	(36.8)	8.47	(3.47–20.7)	
20+	173	(26.8)	169	(56.5)	12.9	(5.30–31.5)	
Alcohol (g/day)							
0–20	150	(23.2)	116	(3.6)	1		
21–40	136	(21.1)	15	(5.0)	1.32	(0.57–3.03)	<0.0001
41–80	278	(43.1)	97	(32.4)	3.31	(1.69–6.48)	
81–120	65	(10.1)	107	(35.7)	14.3	(7.05–29.0)	
>120	16	(2.5)	69	(7.7)	33.8	(14.5–78.8)	

*Risk adjusted for alcohol or tobacco, age and environment.

Table 4. Risk associated with alcohol and tobacco consumption according to cancer site

Sites	Risk associated with alcohol consumption adjusted for tobacco						Risk associated with tobacco consumption adjusted for alcohol					
	0–40 (g/day)		41–100 (g/day)		>100 (g/day)		0–7 (g/day)		8–19 (g/day)		20+ (g/day)	
	Cases	OR	Cases	OR CI (95%)	Cases	OR CI (95%)	Cases	OR	Cases	OR CI (95%)	Cases	OR CI (95%)
Endolarynx	6	1	29	4.07 (1.52–11.5)	27	17.8 (6.45–49.1)	5	1	24	4.17 (1.52–11.5)	33	5.80 (2.12–15.8)
Epilarynx/hypopharynx	10	1	43	2.78 (1.35–5.73)	39	23.0 (10.0–52.7)	5	1	35	6.40 (2.35–17.4)	52	9.10 (3.36–24.6)
Oropharynx	6	1	22	5.01 (2.08–12.1)	55	30.1 (11.5–80.3)	7	1	28	3.44 (1.40–8.42)	48	5.60 (2.33–13.5)
Oral cavity	4	1	35	5.43 (1.88–15.7)	23	29.7 (9.26–95.1)	3	1	23	6.24 (1.79–21.8)	36	8.22 (2.38–28.4)

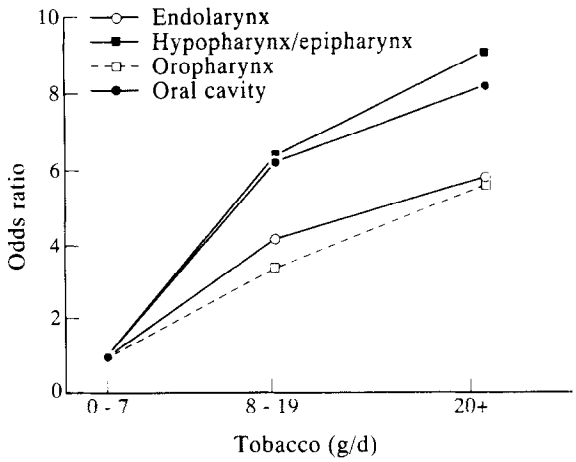

Fig. 1. Relative risk of cancer of the endolarynx, hypopharynx/epilarynx, oropharynx and oral cavity according to daily tobacco consumption.

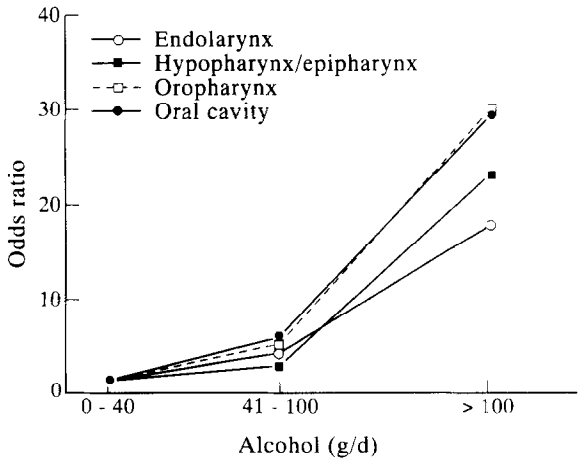

Fig. 2. Relative risk of cancer of the endolarynx, hypopharynx/epilarynx, oropharynx and oral cavity according to daily alcohol consumption.

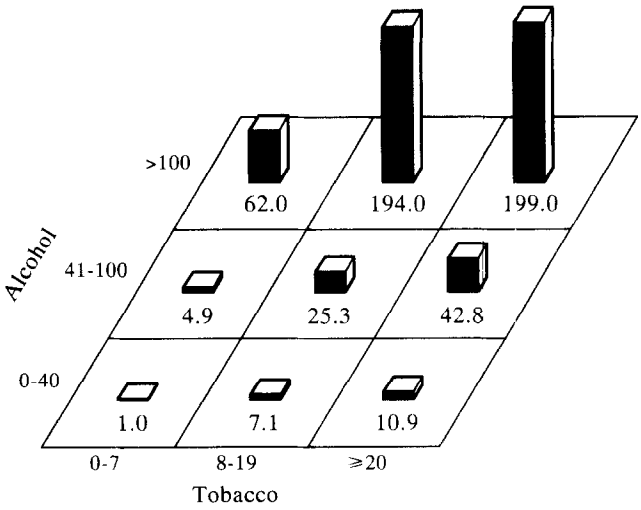

Fig. 3. Relative risk according to daily consumption of alcohol and tobacco.

Table 5. Combined effect of alcohol and tobacco—estimated risk and number of cases and controls

Tobacco (g/day)	Alcohol (g/day) 0–40 Cases/controls	OR* CI (95%)	41–100 Cases/controls	OR* CI (95%)	>100 Cases/controls	OR* CI (95%)	Total ORt tobacco CI (95%)
0–7	3/148	1	10/97	4.87 (1.3–18.2)	7/5	62 (12.2–316)	1
8–19	12/86	7.12 (1.94–26.1)	64/127	25.3 (7.72–82.9)	34/9	194 (49.4–760)	4.97 (2.86–8.63)
20+	11/52	10.9 (2.9–40.8)	86/102	42.8 (13.1–140)	72/19	199 (56.5–699)	7.6 (4.37–13.2)
Total ORt alcohol CI (95%)	1		3.92 (2.47–6.2)		24.2 (13.5–43.3)		

*Risk adjusted for age and environment; †Risk adjusted for alcohol or tobacco, age and environment.

Table 6. Combined effect of alcohol and tobacco according to cancer site

Tobacco (g/day)	Alcohol (g/day) 0–40 Cases/controls	OR	CI (95%)	41–80 Cases/controls	OR	CI (95%)	>80 Cases/controls	OR	CI (95%)
Endolarynx									
<20	5/234	1		11/196	2.63	(0.89–7.70)	13/42	14.5	(4.90–42.8)
20+	1/52	0.9	(0.10–7.9)	18/82	10.3	(3.69–28.6)	14/39	16.8	(5.72–49.4)
Epilarynx hypopharynx									
<20	4/234	1		12/196	3.58	(1.13–11.3)	24/42	33.4	(11.0–101)
20+	6/52	6.75	(1.83–24.8)	14/82	9.99	(3.19–31.3)	32/39	48.0	(16.1–143)
Oropharynx									
<20	4/234	1		9/196	2.69	(0.81–8.87)	22/42	30.6	(10.0–93.6)
20+	2/52	2.25	(0.40–12.6)	13/82	9.27	(2.94–29.3)	33/39	49.5	(16.6–148)
Oral cavity									
<20	2/234	1		11/196	6.57	(1.43–30.1)	13/42	36.2	(7.86–167)
20+	2/52	4.5	(0.61–32.8)	9/82	12.8	(2.71–60.8)	25/39	75.0	(17.0–330)

tobacco smokers could be underestimated by this classification. Black tobacco smokers had an increased non-significant risk (OR = 2.59, CI = (0.76–8.79)) (Table 7).

Use of filter

The risk associated with non-filter cigarettes was twice that associated with filter cigarettes (OR = 1.98, CI = (1.02–3.85)).

Inhalation of smoke

Smokers who inhaled the smoke had a significantly higher risk than those who did not inhale the smoke (OR = 1.51, CI = (1.01–2.27)).

Hand-rolled or manufactured cigarettes

Among cigarette smokers, 14% of controls and 31% of cases, smoked hand-rolled cigarettes. Hand-rolled cigarettes had a cancer risk that was double that of manufactured cigarette smokers.

Duration and age at which smoking began (Table 8)

The effects of these two parameters were highly correlated and could not be analysed alone. After adjusting for daily dose of tobacco and alcohol, the risk associated with the duration of smoking followed a significant linear duration effect ($P < 0.0001$): the longer a person smoked the higher the cancer risk and this was significantly increased over the age of 35 years.

The age when smoking began was also a risk factor for head and neck cancer. People who started smoking before the age of 18 years had an increased risk (OR = 1.5).

Period of time stopped smoking

Stopping smoking for at least 5 years was a prospective factor. However, this must be rationalised. If one takes non-smokers as a reference, then after stopping for at least 5 years, only those who smoked less than 7 g/day had a risk that was divided by 3 and became non-significantly different from non-smokers. After stopping smoking for 15 years, smokers of more than 8 g/day of tobacco still had a risk that was three times higher than that of non-smokers (Table 9).

Table 7. Risk associated with type of cigarettes and smoking habits

	Controls	Cases	OR*	CI (95%)
Type of tobacco				
Blond (>90%)[R]	42	4	1†	
Mixed	59	16	1.04	(0.26–4.09)
Black (>90%)	385	272	2.59	(0.76–8.79)
Use of filter				
Always[R]	76	20	1†	
Irregularly	128	63	1.24	(0.61–2.52)
Never	282	209	1.98	(1.02–3.85)
Smoke inhaled				
No[R]	211	86	1	
Yes	275	206	1.51	(1.01–2.27)
Type of cigarette				
Manufactured > Rolled[R]	416	223	1	
Rolled > Manufactured	70	69	1.93	(1.18–3.15)

[R]Reference category.
*Risk adjusted for the three other categories as well as age, lifetime mean daily consumption of cigarettes and alcohol, duration and period stopped smoking; †Impossibility of adjusting type of tobacco for the use of filter and vice versa.

Table 8. Risk associated with duration of smoking, age at start and period of time stopped smoking

	Controls	Cases	OR	CI (95%)	*P* of linear trend
Duration					
1–14 years	51	2	1*		
15–24 years	91	18	2.02	(0.40–10.1)	<0.0001
25–35 years	120	49	3.07	(0.63–14.8)	
35–44 years	149	130	6.52	(1.36–31.4)	
45+	99	94	7.42	(1.51–36.4)	
Period stopped smoking					
Current smoker	194	174	1†		
1–4 years	88	72	0.90	(0.58–1.39)	<0.0001
5–9 years	46	13	0.29	(0.14–0.62)	
10–14 years	58	14	0.28	(0.14–0.58)	
15+	124	20	0.23	(0.12–0.42)	
Age started smoking					
>18 years	226	91	1*		
<18 years	284	202	1.54	(1.07–2.22)	

*Risk adjusted for the lifetime mean daily consumption of alcohol and tobacco and period stopped smoking; †Risk adjusted for the lifetime mean daily consumption of alcohol and tobacco and age started smoking.

As wine is the type of alcohol that is most frequently drunk in the Doubs region (Table 10), an analysis of the different types of alcohol was not necessary. However, it was estimated that the risk to those who only drank wine was twice as high as that of those who drank wine associated with other types of alcohol: the risk remained significant after adjustment with the daily consumption of tobacco and alcohol, socio-occupational category and dietary habits.

DISCUSSION

This study confirms the aetiological role of tobacco and alcohol in the onset of head and neck cancer as the attributable risk is estimated at 95% [18, 19] with joint consumption. This result is similar to that of Zatonski *et al.* [20] whereas other studies have shown a lower risk: 80% for Blot *et al.* [21]; and 75% for Franceschi *et al.* [22].

The results of our study focus on certain factors.

Alcohol contributes to the risk of head and neck cancer contrary to the conclusions of the American study by Wynder *et al.* [23] which reported a population which was a moderate consumer of alcohol in relation to our study. This result agrees with those of Brugère *et al.* [24], Elwood *et al.* [25], Tuyns *et al.* [13] and Mashberg *et al.* [26] who also observed a deleterious effect of the consumption of alcohol even with non-smokers or casual smokers. Tuyns *et al.* [13] showed that tobacco was the major risk factor, whereas Brugère *et al.* [24], Elwood *et al.* [25] and in particular, Mashberg *et al.* [26], attribute a more important role to alcohol. Tobacco is, thus, not the compulsory cofactor for the indirect action of alcohol, as Talami *et al.*

Table 9. Combined effect of quantity of tobacco consumed and period of time stopped smoking

Period stopped smoking	Tobacco (g/day) 1–7 Cases/controls	OR* CI (95%)	8–19 Cases/controls	OR* CI (95%)	20+ Cases/controls	OR* CI (95%)
Current smoker	6/35	3.46 (0.99–12.1)	68/100	11.4 (4.51–28.7)	100/59	23.8 (9.35–60.7)
1–4 years	4/18	3.23 (0.72–14.4)	25/38	10.1 (3.64–28.1)	43/32	20.5 (7.55–55.5)
5–14 years	1/20	1.31 (0.14–12.0)	9/39	5.54 (1.76–17.4)	17/45	4.81 (1.66–14.0)
15+ years	3/42	1.38 (0.3–6.21)	8/45	3.65 (1.14–11.7)	9/37	3.43 (1.06–11.1)

*Risk adjusted for age, environment, and lifetime mean daily consumption of alcohol.

Table 10. Alcohol consumption data of controls

Type of beverage	Maximum daily consumption (g/day)	Proportion in relation to total quantity of alcohol consumed (%)
Wine	209	84.46
Beer	65	7.38
Cider	30	0.41
Aperitif	33	3.96
Digestive	36	3.66

[27] showed in their study of the influence of alcohol on non-smokers and the influence of tobacco on non-drinkers. Other mechanisms induced by alcoholic beverages have been reported, such as the composition of carcinogens (*N*-nitrosamines and aromatic hydrocarbons in beer), induction of high doses of nutritional deficiencies, increase of epithelial permeability, decrease of saliva protection and solvent power in relation to carcinogens. As in other Latin countries, wine is the alcohol that is most frequently consumed as it was drunk by all cases and by 97% of the controls who usually consumed alcohol. The risk significantly increased in those who only drank wine in relation to those who drank two or three types of alcoholic beverages. This was also found by Barra *et al.* [28]. The risk is not due to specific consumption of a particular population since after adjustment for socio-occupational category, marital status and dietary habits, the risk remained.

This risk could be linked to consumption habits, such as time, i.e. during or between meals as suggested by Merletti *et al.* [29]. Although the results concerning the different cancer sites are difficult to compare with those of Tuyns *et al.* [13] for the larynx–hypopharynx, they are compatible in relation to the relative impact of tobacco and alcohol. Alcohol had a greater carcinogenous effect on parts of the digestive tract such as the oral cavity, hypopharynx, epilarynx and even the oropharynx, whereas tobacco affected the digestive and airway passages (endolarynx).

The period of time stopped smoking has largely been reported as a protective factor in many studies (Wynder *et al.* [23]; Blot *et al.* [21]; Tuyns *et al.* [13]; Merletti *et al.* [29] and Franceschi *et al.* [22]). However, these studies report a decreasing risk close to that of non-smokers after 5, 10 or 15 years of non-smoking without specifying that this is only possible over these periods of time in casual smokers (less than 7 g/day). Other factors, such as the use of a filter, type of tobacco and cigarette paper, also play a role. The use of a filter reduced the cancer risk by half as already reported by Tuyns *et al.* [13], Wynder *et al.* [23], Elwood *et al.* [25] and Blot *et al.* [21].

The type of tobacco corresponds to the drying method. Black or flue-cured tobacco would produce more carcinogenic tars than blond or air-cured tobacco according to Patrianakos and Hoffmann [30, 31]. As black tobacco contains more *N*-nitrosocompounds and aromatic amines, it is more alkaline. Thus, it is less easy to inhale and remains in contact longer with the larynx mucous whereas blond tobacco is easier to inhale. Our study showed a risk that was more than double, but still not significant, for black tobacco over blond tobacco. As the significantly increased risk associated with hand-rolled cigarettes as opposed to manufactured cigarettes was independent of the filter, it can be explained by the fact that the thin paper is permeable to air, making the dilution of the smoke and the external distribution of certain gases less efficient or by the fact that the tobacco is less compressed increasing the quantity of inhaled smoke. The different smoking practices considerably modify the smoker's exposure to carcinogens. Thus, inhaling the smoke was also a significant risk factor in our study as well as in those of Schwartz *et al.* [32] and Tuyns *et al.* [13]. A smoker who rapidly exhales smoke will hardly contact with the carcinogens. The joint effect of alcohol and tobacco would seem to follow a multiplicative model without interactions. The risk associated with a high consumption of alcohol and tobacco reached exceptionally high values (OR = 199).

The risk increased with socio-occupational category, the lowest education level and non-married status cannot be explained by a dietary biological mechanism alone as Elwood *et al.* [25] suggest because Bontemps *et al.* [12] have confirmed that all these variables, when adjusted with food, remain significant. Thus, they are risk factors in their own right.

Preventive measures can be ascertained directly from these results. As the highest risk is associated with alcohol, the most important measure is to encourage the reduction of regular consumption of alcohol in a country which is the world leader in the consumption of alcohol (15.6 per person per day) and where wine consumption is a normal social and dietary practice.

The distribution of smokers according to age, sex and social category evolves with time, but the proportion of smokers remains constant as is the case with the incidence of head and neck cancer in the Doubs region. The preventive anti-smoking campaigns which encourage smokers to stop smoking and dissuade others from starting have had a limited impact. However, the results observed on smokers' habits confirm the usefulness of these campaigns. It has been shown that even if the risk remains high after having stopped smoking for a period of 15 years of heavy smoking (more than 8 g/day), casual smokers can return to a risk close to 1 after having stopped smoking for a period of 5 years. In addition, the current trend to smoke blond cigarettes with a filter and low tar content could suggest a decrease in head and neck cancer in the years to come.

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Acknowledgements—We would like to thank the two dieticians P. Clivio and C. Despraz who interviewed the subjects, H. Sancho-Garnier, INSERM (Villejuif), A. J. Tuyns and J. Esteve, IARC (Lyon) for their help and advice. This research was carried out with an external INSERM contract No. 858032.