Pergamon

Oral Oncol, Eur J Cancer, Vol. 31B, No. 3, pp. 181–187, 1995

0964–1955/95 $9.50 + 0.00

0964–1955(95)00005–4

Alcohol, Tobacco, Diet and the Risk of Oral Cancer: a Pooled Analysis of Three Case–Control Studies

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This combined analysis of data from three large case–control studies of oral cancer confirms the important effect of tobacco in the aetiology of the disease. The studies have been conducted in the United States, Italy and China and results for risks associated with tobacco smoking were generally consistent across centres, while those for alcohol were not; increased risks amongst alcohol drinkers were evident in two centres but not in the study conducted in Turin, Italy. In addition, the combined analysis had large enough numbers to analyse the risk of tobacco consumption in non-drinkers. In females these showed increased risks while in males the effect of tobacco alone was weaker. Given the popularity of tobacco smoking, and its consequent high attributable risk in terms of oral cancer it is reassuring, in terms of public health, that cessation will result in a substantial reduction in risk; a 30% reduction in risk for those stopping smoking between 1 and 9 years, and a 50% reduction for those stopping more than 9 years. Although encouraging smokers to stop should be the principal aim, decreases in risk for everyone could be achieved by encouraging high fruit and vegetable consumption.

Keywords: oral cancer, alcohol, tobacco, diet

Oral Oncol, Eur J Cancer, Vol. 31B, No. 3, pp. 181–187, 1995.

INTRODUCTION

ALCOHOL AND tobacco are the two most important known risk factors for the development of oral cancer, while aspects of diet, although thought to play a lesser role in the aetiology of the disease, have consistently been found to confer a protective effect [1]. Cohort studies of subjects with high alcohol consumption consistently find an excess of oral cancers over that expected [2–5], while alcohol abstainers such as Seventh Day Adventists and Mormons have a decreased risk [6, 7]. However, the lack of additional relevant information in these studies (such as tobacco consumption) prevents an assessment of the contribution to the risk of disease of each factor. Case–control studies generally report increased risks in alcohol drinkers compared to non-drinkers [8] and tobacco smokers compared to non-smokers even after adjustment for the other factor. Almost all such studies in addition report a dose–risk relation for alcohol and/or tobacco [9–12]: increasing consumption leading to increasing risk. The combined effects of the three factors (alcohol/tobacco/diet) has, however, been more difficult to assess. Individual studies frequently have too few subjects. We have, therefore, analysed data available from three recent case–control studies of oral cancer, all of which have had an assessment of total dietary intake. This combination of studies, from the United States, Italy and China has resulted in a greater number of subjects with which to analyse the separate and joint effects of alcohol, tobacco and diet.

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Received 25 Oct. 1994; provisionally accepted 4 Dec. 1994; revised manuscript received 5 Jan. 1995.

MATERIALS AND METHODS

The current analysis incorporates data from three case–control studies conducted in the United States (Western New York), China (Beijing) and Italy (Turin). The study designs have already been described in detail elsewhere. The first study, conducted in Beijing [13] included 404 incident histologically confirmed oral cancer patients (ICD-9 codes

141, 143–145) [14] admitted to one of seven participating hospitals in the city between May 1988 and December 1989. Controls were age and sex matched (1:1 ratio) and were randomly selected from patients attending hospital as a result of minor surgery, ophthalmic and ear conditions, lower back pain, urinary tract infection, etc. They were restricted to patients whose current hospital admission was for a condition diagnosed within 1 year of interview.

The second study [15] was conducted using 309 pathologically confirmed cases identified between 1975 and 1983 in hospitals of Western New York, and 290 controls matched by sex, age and neighbourhood. Eligible cases were those with tumours diagnosed to ICD-9 [14] codes 140–149 (oral cavity), but excluding ICD-9 140 (lip), ICD-9 142 (salivary glands) and ICD-9 147 (nasopharynx).

The final study was a population-based case–control study of histologically confirmed incident cases occurring in residents of the city of Turin between July 1982 and December 1984 [16]. Cancers of the following sites were included: mucosa of the lip (ICD-9 140.3, 140.4, 140.5); tongue (ICD-9 141); gum (ICD-9 143); floor of mouth (ICD-9 144); other and unspecified parts of the mouth (ICD-9 145) and oropharynx (ICD-9 146). There were 122 cases enrolled in the study while controls were a random sample stratified by sex and age from the files of residents of the city of Turin; 606 were interviewed between 1980 and 1984.

Considering all centres together, the total number of subjects analysed was 835 cases and 1300 controls. Information was collected in each of the three studies by means of an interviewer-administered questionnaire and included items on tobacco and alcohol consumption history, education, dietary intake and occupation.

Data analysis

A copy of the original data set for each study was received and these were used to create one data set incorporating all relevant variables that were common to each centre. This included age, sex, study centre, educational level; lifetime cigarette-equivalent tobacco consumption, age at start, number of years and type of tobacco consumption; lifetime alcohol consumption (kg), age at start, number of years and type of alcohol consumption. Each of the three case–control studies involved the administration of a food frequency questionnaire, from which the daily intake of macro- and micronutrients has been estimated. For the purposes of the combined analysis the variables relating to daily intake of total calories, individual macronutrients (fat, protein and carbohydrate) and markers of fruit and vegetable intake (vitamin C and fibre) were abstracted from each study and combined into the common file.

Classical methods of case–control study data analysis [17] were performed using the SEARCH statistical package [18], while unconditional multiple logistic regression analysis was performed using the Generalised Linear Interactive Modelling (GLIM) package [19] to obtain maximum likelihood estimates from models. The adequacy of model fitting was assessed using a suite of programs [20] including the methods proposed by Hosmer and Lemeshow [21]. The analyses have been conducted generally dividing the variables of interest into thirds or quarters; such classifications have been based on the distribution of the variable of interest in cases and controls combined and over all centres [22].

When considering dietary variables, particular care is necessary when analysing the possible relationship between macro- and micronutrient intake and disease. If the level of total caloric intake was, for example, found to be negatively correlated with risk of disease, i.e. higher energy intake levels being associated with lower levels of disease, then even with macro- or micronutrients not associated with disease, on analysis they too could appear to be negatively related to disease solely by their association with energy intake. Persons with high (or low) energy intake will naturally have high (or low) consumption of many of its constituents. It is, therefore, important to take account of total caloric intake when examining the effects of such macro- and micronutrients. Several methods to achieve this have been proposed [23]. The technique employed in this analysis is the "energy adjusted" method, where instead of considering the actual intake of each nutrient, the measure considered is the "nutrient residual", calculated by the regression of total caloric intake with the nutrient of interest, and has been performed separately for each centre. The nutrient residual is then the difference between the actual intake of the nutrient and that "expected" on the basis of total caloric intake. This nutrient measure is therefore, theoretically, independent of total caloric intake. The nutrients thereafter were categorised into quarters: quartiles 1 and 2 may be considered as generally including those subjects with lower intake of a nutrient than would be expected on the basis of caloric intake (with quartile 1 the lowest intake), and quartiles 3 and 4 represent higher than expected intake of the nutrient of interest (with quartile 4 the highest intake).

RESULTS

The distribution of subjects by study centre, sex and age is presented in Table 1, the distribution of alcohol consumption and level of tobacco smoking in Table 2.

Analysis of the effects of tobacco smoking and alcohol consumption was performed for males and females separately and included terms for centre, age group, education level and a centre/education interaction. In addition the effect of level of lifetime alcohol consumption (but not tobacco smoked) was found to differ between centre, and the fit of the model was significantly improved by the inclusion of a centre/alcohol interaction term. Levels of tobacco smoking and alcohol drinking were categorised into non-consumers and consumers, with consumers being split into two groups, those below and above the median consumption level (considering cases and controls in all centres). The median consumption levels were determined separately for males and females.

The risk associated with levels of tobacco smoking in males over all centres was (relative to non-smokers), 1.7 (95% C.I. (1.2, 2.5)) for those smokers having smoked 33 pack years or less and 3.8 (95% C.I. (2.5, 5.8)) for those having smoked more than 33 pack years. In females the risk relative to non-smokers was 2.7 (95% C.I. (1.6, 4.7)) for those having smoked 18 pack years or less and 6.2 (95% C.I. (3.4, 11.2)) for those having smoked more than this. In addition to the intake of alcohol being strikingly different in each of the study populations (Table 2) there was a significant difference in effect of alcohol at given consumption levels in each of the studies. The median lifetime consumption level of alcohol in males over all populations was 558 kg. In Beijing (relative to never-drinkers), the risk for male alcohol drinkers below this level

Table 1. Distribution of subjects according to study centre, sex and age

	Study centre							
	Beijing		New York		Turin		Total	
	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls
Sex								
Males	248	248	215	201	86	385	549	834
Females	156	156	94	89	36	221	286	466
Age group								
<55	158	166	72	68	36	249	266	483
55–64	153	137	126	116	47	167	326	420
65–74	83	85	85	80	27	112	195	277
>74	10	16	26	26	12	78	48	120

Table 2. Intake of alcohol and tobacco in study populations

		Quartiles of intake					
		25 pc		50 pc		75 pc	
		Cases	Controls	Cases	Controls	Cases	Controls
Males							
Alcohol	Beijing	0	0	162	12	806	398
(lifetime kg)	New York	283	42	701	189	1387	551
	Turin	598	326	1006	616	1599	1007
Pack years	Beijing	2.5	0	20	8	34.5	24
(cig. equiv)	New York	28	6	46	29	58	51
	Turin	29	3	43	24	57	48
Females							
Alcohol	Beijing	0	0	0	0	0	0
(lifetime kg)	New York	8	1	83	25	368	93
	Turin	206	41	473	175	768	380
Pack years	Beijing	0	0	0	0	11	0
(cig. equiv)	New York	2	0	30	1	50	26
	Turin	0	0	6.5	0	22	6

was 1.3 (not-significant (n.s.)) and above, 1.5 (n.s.); in New York the respective risks were 3.1 (n.s.) and 13.1 (significant (sig.)), and in Turin 0.2 (sig.) and 0.6 (n.s.).

Sufficient subjects were available to allow an analysis of the effects of tobacco on sub-sites within the oral cavity (Table 3). Subjects were categorised according to the same methods used for the overall analysis. For both males and females, tobacco smoking confers the highest risk for cancer of the floor of the mouth, indeed for males the risk could not be calculated since there were no cases of cancer of the floor of the mouth who were not current or previous smokers. Risks in both sexes were next highest with cancers coded to site ICD-9 145 "other and unspecified parts of the mouth" (which includes, e.g. cheek, hard and soft palate), and thereafter tongue cancer. Cancer of the gum was significantly associated with tobacco smoking only in women, and only for those smoking more than 18 pack years.

The effect of tobacco was also considered specifically in non-drinkers. The number of female cases (153) included in the analysis exceeds the number of males (88), and the results are presented separately by sex. Amongst persons who had never consumed alcohol the risks increased with increasing consumption of tobacco although the risks found were higher for females amongst whom the increases were significant (Table 4). In addition, the change in risk associated with cessation of smoking was considered; this analysis was performed amongst persons who had ever smoked and the reference category considered as those who continued to smoke, while adjusting for age, sex, centre, education, level of alcohol consumption, previous level of tobacco consumption and including interaction terms for centre/education and centre/alcohol consumption. Persons having stopped for less than 1 year were included in a separate category since it may be hypothesised that for these persons stopping smoking could be associated with their disease, while the remainder of the subjects were divided into those having stopped between 1 and 9 years, and greater than 9 years. For those having stopped for less than 1 year prior to diagnosis there was no change in risk compared with continuing smokers, 1.2 (95% C.I. (0.7, 1.8)). Thereafter the risk of oral cancer decreased with an increase in

Table 3. Tobacco smoking and risk of cancer of oral cavity sub-sites

Site (ICD-9 code)	No. cases	Non-smokers	≤33 py	>33 py
Males				
141 Tongue	118	1.0	1.6 (0.9, 2.8)	2.9 (1.5, 5.6)
143 Gum	83	1.0	1.5 (0.8, 2.7)	1.7 (0.8, 3.8)
144 Floor of mouth	67	—	—	—
145 Other/Unsp. mouth	106	1.0	1.6 (0.8, 2.9)	3.1 (1.5, 6.3)
	No. cases	Non-smokers	≤18 py	>18 py
Females				
141 Tongue	78	1.0	2.5 (1.1, 5.3)	4.9 (2.1, 11.4)
143 Gum	40	1.0	0.5 (0.1, 2.3)	3.8 (1.0, 14.0)
144 Floor of mouth	16	1.0	8.4 (1.6, 44.7)	14.2 (2.4, 84.3)
145 Other/Unsp. mouth	82	1.0	3.6 (1.6, 8.2)	7.5 (3.2, 18.1)

Results from multiple logistic regression model with terms: age, centre, education, tobacco consumption, alcohol consumption, alcohol/centre interaction.
No estimates could be made for the risk of floor of the mouth cancer in males since there were no cases of such cancer who were non-smokers.

Table 4. Risk of oral cancer associated with tobacco in non-drinkers

Tobacco consumption (non-drinkers)	OR	95% C.I.
Males		
Non-smokers (reference)	1.0	
1–33 pack years	1.1	(0.6, 2.2)
>33 pack years	1.3	(0.6, 3.1)
Females		
Non-smokers (reference)	1.0	
1–18 pack years	2.6	(1.2, 5.6)
>18 pack years	4.6	(1.9, 10.9)

the time a person had stopped smoking such that those who had stopped between 1 and 9 years had a risk of 0.7, (95% C.I. (0.5, 1.1)) and those stopping for more than 9 years had a risk half that of current smokers: 0.5, (95% C.I. (0.3, 0.7)).

There is a wide variation in caloric intake between study populations; subjects in China reported a caloric intake almost double that of those in the New York study, with Italy occupying an intermediate position (Table 5). This large difference is partly due to differences in carbohydrate intake which is particularly high in the Chinese population; smaller differences exist for protein intake, while there is little difference in absolute fat intake (but a large difference in fat as a percentage of calories) between the Chinese and American study. Such large differences in caloric intake make the interpretation of the absolute intake of micronutrients difficult. However, the high intake of vitamin C in the Chinese and American study populations relative to that in Italy is of note. Table 6 presents the results from analysis in individual centres, of the effects of caloric intake, macro- and micronutrient intake on oral cancer risk.

There is no consistent effect on oral cancer risk across the three studies with level of caloric intake or with intake of the macronutrients fat, protein or carbohydrates (after controlling for total calories). Consistent results are, however, reported for vitamin C and fibre intake: high consumption leading to low risk, with an inverse dose–risk relationship evident. In all centres the risk of disease for those in the highest relative consumption category of vitamin C or fibre (using the "nutrient residual" method) is approximately half or less than for those subjects in the lowest relative consumption category.

Given the homogeneity of results for vitamin C and fibre intake, the results have been combined over all centres to give a combined estimate of the changes in risk associated with high relative consumption levels. Controlling for smoking, alcohol, centre, sex, age, total calories, and including interaction terms for centre/education and centre/alcohol consumption, the risk relative to the lowest consumption of vitamin C was 0.94 (95% (0.67, 1.31)) in quartile 2, 0.76 (95% C.I. (0.50, 1.15)) in quartile 3, and 0.49 (95% C.I. (0.28, 0.83)) in the highest quartile. Although this simple model was adequate to obtain a good fit to the data for vitamin C intake, the analysis involving fibre necessitated the addition of interaction terms between fibre and centre, sex and tobacco consumption before a good fit was obtained. The subsequent decreases in risk with increasing fibre intake were very similar to those obtained for vitamin C. When both terms are entered in the same logistic regression model, decreased risks with increasing consumption are still found for both factors indicating that they have effects independent of each other in spite of having many dietary sources in common.

It is of particular interest whether the protective effect of dietary factors is consistent in non-smokers, light and heavy smokers. For this purpose, data have been combined from all centres relating to lifetime alcohol consumption, lifetime tobacco smoking and average daily relative vitamin C consumption. Alcohol and tobacco consumption have been categorised into non-consumers, light and heavy consumers (the cut-off point being the median intake) while relative vitamin C consumption has been categorised as low, average and high (in tertiles). The effects of centre, age, education and total energy intake were controlled for in the analysis. The results are shown in Table 7 where, although the interaction term was not significant, it is seen that the protective effects of vitamin C tended to be stronger amongst those in the highest smoking category.

DISCUSSION

There is a substantial amount of evidence associating the habits of tobacco smoking and alcohol drinking with cancers of

Table 5. Intake of calories, macro- and micronutrients in study populations

		Quartiles of intake					
		25 pc		50 pc		75 pc	
		Cases	Controls	Cases	Controls	Cases	Controls
Calories (kcal)	Beijing	2927	2832	3599	3523	4275	4304
	New York	1514	1382	1922	1759	2484	2405
	Turin	2133	2070	2612	2490	3225	3061
Fat (g)	Beijing	60	64	78	80	102	106
	New York	61	51	79	71	105	92
	Turin	75	79	97	98	110	117
Carbohydrate (g)	Beijing	494	460	616	604	738	725
	New York	174	158	224	227	298	290
	Turin	211	204	257	265	332	324
Protein (g)	Beijing	88	91	110	109	132	135
	New York	60	58	80	75	105	98
	Turin	67	67	82	81	99	97
Vitamin C (mg)	Beijing	108	127	141	157	191	208
	New York	89	102	135	149	196	192
	Turin	56	77	82	99	99	118
Fibre (g)	Beijing	35	42	45	52	57	61
	New York	16	17	21	23	28	29
	Turin	12	15	15	18	18	22

Table 6. Dietary intake and oral cancer risk

		Risk by quartiles of intake			
		1 (Low)	2	3	4 (High)
Calories (kcal)	Beijing	1.0	0.9	1.2	0.9
	New York	1.0	1.4	2.4*	2.3*
	Turin	1.0	0.9	0.9	0.8
Fat (g)	Beijing	1.0	0.8	0.8	0.5*
	New York	1.0	1.6	1.8	2.6*
	Turin	1.0	0.6	0.6	0.4
Carbohydrate (g)	Beijing	1.0	0.9	1.3	1.4
	New York	1.0	1.1	0.6	0.7
	Turin	1.0	0.7	0.5	0.9
Protein (g)	Beijing	1.0	1.0	0.7	0.7
	New York	1.0	1.0	0.9	0.7
	Turin	1.0	1.0	0.8	1.5
Vitamin C (mg)	Beijing	1.0	0.8	0.6	0.5
	New York	1.0	1.1	0.9	0.2*
	Turin	1.0	0.7	0.8	0.5
Fibre (g)	Beijing	1.0	0.9	0.5*	0.4*
	New York	1.0	0.6	0.9	0.3*
	Turin	1.0	0.6	0.3*	0.2*

*Risks significant at the 0.05 level.

the oral cavity [24, 25]. This combined analysis of three case–control studies conducted between 1975 and 1989 in the United States, China and Italy confirms such an association with tobacco smoking which is consistent over centre and persists after adjustment for alcohol intake. The risk associated with alcohol, however, varied when examined categorised by non-drinkers, and thereafter consumption dichotomised at the median level. The highest risk was found in the study from New York, while, when examined in this way, no increased risks were found for male alcohol drinkers compared to non-drinkers in the study from Turin.

The predominant form of alcoholic beverage consumed varied between centre. In Beijing, spirits were by far the most common type of alcohol consumed: in Turin, wine was predominant, while in New York, spirits, beer and wine were frequently consumed. When individual types of alcohol were related to risk of oral cancer, while "ever drinkers" of beer or spirits were found to be at an increased risk, there was no such corresponding increased risk for "ever drinkers" of wine which remained true after controlling for centre, sex and tobacco intake (data not shown). Although it is generally recognised that the risk of each type of alcoholic beverage corresponds to its alcoholic content, this low or lack of risk associated with wine intake has been previously reported [26, 27] and a previous case–control study conducted in Italy reported increased risks only for those with very high wine consumption (over 8 drinks per day) [28].

The results reported for tobacco smokers are strong and consistent: significantly increased risks in both sexes in every centre and increasing risks with increasing tobacco consumption. The risks reported by amount of tobacco consumed were

Table 7. The effects of vitamin C and tobacco smoking on the risk of oral cancer; risks (and 95% C.I.) relative to non-smokers with a high relative consumption of vitamin C

	Vitamin C intake level			
Smoking	1	2	3	4
Non-smoker	1.6 (0.8, 3.1)	2.5 (1.4, 4.7)	1.7 (1.0, 2.9)	1.0 (reference)
Level 1	3.7 (1.9, 7.3)	3.3 (1.7, 6.4)	3.3 (1.9, 5.9)	2.8 (1.6, 4.9)
Level 2	10.7 (5.3, 21.7)	7.1 (3.7, 13.6)	6.8 (3.6, 12.8)	3.7 (1.9, 7.3)

higher in females. Analysing the effect of tobacco amongst the sub-group of subjects who have never consumed alcohol also shows increased risk with increasing consumption of tobacco; effects which in this study were found to be higher (and significant) in females compared to males. Such findings amongst non-drinkers are consistent with current available evidence in this field [8–10, 26, 27]. Finally, further evidence for the importance of tobacco on disease risk is gained from the analysis of persons stopping smoking. Risks decreased with increasing duration of cessation, with risks reduced to 70% after between 1 and 9 years quitting and to 50% after more than 9 years quitting when compared to those still smoking, adjusting for previous level of tobacco use and lifetime alcohol intake.

Few previously conducted studies have had sufficient numbers of subjects to analyse the effects of tobacco on individual sites within the oral cavity, whereas this combined analysis had over 100 cases each of tongue, gum and cancers at other parts of the mouth, and over 80 cases of cancer of the floor of the mouth. Blot *et al.* [26], found that the positive trends of tobacco consumption and oral cancer risk were slightly weaker for the tongue, when compared with other intra-oral sites, while Boffetta *et al.* [29] found risk more strongly associated with the "soft palate complex" which would include the "other/unspecified parts of the mouth" term used in this study. Results are consistent in both sexes: the highest risks are associated with cancer of the floor of the mouth, lesser but still significant results with cancer of the tongue and other parts of the mouth. The lowest (and non-significant) results were associated with cancers of the gum.

Consistent results have been reported associating a high intake of fruit and vegetables with a lower risk of oral cancer [1], and in this study the most consistent decreased risks were reported from vitamin C and fibre intake, which have many sources in common and may, in general, be considered as markers for the level of fruit and vegetable consumption. Subjects in the highest "relative" quartile of consumption of vitamin C had half the risk of oral cancer compared with those in the lowest "relative" quartile. Of particular interest, however, is the finding that reduced risk of oral cancer with high vitamin C intake persists even in those at highest risk of disease, i.e. heavy tobacco smokers. The results from the present study suggest that the effects may even be slightly greater in this group. Such results should be treated with caution, coming from a combined analysis of studies conducted in three diverse populations with quite different diets and levels of tobacco smoking. It would, however, be important to investigate this area further, since it may consequently be possible to reduce the risk of this disease significantly, even in those who continue to smoke.

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Acknowledgements—The authors would like to acknowledge the following people involved in the individual studies: H. Hu, J. Duan, P. Jiang, D. Ma, L. Shui, B. MacMahon, S. Graham, B.P. Haughey, D. Shedd, R. O'Shea, G.S. Wilkinson, D. West, G. Ciccone, A. Mashberg, and B. Terracini. This work was supported in part by research grants (R01 CA 47473) from Associazione Italiana per la Ricerca sul Cancro (Dr Macfarlane, Dr Boyle), and the DuPont Company (Dr Zheng). Individual studies included in this manuscript have been supported by Public Health Grant CA 11535 from the National Cancer Institute, DHHS, U.S.A., and Consiglio Nazionale delle Ricerche, Rome (Progetto Finalizzato Oncologia), contracts 85.02391.44 and 86.00595.44.