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Case–Control Study of Oral Dysplasia and Risk Habits Among Patients of a Dental Hospital

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Several studies have investigated risk factors for oral cancer but few have considered precancer. Records accumulated from 1975 to 1993 of dental hospital patients with histologically confirmed oral dysplasia provided the opportunity for a retrospective case–control study of the association between oral precancer and smoking tobacco and drinking alcohol. Seventy sets of case notes were available and each case was matched with records of a control subject, known to be free from dysplasia from another study, for birth date, gender and presumed ethnicity. The relative risk (OR) of having a dysplastic lesion for smokers compared with non-smokers, or ex-smokers for >10 years, was 7.00. Logistic multiple regression revealed a dose–response relationship for tobacco dependent upon the level of cigarette consumption. Also subjects with moderate or severe dysplasia included a higher proportion of smokers than those with mild dysplasia. No overall increased risk from alcohol was found. However, the proportion of subjects who drank spirits was significantly higher among cases than controls. The study reaffirms the role of dental practitioners in identifying individuals at risk of mucosal disease, the importance of public education about the risk factors, and the necessity for counselling patients with precancerous lesions on avoiding further risk.

Keywords: alcohol, case–control, oral dysplasia, smoking, tobacco

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INTRODUCTION

ORAL CANCER is a significant cause of morbidity and mortality and appears to be increasing in adults aged 35–64 years in the United Kingdom [1, 2]. Reducing the incidence of the disease and its morbidity in sufferers is an important goal [2, 3].

Despite advances in treatment and reconstructive surgery, there has been no improvement in oral cancer prognosis for over four decades [4]. It would seem that the key to better quality and length of survival is more effective detection of disease at a premalignant stage or when the invasive lesion is small. Today the future is relatively optimistic for patients whose disease is identified early. However, many of those affected are heavy smokers or consumers of high levels of alcohol and it is important for successful treatment and control to reduce their dependency on these known major risk factors [5].

Macfarlane [6] has reviewed extensively the analytical epidemiology linking oral cancer with smoking tobacco and drinking alcohol and concluded that, in industrialised countries, these are the main aetiological factors. The International Agency for Research on Cancer has stated that there is sufficient evidence to show that tobacco is carcinogenic [7], though the precise role of alcohol remains to be established [8, 9]. Both agents are important independent risk factors [10–12] and there is evidence that their combined effect is greater than the sum of the risks from exposure to either on its own [10, 13, 14]. The epidemiological investigations cited were all based on data from oral cancer patients. With regard to potentially malignant oral lesions, Gupta *et al.* [5] have demonstrated the opportunity for their prevention among populations in India through reducing people's exposure to risk factors. However, the roles of tobacco and alcohol as risk factors for oral precancer in European populations have not hitherto been investigated.

The present study was concerned specifically with the relationship between these two risk factors and oral precancer among residents of London, U.K. Since 1975 detailed case notes of patients with histologically diagnosed dysplasia have been kept by the oral medicine department of a postgraduate dental teaching hospital. It was considered that this series of records would form the basis for a case–control study. The objective was to quantify and reaffirm the association between tobacco smoking, alcohol consumption and potentially malignant oral lesions based on histologically confirmed dysplasia.

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MATERIALS AND METHOD

The investigation was designed as a retrospective case–control study. Eligible cases included all patients who presented with oral dysplasia at the hospital from 1975 to 1993. These were identified from computerised lists held in the oral medicine department and their case notes were then obtained from the medical records department. Controls were selected from among 985 individuals on the list of a neighbouring north London NHS medical practice who had been screened for oral cancer and precancer and had been diagnosed by an oral medicine specialist, in a separate study [15], as being free from oral lesions.

Test and control subjects were matched individually for date of birth, gender and presumed ethnicity (i.e. Asian or non-Asian according to name). Where there was more than one matched control available, the individual whose date of birth most closely approximated that of the test subject was chosen. Except in two instances the control subjects' dates of birth were matched to within 6 months of those of the corresponding dysplasia cases. Anonymity was preserved throughout by identifying each subject only through a unique identification number.

Of the 117 eligible cases, not all could be included since their records were either incomplete, or missing and untraceable. Records of 70 cases were eventually collected for study. For some patients presenting before the early 1980s, information on their smoking habits, and more particularly their alcohol consumption was incomplete and for 19 cases data on type of alcohol consumed was not available. For test subjects the lesions had been histologically confirmed as dysplastic and graded as mild, moderate or severe by a single pathologist.

Data were collected on a standardised form and entered into a computer database for analysis. Each individual's record contained personal information, a note of the referral source for test group subjects, and histories of past or present tobacco use and consumption of alcohol. Tobacco use covered type, daily frequency, duration of habit at presentation and number of years since cessation of smoking if applicable. For those who consumed alcoholic beverages, type and volume per week were recorded.

For analysing the overall risks from smoking and alcohol consumption, the 140 case and control subjects were paired. The paired frequencies were then cast into 4-fold tables, dichotomised for risk status according to Altman's recommended method for paired samples [16]. McNemar tests were applied and odds ratios estimating relative risk and their 95% confidence intervals computed. In order to examine the relationship between smoking and the absence or presence of oral dysplasia and its degree of severity (categorised as mild, moderate or severe) a chi-squared test for trend was performed [16]. In addition, a logistic multiple regression analysis estimating relative risk was carried out with the presence of an oral dysplastic lesion classified as positive or negative as the dependent variable. Personal data and reported exposure to the risk factors, expressed in binary form, constituted the independent variables. Age was entered as a continuous measurement taking values between 0 and 1. Cut-off points for dichotomising the data were partly determined by the need to secure adequate frequencies in the sets.

RESULTS

The mean age of the 70 oral dysplasia cases was 57.0 years (S.D., 13.5), and of the 70 control subjects 60.8 years (S.D., 12.8). Each group consisted of 39 males and 31 females. Of the dysplasia cases, 35 were categorised as mild, 21 as moderate and 14 as severe.

Table 1 shows the self-reported pattern of smoking among dysplasia cases and control subjects. Among the cases, 71.4% were current smokers or had ceased smoking less than 10 years prior to presentation. The corresponding proportion among controls was 37.1%. The differences in frequencies in the four categories of smoking pattern shown in the table between cases and controls were statistically highly significant ($P<0.001$).

A contingency table categorising pairs of dysplasia cases and matched controls according to smoking risk status is presented as Table 2. The odds ratio, estimating the relative risk of having a dysplastic lesion for current smokers or recent ex-smokers, compared with non-smokers or ex-smokers of 10 or more years' standing, was 7.00. The difference between frequencies according to risk status among cases and controls was statistically highly significant ($P<0.001$).

Table 3 examines the relationship between smoking and the absence or presence of oral dysplasia and its degree of severity. There was a highly significant trend ($P<0.001$) towards having any dysplastic lesion, and having a lesion categorised from its histological features as moderate or severe, according to reported smoking status (smokers versus non-smokers, including ex-smokers of more than 10 years' standing). The observed differences in smoking status between the dysplasia groups could be attributed to a linear trend.

Table 4 is a contingency table in which dysplasia cases and matched controls are categorised according to whether or not they reported consuming alcoholic beverages. The odds ratio estimating the relative risk of having a dysplastic lesion for drinkers compared with abstainers was less than unity (0.62). The difference between frequencies according to risk from drinking alcohol among cases and controls was statistically non-significant.

Table 1. Self-reported pattern of smoking among oral dysplasia cases at presentation and control subjects

	Cases		Controls	
Smoking status	*n*	(%)	*n*	(%)
Never (non-smokers)	15	(21.43)	28	(40.00)
Not for > 10 years	5	(7.14)	16	(22.86)
Ceased within last 10 years	16	(22.85)	8	(11.43)
Current smoker	34	(48.57)	18	(25.71)
Total	70	(100.00)	70	(100.00)

Chi-squared = 17.28, df = 3, $P<0.001$.

Table 2. Paired comparison of oral dysplasia cases and controls for smokers and non-smokers (including ex-smokers for > 10 years) with odds ratio (OR) estimating relative risk and 95% confidence interval (C.I.)

		Cases		Total pairs
		Smokers	Non-smokers	
Controls	Smokers	22	4	26
	Non-smokers	28	16	44
	Total pairs	50	20	70

Chi-squared (McNemar) = 16.53, $P<0.001$.
OR = 7.00, 95% C.I. = 2.45–27.50.

Table 3. Frequencies of subjects with no dysplasia, mild dysplasia and moderate or severe dysplasia among smokers and non-smokers (including ex-smokers for >10 years)

Smoking status	No dysplasia	Mild dysplasia	Moderate or severe dysplasia	Total
Smokers	26	24	26	76
Non-smokers	44	11	9	64
Total	70	35	35	140

Chi-squared = 17.27, df = 2, $P < 0.001$.
Chi-squared$_{trend}$ = 15.11, df = 1, $P < 0.001$.
Chi-squared − Chi-squared$_{trend}$ = 2.16, df = 1, $P > 0.05$.
(Observed difference between groups can be attributed to a linear trend.)

Table 4. Paired comparison of oral dysplasia cases and controls for drinkers of alcohol and non-drinkers with odds ratio (OR) estimating relative risk and 95% confidence interval (C.I.)

		Cases		Total pairs
		Drinkers	Non-drinkers	
Controls	Drinkers	41	13	54
	Non-drinkers	8	8	16
	Total pairs	49	21	70

Chi-squared (McNemar) = 0.76, $P > 0.05$.
OR = 0.62, 95% C.I. = 0.22–1.60.

Table 5 presents a logistic multiple regression analysis producing estimates of the relative risk of having a dysplastic lesion with five independent variables included. The regression coefficients for the two independent variables related to smoking were statistically significant ($P < 0.05$). Moderate smoking, as defined, produced an odds ratio of 3.76 and heavy smoking an odds ratio of 13.75. The regression coefficients for the remaining independent variables (gender, age and alcohol consumption) were statistically non-significant.

Although overall a hightened risk of having oral dysplasia was not shown among self-reported consumers of alcohol, Table 6 provides some indication that spirit drinking may be more important as a risk factor than beer or wine consumption. The proportion of spirit drinkers among cases amounted to 33.3% and was significantly higher than that of 12.9% in the controls ($P < 0.01$).

DISCUSSION

The dose–response relationship between tobacco smoking and oral cancer demonstrated in a number of investigations [10–13, 17–19] is reproduced in this case–control study of patients with a histologically confirmed diagnosis of oral dysplasia. The increase in risk according to the reported number of cigarettes smoked per day (Table 5) would seem to support a causal relationship between smoking and dysplasia rather than just one of association. Among the dysplasia cases, 71% were smokers compared with 37% of control subjects and overall, the relative risk of having a dysplastic lesion for smokers was shown to be seven times that for non-smokers or ex-smokers of more than 10 years' standing (Table 2). Feller *et al.* [20], reviewing 138 cases of leukoplakia and erythroplakia, reported that 72% were smokers.

Varying frequencies of smokers and non-smokers were found among cases and controls when the subjects were classified according to the absence of dysplasia or the presence of mild dysplasia, and moderate or severe dysplasia (Table 3). The trend towards a corresponding increase in the proportion of smokers was linear and highly significant, offering further support to the notion of a dose response. This trend was apparent despite the fact that the histological grading of dysplasia according to severity is inevitably subjective.

More than 70% of the smokers in the study used manufactured cigarettes as opposed to 18% who rolled their own, 9% who smoked cigars and 3% who were pipe smokers. In England this implies that the great majority smoked blond tobacco while over half reported using filter cigarettes. Differential relative risks according to type of use, type of tobacco or tar content which, for oral cancer, have been demonstrated by others [14, 21, 22], could not be investigated satisfactorily with this group which used a relatively homogeneous range of products.

An independent role for alcohol consumption, and a synergism between drinking and tobacco smoking, which have been shown in several investigations of oral cancer risk [6, 10–13], could not be replicated for these dysplasia cases. A likely reason is that the majority of subjects in both groups drank alcohol yet few admitted to being heavy drinkers. Only three among the cases and two among the controls consumed 30 or more units of alcohol per week, although a high proportion in both groups (70% of the cases and 77% of the controls) reported at least some drinking. At the same time only six cases and 12 control subjects claimed to neither smoke nor drink. With frequencies of this order, a satisfactory examination of alcohol consumption as a risk factor for oral dysplasia could not be achieved.

There was some evidence that consumption of spirits might be more closely associated with oral dysplasia than other types of alcoholic beverage. Thus, the proportion of spirit drinkers was significantly higher among the cases than the controls whereas there were no significant differences in the proportions using the other specified forms of alcohol (Table 6). Blot *et al.* [12] and Merletti *et al.* [21] produced evidence that spirits and beer were more important risk factors than wine, although other workers have found the highest risks to be associated with wine consumption [18, 23]. Mashberg *et al.* [24] and Doll [25] take the view that there is no difference in risk potential between different types of alcoholic beverage.

Grading oral dysplasia according to severity does not provide a reliable guide to the likelihood of malignant change. All patients under the care of the dysplasia clinic were under regular observation and, at the time of the study, only two of the lesions included had progressed to invasive carcinoma. One of these patients (a smoker) subsequently died of lung disease while the other (a non-smoker) underwent marginal resection for the small malignant lesion that had developed.

In conclusion, the results of this case–control study, bearing in mind all the necessary caveats about self-reported behaviour, allow a null hypothesis of no difference between individuals with and without oral dysplastic lesions in respect to tobacco smoking as a risk factor to be rejected. With regard

Table 5. Logistic multiple regression analysis with oral dysplasia as dependent variable and gender, age and reported life style factors as independent variables

Independent variable	*b* coefficient (S.E.)	*P*	Odds ratio	95% C.I. for OR
Gender	0.33 (0.39)	>0.05	1.40	0.64–3.03
Age (years)	−0.01 (0.01)	>0.05	0.99	0.96–1.02
Moderate smoker	1.33 (0.40)	<0.05	3.76	1.73–8.17
Heavy smoker	2.62 (0.84)	<0.05	13.75	2.66–71.08
Drinker	−0.43 (0.43)	>0.05	0.65	0.28–1.51
Constant	−0.17 (0.96)	>0.05		

Gender: male = 1, female = 0; moderate smoker: current smoker of less than 20 cigarettes per day = 1, non-smoker (currently or for at least 10 years) = 0; heavy smoker: current smoker of 20 or more cigarettes per day = 1, non-smoker (currently or for at least 10 years) = 0; drinker: consumer of alcoholic beverages = 1, non-drinker = 0.

Table 6. Type of alcoholic beverages consumed by oral dysplasia cases at presentation and control subjects (data not known for 19 cases; categories not mutually exclusive)

	Cases				Controls			
Type of drink	Yes	%	No	%	Yes	%	No	%
(a) Beer	20	(39.22)	31	(60.78)	29	(41.43)	41	(58.57)
(b) Wine	19	(37.25)	32	(62.75)	24	(34.29)	46	(65.71)
(c) Fortified wine	8	(15.69)	43	(84.31)	5	(7.14)	65	(92.86)
(d) Spirits	17	(33.33)	34	(66.67)	9	(12.86)	61	(87.14)

(a) Difference (S.E.) = 2.21 (9.04)%, $P > 0.05$, 95% C.I. = −15.51–19.93%.
(b) Difference (S.E.) = 2.96 (8.81)%, $P > 0.05$, 95% C.I. = −14.31–20.23%.
(c) Difference (S.E.) = 8.55 (5.70)%, $P > 0.05$, 95% C.I. = −2.62–19.72%.
(d) Difference (S.E.) = 20.47 (7.56)%, $P < 0.01$, 95% C.I. = 5.65–35.29%

to heavy smoking, the results support the findings from two other recent investigations by this group [15, 26]. The study also demonstrated a dose–response relationship between smoking and oral dysplasia. With regard to alcohol, the risk of developing a dysplastic lesion associated with drinking spirits was shown to be greater than that from a similar intake of other alcoholic beverages. However, no overall increased risk from alcohol, at least consumed in moderation, was shown. Three-quarters of the dysplasia patients were referred by general dental practitioners, which would be expected for a dental hospital, and 4 patients were detected in a pilot population screening programme [15]. This highlights the important role of dental practitioners in detecting oral mucosal lesions and screening their patients who fall into the known risk groups for oral cancer and precancer, opportunistically, on a regular basis. The study also re-affirms the importance of public education, stressing the risk factors for oral cancer and precancer, and the necessity of counselling patients with dysplastic lesions on avoiding further risk. Although the difficulties of achieving this should not be underestimated [27], the evidence of a reduced risk of oral cancer for ex-smokers who have discontinued the habit for at least 10 years is pursuasive [5, 6, 12].

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