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Pharyngeal cancer prevention: evidence from a case–control study involving 232 consecutive patients

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Abstract

The aim of this study was to determine risk factors for pharyngeal cancer and to propose 10 result-based preventive measures. It was a case-control study conducted in Madrid, Spain, with 232 consecutive patients diagnosed between January 1 1990 and December 31, 1995, sex- and age-matched with 232 control individuals with no oncological disease or history. By means of an interviewer-administered questionnaire, seven different epidemiological areas were surveyed, namely: (1) sociodemographic variables, (2) familial all-site cancer history, (3) medical history, (4) lifestyle (habits), (5) diet, (6) occupational exposure, and (7) non-occupational exposure. Of the great number of factors within each epidemiological area, the following were found to be risk factors after adjustment for tobacco smoking and alcoholic beverage drinking: (1) tobacco smoking, (2) alcoholic beverage drinking, (3) low and low-middle socioeconomic background, (4) low educational level, (5) rural milieu, (6) working, or having worked, as a manual worker in agriculture, (7) working, or having worked as a manual worker in building industry, (8) having an upper aerodigestive tract cancer familial history, (9) having a medical history of alcholism, low weight/malnutrition, gastroesophageal reflux or chronic obstructive bronchopneumonia, (10) low dietary intake of fruit, fruit juice, uncooked vegetables, dietary fibre-containing foods, fish and milk and dairy products, (11) high dietary intake of meat and fried foods, (12) deficient oral and dental hygiene, (13) abuse of black coffee, (14) abuse of 'carajillo' (a typical Spanish drink composed of black coffee and flambéed brandy), (15) occupational exposure to pesticides, solvents and dust of different origins.

On the basis of our results and those reported by other authors, we put forward 10 measures for the prevention of pharyngeal cancer. However, due to the small size of the nasopharyngeal cancer subsample (n = 35, 15.08 per cent), our results as well as the preventive measures are to considered as referring uniquely to oropharyngeal and hypopharyngeal cancers. In addition, from descriptive statistical data inspection one can conclude that nasopharyngeal cancer is likely to bear risk factors different from those for oropharyngeal and hypopharyngeal cancers, thus nasopharyngeal cancer warrants specific epidemiological investigation with a sufficiently large patient sample.

Key words: Pharyngeal Neoplasms; Case-Control Study; Risk Factors; Primary Prevention

Introduction

Both oropharyngeal and hypopharyngeal malignant tumours are in the majority of cases squamous cell carcomas with varying grades of differentiation. Non-Hodgkin lymphomas, sarcomas, cystic adenoid carcinoma, mucoepidermoid carcinoma, and melanomas are much less frequently encountered in these sites. The incidence of squamous cell carcinomas of the oropharynx (OP) and hypopharynx (HP) is increasing in all industrialized countries, increasingly affecting women and younger individuals of both sexes. However, these malignancies mainly affect males in their fifth or sixth decade of life, with a peak incidence consistently reported at the age of 59–60 years. Nonetheless, it is not easy to accurately estimate their true worldwide incidence because descriptive epidemiological studies usually report incidence figures for mouth, OP and HP cancers conjointly. In addition, it is argued whether some anatomical sites (notably the retromolar trigone) should be included in figures for the mouth or OP. In this respect, Parkin *et al.*[1] conducted a study, supported by UICC, on worldwide cancer incidence for the period 1980–1985, reporting an increase in mouth, OP and HP cancer incidence in 1985 in men

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of 4.7 per cent relative to 1980 and of 13.7 per cent in relation to 1975. In women, the authors reported an increase of 15.3 per cent and 26.1 per cent relative to 1980 and 1975, respectively. An increase of 26.1 per cent in 10 years, coupled with a reported lung cancer incidence increase in women of 42.1 per cent in the same period, strongly supports the important role of tobacco smoking and alcoholic beverage abuse in mouth, OP and HP cancer.[2]

Apart from tobacco smoking and alcohol, a low dietary intake of fruit and cooked and uncooked vegetables,[3] and less conclusively of dietary fibre-containing foods,[4] fish[5] and milk and dairy products,[6] have been reported as risk factors for OP and HP cancers. On the contrary, frequent consumption of meat,[7] sausages, cold meat and fried food[8] has been found to be positively associated with OP and HP cancer occurrence, presumbly due to low ratio of polysaturated to saturated fats.[9] However, the latter is a very inconsistent finding for OP cancer and has been reported by several, authors only for HP malignancy, apart from laryngeal cancer. While the protective action of fruit (particularly citrus fruit) and vegetables (especially uncooked vegetables) seems to rely on antioxidant vitamins (i.e. C and E) and other micronutrients (especially carotenoids) that would protect pharyngeal mucosa against aggression by carcinogenic agents contained in tobacco and alcoholic beverages, to date no convincing explanations on a biological basis have been put forward for the protective role of dietary fibre-containing foods, fish, and milk and dairy products. In fact, it has been reported that both epidemiological studies and animal investigation that retinol, which is contained in whole milk, could exert a pro-carcinogenesis effect (especially in upper aerodigestive tract malignancies).[10] In addition, frequent maize consumption has been associated with an increased risk of OP and HP cancers, although this association seems to be confined to people reporting alcoholic beverage abuse.[11]

Occupational exposure to a wide variety of potential carcinogenic agents[12] and upper aerodigestive tract cancer familial history have been reported also as risk factors for OP and HP cancers. While all-site familial cancer history has not been reported to be linked to risk excess, a familial history of upper aerodigestive tract cancer increases the risk one to four folds.[13] Three different hypotheses have been put forward to explain this risk excess: tobacco smoking and alcoholic beverage abuse may give rise to genetic alterations that pass on to the offspring and result in increased susceptibility to carcinogenic agent action, there is a genetically-determined tendency to risk behaviours (i.e. smoking and alcohol abuse), or alternatively, the offspring learn from childhood risk behaviours from their parents and older siblings. Naturally, these three hypotheses are not mutually exclusive. Furthermore, it should be borne in mind that dietary habits are learnt in childhood and stabilized during adolescence, which could also contribute to account for this slight familial aggregation of upper aerodigestive tract cancers.

As far as nasopharyngeal (NP) cancer is concerned, from a histological point of view it is in a majority of cases a squamous cell carcinoma with varying grades of differentiation. Histological classification of NP squamous cell carcinoma used to be confusing and cumbersome, so WHO has proposed a simpler classification as follows: keratinizing, non-keratinizing and undifferentiated carcinoma of nasopharyngeal type (UNCT).[14] Aetiologically, it has been shown conclusively to be linked to Epstein-Barr virus (EBV),[15] although this association varies with the three different types of NP squamous cell carcinoma. However, since EBV has been found to colonize nasopharyngeal and oropharyngeal mucosa chronically, it is reasonable to claim that there is a variety of genetic, environmental and dietary factors that increase the likelihood of EBV activation. Nevertheless, epidemiological investigation on NP cancer risk factors has been handicapped by the extremely low incidence of this malignancy in Europe, and North, Central and South America (below two cases per 100 000 persons/year). However, it is one of the commonest cancers in the People's Republic of China (notably in Hong Kong, where the highest incidence in the world is found), Taiwan, Philippines, Thailand, Singapore, and some Eskimo populations, with a standardized incidence rate ranging from 10 to 30 cases per 100 000 persons/year. North Africa and some Mediterranean populations (e.g. Malta) constitute a middle-risk area (two of 10 cases per 100 000 persons/year), this extremely unequal world incidence being a striking feature of NP cancer.[16]

In high-risk areas, excessive consumption of steam-cooked salted fish[17] (a traditional typical dish in Chinese provinces with the highest risk), exposure to herbs used in Chinese traditional medicine, history of recurrent nose and ear infections, exposure to wood and coal smoke in poorly ventilated houses,[18] occupational exposure to formaldehyde[19] and raw materials for textile and wood industries[20] and tobacco smoking[21] (including second-hand smoking) have been found to be risk factors for NP cancer as well. However, in low-risk areas only formaldehyde exposure and tobacco smoking have been reported as risk factors, although smoking still remains controversial. In high-risk areas, a strong familial aggregation has been found, that suggests a genetic tendency to this malignancy. In fact, HLA antigens indicating the presence of genes susceptible to NP cancer have been encountered in different members of afflicted families.[22] Alternatively, strong familial aggregation can be explained by shared exposure to risk factors of all members of the family, particularly to steam-cooked salted fish. Cooking salted fish in this way releases a large number of volatile nitrosamines that have been found to be carcinogenic in both humans and animals. Air-borne nitrosamine concentration indoors is promoted by poor ventilation, usually

found in houses in low socioeconomic background areas because fuels used to heat the house are expensive. Furthermore, in several provinces in China it is traditional to wean infants with steam-cooked salted fish. Distinctively, NP cancer is the only head and neck squamous cell carcinoma affecting the paediatric population in both high- and low-risk areas. There is some evidence suggesting that exposure from birth to tobacco smoke in the home may play a role in NP cancer causation in children and teenagers.[23]

Despite advances in treatment (surgery, chemotherapy and radiotherapy), five-year survival rates for OP, HP and NP cancers remain poor, ranging from 30 to 40 per cent in a majority of series reported in developed countries. The main reason is the advanced stage of the disease at diagnosis. The best prognosis is for NP cancer, while HP cancer bears the worst outlook, for many HP cancer patients are alcoholic with poor nutritional and general health status. In addition, patients surviving with OP, HP and NP cancers frequently suffer from severe digestive and respiratory deficits. The loss of voice due to laryngectomy and facial disfiguration have the potential to cause psychological disturbances that eventually may result in psychiatric disorders. On the other hand, chemoprevention and screening for early diagnosis would not be cost-effective at all because of the magnitude of the population exposed to risk factors (mainly tobacco smoking and alcoholic beverage drinking). Thereby, it is crucial to understand as accurately as possible risk factors for OP, HP and NP cancers in order to improve primary prevention.

Therefore, we have conducted a case-control study on pharyngeal cancer risk in a health catchment area in the region north of Madrid, Spain, involving 232 consecutive pharyngeal cancer patients, diagnosed between January 1 1990 and 31 December 1995 at La Paz University Hospital, sex- and age-matched with 232 control individuals with no oncological disease or history. Here we report the results of this case-control study and additionally put forward 10 measures for OP and HP prevention. To the best of our knowledge, this is the first case-control study on pharyngeal cancer risk conducted in Spain.

Methods and materials

Setting The present case-control study was conducted in a health catchment area situated in the region north of Madrid, with a population of 584 510 inhabitants. The area is served by La Paz University Hospital as a tertiary medical centre. Between January 1 1990 and December 31, 1995, a total of 987 cases of head and neck cancer were diagnosed at this hospital. Of the 987 cases, 258 (26.1 per cent) were pharyngeal cancers, ranking third following laryngeal (33.5 per cent) and lip and mouth (30.4 per cent) cancers. So, the standardized pharyngeal cancer incidence rate in the quinquennium 1990–1995 in this area was 8.8:1000 person/year. Of the 258 cases of pharyngeal cancer, 144 (55.8 per cent) were OP (standardized incidence rate = 4.9:100 000 persons/year), 78 (30.2 per cent) HP (2.6:100 000 persons/year), and 37 (14.3 per cent) NP cancers (1.2: 100 000 persons/year).

Case sample Two exclusion criteria were used: (1) histological types other than squamous cell carcinoma, (2) lack of data from patients on risk factors, because the patient refused to collaborate in the investigation, or unreliable data due to different causes (e.g. excessively conflicting data between the first and second interviews, see below). As a consequence, 26 patients were excluded from the study, hence the case sample was composed of 232 patients, which represented 89.9 per cent of all consecutive patients diagnosed of pharyngeal cancer at La Paz University Hospital between January 1 1990 and December 31 1995. Of the 232 patients, 120 (51.7 per cent), 78 (33.2 per cent) and 35 (15.08 per cent) had OP, HP and NP cancer, respectively. The OP subsample was composed of 110 males and 10 females, with a male-to-female ratio equal to 12.2:1. In this subsample, the mean age was 59.09 ± 10.13 for males and 48.96 ± 21.02 for females. The HP subsample was composed of 75 males and three females, with a male-to-female ratio equal to 25:1. In this subsample, the mean age for males was 58.24 ± 9.61 and 53.66 ± 1.24 for females. Finally, the NP subsample was composed of 21 males (mean age = 57.28 ± 15.72) and 14 females (mean age = 41.29 ± 22.6), with a male-to-female ratio equal to 1.5:1. Thus, in the case sample there were 206 (88.8 per cent) males (mean age = 59.09 ± 10.3, range = 12–84) and 26 (11.2 per cent) females (mean age = 48.96 ± 21.02, range = 11–86), with a male-to-female ratio equal to 7.9:1. There were four paediatric cases, all of them in the NP subsample (one boy and three girls, mean age = 12.5 ± 3.2, range = 11–15).

Control sample A control sample composed of 232 sex- and age-matched individuals with no current oncological disease or history was obtained by structured random sampling from the 21 136 subjects who attended the Department of Emergency of our medical centre in May 1996. The computerized register provided by the Hospital Management Board was used. First, 300 individuals were selected by means of a random number table. Then, all 300 subjects were sent the data collection questionnaire used for cases by post, accompanied by a covering letter explaining the importance, purposes and aims of the study, once we checked that their postal addresses were within the health catchment area served by our Hospital.

Data collection questionnaire Prior to data collection, we conducted desk research and reviewed all significant literature on pharyngeal cancer risk factors published in the 10 last years. Then, we developed a data collection interview-administered questionnaire, in which all potential risk factors were categorized into seven groups as follows: (1) socio-demographic variables, (2) familial all-site cancer history, (3) medical history, (4) lifestyle (habits), (5) nutrition, (6) occupational exposure, and (7) non-occupational exposure. Before data collection, the

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questionnaire was tested with fictitious voluntary responders with an educational level similar to that expected in the average pharyngeal cancer patient. Maximum questionnaire administration time was 36 minutes per person (average = 31 minutes). All technical terms that proved excessively difficult to be understood were deleted. Finally, the questionnaire was worded in a simple way, and the interviewers were asked to help interviewees with all types of difficulties.

Data collection The cases were all interviewed by two of the authors (A.E. and I.R.) of the present study while routinely attending a surveillance visit at the out-patient department of our Hospital. The importance, purposes and methods of the study were explained to all of them. Our Hospital ethics committee does not require written informed consent for case-control studies. Confidentiality was promised to all cases and controls and complied with. Thus, data from all fulfilled questionnaires was entered anonymously in a computer database, then questionnaires were destroyed. When the patient could not speak because he/she had been laryngectomized, a close relative answered the questions, but the patient was present at all times and confirmed the information by nodding in agreement when necessary. Two months later, the information was checked on the telephone. The discrepancy rate was 24.6 per cent, and was settled on the telephone. Of 300 eligible control subjects who received the questionnaire by post, 202 returned it filled in appropriately (participation rate = 67.3 per cent). We excluded one of them from the study because he had a bladder malignancy. The remaining 31 control individuals were approached on the telephone, with data collection questionnaire filled in by the interviewer according to information provided by the interviewees. Interviewers were the same for cases and controls. Two months later, information from cases was checked on the telephone, that yielded a 21.9 per cent discrepancy rate. Any discrepancies were cleared up on the telephone.

Data statistical analysis A computerized database developed on the software programme File Maker 2.0 was used. The database consisted of 93 variables corresponding to the items in the data collection questionnaire plus nine variables developed from File Maker 2.0 by combining the original variables. The software program SPSS/PC was used for data statistical analysis. The Student *t* test was employed

TABLE I

RISK FACTORS FOR PHARYNGEAL CANCER AFTER ADJUSTMENT FOR TOBACCO SMOKING AND ALCOHOLIC BEVERAGE DRINKING (IN DECREASING ORDER)

Risk factor	OR	95% CI	*p*	Percentage contribution to risk
History of alcholism	12.6	7–22.6	0.000001	9.4
History of low weight/malnutrition	10.2	4.9–21.7	0.000001	7.6
'Carajillo' abuse[1]	7	3.2–11	0.001	5.2
Rural residence[2]	6.9	2.8–17.9	0.0001	5.1
Smoker	6.5	3.5–12	0.00001	4.8
Low socioeonomic background	5.9	2.2–16.2	0.001	4.4
Illiteracy	5.6	3.8–7.7	0.001	4.1
Poor dental and oral hygiene	5.2	3.4–7.8	0.00001	3.8
Ex-drinker	4.9	2.5–9.5	0.00001	3.6
Occupational exposure to pesticides	4.7	1.9–11.4	0.01	3.5
Work in building industry	4.6	2.5–8.8	0.0001	3.4
Deficient dietary intake of fruit and fruit juice[3]	4.4	2–9.4	0.0000001	3.2
Work in agriculture	4.4	2.1–9.4	0.0001	3.2
History of chronic obstructive bronchopneumonia	4.2	3–7.9	0.00001	3.1
Occupational exposure to solvents	4	1.1–14.8	0.01	2.9
Deficient dietary intake of milk and dairy products	3.9	2–5.9	0.000001	2.9
Drinker	3.8	2.4–6.2	0.000001	2.8
Deficient dietary intake of uncooked vegetables	3.8	1.5–9.1	0.0001	2.8
Low-middle socioeconomic background	3.4	1.5–9.1	0.001	2.5
Deficient dietary intake of fibre-containing foods	3.3	1.5–7.1	0.00001	2.4
Low educative level[4]	3.2	2.4–5.6	0.001	2.3
Familial upper aerodigestive tract cancer history	3	1.4–6.6	0.001	2.2
Black coffee abuse	2.8	1.6–5.1	0.01	2.08
Blue-collar worker	2.5	1.5–4.1	0.001	1.8
Ex-smoker	2.4	1.2–4.7	0.01	1.7
Very hot foods and drinks	2	1.3–3.1	0.01	1.5
Deficient dietary intake of fish	1.9	1.3–4.6	0.0001	1.4
Excessive dietary intake of meat	1.7	1–4.7	0.000001	1.2
Excessive dietary intake of fried foods	1.7	1–2.9	0.001	1.2
Occupational exposure to dust of different origins	1.7	1.1–2.6	0.01	1.2
History of gastroesophageal reflux	1.7	1.1–2.4	0.01	1.2

[1] A typical Spanish drink composed of black coffee and flambéed brandy. It is always drunk very hot, most often by building industry blue-collar workers as a supplement for breakfast.
[2] When the subject had lived for longer in rural than urban milieu, 'rural residence' was considered. If the inverse, we considered 'urban residence'. If the subject had lived in both rural and urban residence and the time difference (in years) was not statistically significant, we considered 'mix residence'.
[3] ORs for dietary variables refer to the lowest (when deficient) or the highst (when excessive) intake level.
[4] Individuals who could read and write but had not completed primary school.

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TABLE II
PERCENTAGE CONTRIBUTION TO RISK OF EACH FACTOR CATEGORY

Risk factor category	Percentage contribution to risk
Sociodemographic variables	27.2
Familial cancer history[1]	1.6
Medical antecedents[2]	17.08
Lifestyle (habits)	25.8
Nutrition	15.4
Occupational exposure	7.7
Non-occupational exposure	0

[1]Only familial upper aerodigestive tract cancer history.
[2]Excluding cancer history.

for quantitative variable comparisons, with a five per cent significance level. χ^2 test was used for qualitative variable comparisons. Confidence interval (CI) and odds ratios (ORs) were estimated by the Cornfield method based on the Fisher test. Dose-response relationship was analysed by means of the Mantel method. Finally, adjustment for tobacco smoking and alcoholic beverages drinking was made by the Mantel-Haenzsel method. Adjustment of all risk factors showing statistical significance for tobacco and alcohol drinking was made because these two variables were shown to be the most important ones for predicting pharyngeal cancer occurrence in the preliminary logistic regression model. Percentage contributions to risk was estimated for all risk factors by adding all ORs (total risk), and multiplying each OR per the total risk then dividing into 100 (Tables I & II).

Results

Sociodemographic variables Of the large number of sociodemographic variables addressed the following were shown to be risk factors for pharyngeal cancer after adjustment for tobacco smoking and alcoholic beverage drinking: (1) rural residence (OR = 6.9, 95 per cent CI = 2.8–17.9, $p = 0.0001$); (2) illiteracy (OR = 5.6, 95 per cent CI = 3.8–7.7, $p = 0.001$); (3) low educational level (OR = 3.2, 95 per cent CI = 2.4–5.6, $p = 0.001$); (4) low-middle socioeconomic background (OR = 3.4, 95 per cent CI = 1.7–8.1, $p = 0.001$); (5) low socioeconomic-background (OR = 5.9, 95 per cent CI = 2.2–16.2, $p = 0.001$); (6) blue-collar worker (OR = 2.5, 95 per cent CI = 1.5–4.1, $p = 0.001$); (7) working, or having worked, in building industry (OR = 4.6, 95 per cent CI = 2.5–8.8, $p = 0.0001$); and (8) worked, or having worked, in agriculture (OR = 4.4, 95 per cent CI = 2.1–9.4, $p = 0.0001$). Rural residence means that the individual had lived in a rural area for longer than in an urban milieu. When this difference did not reach statistical significance, we considered it 'mixed residence'. Working, or having worked, in the manufacturing or mining industry approached statistical significance (OR = 1.4, 95 per cent CI = 0.9–1.3, p = NS).

Familial all-site cancer history Familial all-site cancer history was found not to be a risk factor after adjusting for tobacco smoking and alcoholic beverage drinking; however, familial upper aerodigestive tract cancer history was (OR = 3, 95 per cent CI = 1.4–6.6, $p = 0.001$). We asked about father, mother, sisters, brothers and 'other relatives (please, specify)'. The father was the most frequently affected relative, in both all-site and upper aerodigestive cancer history (statistically significant difference, $p < 0.005$).

Medical history The following were risk factors once adjusted for tobacco smoking and alcoholic beverage: (1) history of low weight/malnutrition (OR = 10.2, 95 per cent CI = 4.9–21.7, $p = 0.000001$); (2) history of alcoholism (OR = 12.6, 95 per cent CI = 7–22.6, $p = 0.000001$); (3) history of chronic obstructive bronchopneumonia (OR = 4.2, 95 per cent CI = 3–7.9, $p = 0.0001$); and (4) history of gastroesophageal reflux (OR = 1.7, 95 per cent CI = 1.1–2.4, $p = 0.01$). Low weight/malnutrition referred to at least one year before pharyngeal cancer diagnosis. Cases and controls were not asked about oncological history, except to ascertain lack of current neoplastic disease or history for the controls.

Lifestyle (habits) (1) smoker (OR = 6.5, 95 per cent CI = 3.5–12, $p = 0.00001$); (2) ex-smoker (OR = 2.4, 95 per cent CI = 1.2–4.7, $p = 0.01$; (3) having started smoking under 15 years of age (OR = 2.3, 95 per cent CI = 1.9–18.6, $p = 0.00001$); (4) having started smoking between 15 and 20 years of age (OR = 4.5, 95 per cent CI = 2.5–8.3, $p = 0.000001$); (5) drinker (OR = 3.8, 95 per cent CI = 2.4–6.2, $p = 0.000001$); (6) ex-drinker (OR = 4.9, 95 per cent CI = 2.5–9.5, $p = 0.00001$); (7) having started drinking under 15 years of age (OR = 2.6, 95 per cent CI = 1.7–16.5, $p = 0.000001$); (8) black coffee abuse (OR = 2.81, 95 per cent CI = 1.6–5.1, $p = 0.01$); (9) 'carajillo' abuse (OR = 7, 95 per cent CI OR = 3.2–11, $p = 0.001$); (10) poor dental and oral hygiene (OR = 5.2 per cent CI = 3.4–7.8, $p = 0.00001$); and (11) usually eating and drinking very hot food and drinks (OR = 2, 95 per cent CI = 1.3–3.1, $p = 0.01$). Second-hand smoking proved not to be a risk factor. Black tobacco (particularly filterless cigarettes) was shown to be more dangerous than Virginia tobacco. Patients had started smoking as a mean at the age of 16.08 years and controls at 17.6 years (non-significant difference). Patients had smoked for 40 years and controls 28.6 (significant difference, $p<0.005$). Patients smoked a mean of 35 cigarettes a day and controls 18.8 (significant difference, $p<0.005$). Patients had started drinking as a mean at the age of 18.7 years and controls at 18.8 (non-significant difference $p>0.005$). Patients had drunk for 36 years and controls 24.2 (significant difference, $p<0.005$). Finally, patients used to drink a mean of 132 g/day of pure ethanol and controls 58.8 (significant difference, $p<0.005$). Variables other than tobacco smoking and alcohol drinking were adjusted for tobacco and drinking. Carajillo' is a typical Spanish drink composed of black coffee and flambéed brandy that is always drunk very hot.

Nutrition Deficient intake of: (1) fruit and juice (OR = 4.4, 95 per cent CI = 2.0–9.4, $p = 0.0000001$); (2) uncooked vegetables (OR = 3.8, 95 per cent CI = 1.5–9.1, $p = 0.0001$); (3) fish (OR = 1.96, 95 per cent CI = 1.3–4.6, $p = 0.0001$) and; (4) milk and dairy

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TABLE III
LOGISTIC REGRESSION RESULTS (I)

	χ^2	p
–2 Log ML	408.959	0.9999
χ^2	232.893	0.0000
Prediction	7.979	0.0047
Fitting goodness	445.645	

products (OR = 3.9, 95 per cent CI = 2–5.9, $p = 0.000001$); and (5) dietary fibre containing-foods (OR = 3.3, 95 per cent CI = 1.5–7.1, $p = 0.00001$); and excessive intake of: (1) meat (OR = 1.7, 95 per cent CI = 1.0–4.7, $p = 0.000001$); and fried foods (OR = 1.7, 95 per cent CI = 1.0–2.9, $p = 0.001$) were all risk factors when data was adjusted for tobacco smoking and alcohol drinking. Five different levels of intake were considered: high intake (five to seven days a week), frequent intake (three to four days a week), low intake (one to two days a week), very low intake (one to three days a month), and no intake (never). ORs for highest or lowest intake level are reported here (Table I).

Occupational exposure Of the large number of potential carcinogenic agents at workplace, only the following were shown to be an independent risk factor once adjusted for tobacco smoking and alcoholic beverage drinking: (1) solvents (OR = 4, 95 per cent CI = 1.1–14.8, $p = 0.01$; (2) pesticides (OR = 4.7; 95 per cent CI = 1.1–14.8, $p = 0.01$); and (3) dust of different origins (OR = 1.7, 95 per cent CI = 1.1–2.6, $p = 0.01$).

Non-occupational exposure None of the non-occupational factors under study were shown to be a risk factor after adjustment for tobacco smoking and alcoholic beverage drinking. We surveyed exposure to tobacco smoke at home or the workplace, exposure to air-borne pollutants in big or industrialized cities, iatrogenic exposure to radiation (including at dentist's), exposure to smoke from coal/wood/petrol/gas cookers or stoves in the home and poor ventilation of the house/flat/apartment.

Table I shows all risk factors found after adjustment for tobacco smoking and alcoholic beverage drinking, and their corresponding OR, 95 per cent CI, p, and percentage contribution to risk.

Logistic regression (Tables III and IV) Logistic regression showed that the definitive model was composed of six variables: (1) tobacco smoking (OR = 2.47), (2) alcoholic beverage drinking (OR = 2.29), (3) low intake of dietary fibre-containing foods (OR = 1.42), (4) low intake of fruit and juice (OR = 0.41), (5) Oral and dental hygiene (OR = 0.38), and (6) low intake of fish (OR = 0.23) (Tables II and III). With this model, the percentages of misclassified were as flow as 23 per cent and 17 per cent for cases and controls, respectively.

Discussion

Sociodemographic variables Sociodemographic variables in our study proving to be risk factors, after adjustment for tobacco and alcoholic beverage drinking, are likely to be associated with each other. Thus, belonging to low/middle-low socioeconomic background is worldwide strongly associated with illiteracy and low educational level, which in turn are associated with being a blue-collar worker. In Spain, most blue-collar workers who are illiterate or have a low educational level work in the building industry or agriculture. Although several authors have reported that differences in mortality between socioeconomic classes in industrialized countries are closely related to the higher prevalence of tobacco smoking and alcohol abuse in low socioeconomic background,[24] we cannot accept this explanation for our findings, since data were adjusted for tobacco smoking and alcoholic beverage drinking. However, they were not adjusted for alcoholism (46.5 per cent in the case sample *vs* 6.4 per cent in the control sample), inadequate dietary habits, poor oral and dental hygiene, 'carajillo' abuse, and occupational exposure to solvents, pesticides and dust of different origins, all these factors being more prevalent in low socioeconomic classes in Spain.

Familial all-site cancer history Our results show that familial all-site cancer history is not a risk factor for pharyngeal cancer. However, when familial upper aerodigestive tract cancer history was considered, the risk tripled. This finding is consistent with those reported by several authors.[13] Yet, the reason remains unclear. It is likely that parents and older siblings had hazardous behaviours (notably tobacco smoking and alcohol abuse), which were learnt by modelling, or smoking and alcohol abuse caused genetic alterations that were passed on to the next generation as more pronounced susceptibility to these risk factors action or to pharyngeal and other tobacco- and alcohol-related head and neck cancers.[25] Finally, the hypothesis that there is a genetic tendency that makes individuals engage in hazardous habits (i.e. smoking and drinking), should be taken

TABLE IV
LOGISTIC REGRESSION RESULTS (II)

Variables	β	ES	p	OR
Tobacco smoking	0.9068	0.3303	0.0060	2.47
Alcohol drinking	0.8309	0.2965	0.0051	2.29
Dietary fibre-containing foods	0.3557	0.0950	0.0002	1.42
Fruit and juice[1]	–0.8911	0.1195	0.0000	0.41
Oral and dental hygiene	–0.9508	0.2531	0.0002	0.38
Fish	–1.4364	0.2731	0.0000	0.23
Constant	2.4347	0.5046	0.0000	

[1]Low dietary intake.

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into account, like that reported for addictions. Of course, these hypotheses are not mutually exclusive. On the other hand, it should be kept in mind that dietary habits (e.g. poor consumption of fruit and vegetables) are learnt mostly during childhood and adolescence, and these detrimental habits are to be suspected in parents with upper aerodigestive tract cancer. In our opinion, this latter hypothesis has been underrated until now in epidemiological studies on cancer risk.

Medical history All risk factors found in the present case-control study have been previously reported in the epidemiological literature,[26,27] except for chronic obstructive bronchopneumonia, for which we do not have a convincing explanation. Of note, we have found a percentage of alcoholics in our case sample as high as 46.5 per cent (especially in the subsample of HP cancer patients), relative to 6.4 per cent in the control sample, which again confirms the outstanding importance of alcoholism for head and neck cancer, in general, and for OP and HP cancers, in particular.

Lifestyle (habits) On the basis of our results from logistic regression, we can state that tobacco smoking and alcoholic beverage drinking were by far the two most important risk factors for pharyngeal cancer. This finding is consistent with most authors. Even though the difference in the age at which cases and controls had started smoking or drinking was not statistically significant, the number of cigarettes a day (35 *vs*. 18.8), the total number of years they had smoked for (40 *vs*. 28.6), grams of pure ethanol a day (132 *vs*. 58.8), and total number of years they had drunk for (36 *vs*. 242.) were all statistically significant ($p<0.005$). Interestingly, patients had smoked a mean of 511 000 cigarettes per person relative to 196 570 in the control sample, with an impressive difference of 314 430 cigarettes/person. Poor oral and dental hygiene proved to be risk factors as well, again in keeping with most authors.[28] 'Carajillo' (a typical Spanish drink composed of black coffee and flambéed brandy that is always drunk very hot) abuse was also a risk factor in our study. This drink is mostly consumed by building industry workers as a supplement to breakfast. Eating and drinking very hot foods and drinks was also a risk factor, and several authors have reported risk excess for pharyngeal and mouth cancer for people drinking 'mate' (*Illex paraguayensis*), a very hot herb infusion, in Argentina, Uruguay and Brazil. However, we do not have a convincing explanation for the finding that black coffee (but not white coffee) abuse is a risk factor for pharyngeal cancer, except that people consuming black coffee tend to drink it hotter than people consuming white coffee, or black coffee consumption is more prevalent among blue-collar workers and people from lower educational and socioeconomic background. On the other hand, it is striking that 'ex-drinker' bears a higher risk than 'drinker', according to our results. Tentatively, one can presume that the ex-drinker patient subgroup contained those who had drunk most heavily and a majority of alcoholics; therefore, it being the subgroup with a considerable number of individuals who had had to stop drinking due to severe medical diseases and psychopathological disorders.

Nutrition Like other authors,[29] we found that deficient consumption of fruit, fruit juice, uncooked vegetables, fish, fibre-containing foods, and milk and dairy products is inversely related to pharyngeal cancer. Although protective micronutrients contained in fruit or/and vegetables are not well understood, candidates are: carotenoids (especially α- and β-carotene), vitamins C and E (i.e. antioxidant vitamins), selenium, dietary fibre, dithiolthiones, glucosinolates, indoles, isothiocyanates, thiocyanates, flavonoids, phenols, protease inhibitors, plant serols, allium compounds, and limonene. Of note, many of these micronutrients have been found to exert an anticarcinogenic action, whether inhibitory or blocking in nature, in different studies on chemoprevention of upper aerodigestive tract cancer.[30] Vegetables are known to lose their content of vitamin C, carotenoids and other potentially protective micronutrients when cooked, hence several epidemiological studies have reported a stronger protective effect of uncooked relative to cooked vegetables. On the contrary, there is not a convincing explanation as yet for the protective role played in pharyngeal cancer by fish, fibre-containing foods and milk and dairy products. However, there is certain evidence pointing to the fact that the protective effect of fish might rely on polyunsaturated fatty acids, which are needed for skin integrity maintenance and injured tissue regeneration, however, epidemiological data for the relationship between fish and pharyngeal cancer is conflicting, with some authors finding a neutral and others a positive or negative relationship.[31] Likewise, there is evidence for a protective role of vegetable oils (notably, olive oil) in epithelial cancers due to their content of polyunsaturated fatty acids. Of note, some case-control studies have reported a risk excess for oral and pharyngeal cancer for individuals frequently consuming maize, but the risk excess seems to be confined to subjects abusing alcoholic beverages.[11] Nevertheless, in our study, dietary fibre-containing foods were shown to have have protective factor. Within this category, we consider legumes and cereals (other than wheat bread); and it should be taken into account that in Spain most fibre comes from wheat foods and legumes, because cornflake-like cereals (from maize) are mostly consumed by children and adolescents for breakfast rather than by adults. On the other hand, Franceschi[32] *et al*. in Italy have found a positive association between cheese consumption and pharyngeal cancer. In addition, the role of retinol (contained in non-skimmed milk) remains unclear, with some studies reporting that it may enhance carcinogenesis, especially in the oral cavity, pharynx, larynx, oesophagus, stomach, colon and rectal cancers because of a potential carcinogenic reaction due to an ethanol and retinal interaction.[12] Our results show that consumption of meat and fried foods is positively related to pharyngeal cancer, again in keeping with most

authors.[33] This risk excess is thought to be due to the low ratio of polyunsaturated to saturated fats, but the biological mechanisms remain obscure.

Occupational exposure The picture of occupational risk factors for neck and head cancers, in general, and for pharyngeal cancer, in particular, is quite muddling.[14] We have surveyed a large number of potentially carcinogenic factors at the workplace and have found evidence of a risk excess only for solvents, pesticides, and dust of different origins, after adjustment for tobacco smoking and alcoholic beverage drinking. The finding for pesticides is consistent with the risk excess encountered for working, or having worked, in agriculture, and dust may be related to working, or having worked, in the building industry. However, we have found no risk excess for working, or having worked, in the manufacture or mining industry, although this factor approached statistical significance.

Conclusions

In summary, our results show that unavoidable risk factor (i.e. sociodemographic variables and familial upper aerodigestive tract cancer history) percentage contribution is all together only 28.8 per cent relative to a percentage attributable to avoidable risk factors of approximately 71.2 per cent (Table II). If one considers sociodemographic variables redundant with personal medical antecedents, lifestyle (habits), nutrition and occupational exposure to potential carcinogenic agents, risk attributable to avoidable causes increases up to approximately 98.4 per cent. Furthermore, if one looks at our logistic regression model (Tables III and IV), it is observed that contribution to risk of unavoidable factors is null. Therefore, we conclude that pharyngeal cancer is basically a preventable disease, at least as far as OP and HP cancers are concerned.

On the basis of our results and those reported by other authors, we conclude that the 10 following preventive measures would be of value in preventing OP and HP cancers:

(1) Quit tobacco smoking as soon as possible. Do not start smoking.
(2) Reduce alcoholic beverage drinking to the level considered as being healthy from a cardiovascular point of view (i.e. one glass of wine or beer for lunch and another glass for dinner).
(3) Eat as much as possible of fruit, cooked vegetables, legumes, and fish. Drink as much as possible of natural (with no added sugar, fizz or other additives) fruit juice.
(4) Eat as little as possible of meat (in particular fatty meats, such as lamb and pork) and fried food (especially if fried in animal fat or reheated vegetable oil). Use vegetable oil rather than animal fat. Do not reuse or reheat oil.
(5) Avoid sausages, cold meat, and salted, smoked, pickled, and canned foods. Eat as little as possible of processed foods (packed foods). Choose natural food as opposed to processed food.
(6) Never eat or drink excessively hot foods or drinks.
(7) Maintain a good daily dental and oral hygiene and visit the dentist on a regular basis, even if you do not have any particular complaints.
(8) At workplace, protect yourself (e.g. by using a protective mask) if exposed to pesticides, solvents and/or dust of different origins. Protect yourself against these items at home as well with a mask and by providing adequate ventilation.
(9) Seek prompt medical aid if you suffer from gastroeosphageal reflux, chronic obstructive bronchopneumonia or low weight/malnutrition. Keep yourself as close as possible to your ideal weight. Have a regular medical checkup for potential deficiency of some essential micronutrients.
(10) Seek prompt medical and/or psychological aid if you suffer from alcoholism or compulsive alcoholic beverage drinking.

Medically prescribed and controlled multivitamin/multimineral supplements with a sufficient content of C and E vitamins should be considered for those patients for whom all attempts made to change their toxic and dietary habits have been unsuccessful. Also, the possibility of adding essential fatty acids and selenium should be considered.

Unfortunately, our subsample of NP cancer patients was too small (15.08 per cent of the case sample) to draw reliable conclusions about risk factors for, and prevention of, this malignancy. In addition, when merely looking at descriptive statistical data from NP cancer patients, one can conclude that risk factors for NP cancer considerably differ from those for OP and HP cancers. Consequently, the above 10 preventive measures should be considered as referring uniquely to OP and HP cancers. Since NP cancer incidence is very low in Spain and other western countries (1.2:100 000 /yr in our health catchment area in the quinquennium 1990–1995), it is necessary for specific multicentre collaborative investigation to disclose its risk factors.

In spite of our results, frequent consumption of milk and dairy products should not be recommended until the ambiguous role of retinol in human carcinogenesis is cleared up. Also, physicians should refrain from encouraging frequent dietary cereal intake until the effect of maize on cancers of the upper aerodigestive tract has been elucidated, especially in people suffering from alcoholism (46.5 per cent in our case sample) or reporting alcoholic beverage abuse.

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