J Oral Pathol Med (2004) 33: 525–32

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Risk factors for oral cancer in newly diagnosed patients aged 45 years and younger: a case–control study in Southern England

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BACKGROUND: This case–control study aimed to identify the risk factors for oral cancer in patients aged 45 years and under.

METHODS: Patients were recruited over a 3-year period between 1999 and 2001 from 14 hospitals in the southeast of England, UK.

RESULTS: Fifty-three (80%) newly diagnosed patients with squamous cell carcinoma (SCC) of the oral cavity participated. The mean age of cases at diagnosis was 38.5 years (SD = 7.0) and 53% were male. Patients were interviewed about main risk factors of tobacco, alcohol, cannabis and their consumption of fresh fruit and vegetables in the past. Ninety-one matched control patients were also recruited. Odds ratios (ORs) and 95% confidence intervals (CI) were obtained from adjusted conditional logistic analyses. Significantly elevated ORs were evidenced amongst males who had started to smoke under the age of 16 years (OR = 14.3; 95% CI: 1.1–178.8). A significant reduction in risk was also shown for ex-smokers (OR = 0.2; 95% CI: 0.5–0.8). Consumption of alcohol in excess of recommended amounts also produced an eightfold risk in males (OR = 8.1; 95% CI: 1.6–40.1) and over a fourfold risk of oral cancer from the consumption of excessive amounts of alcohol and having ever smoked (OR = 4.4; 95% CI: 1.1–17.7).

CONCLUSION: The study shows that the traditional behavioural risk factors are present in younger people diagnosed with oral cancer. The relatively short duration of exposure and the substantial number of cases without any known risk factors, particularly amongst females, however, suggest that factors other than tobacco and alcohol may also be implicated in the development of oral cancer in a proportion of these younger patients.

J Oral Pathol Med (2004) **33**: 525–32

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Accepted for publication January 13, 2004

Keywords: oral cancer; risk factors; young people

Introduction

Squamous cell carcinoma (SCC) of the oral cavity and oropharynx is rare in patients of age 45 and younger being primarily a disease that occurs in males in their sixth and seventh decade. Younger patients (age <45 years) account for approximately 6% of all oral cancers in the UK (1).

An alarming rise in the incidence of oral cancer among younger adults has been reported in Europe (2) and in the USA (3).

Case–control studies have implicated tobacco and/or alcohol as the major risk factors for oral cancer in adults of any age (4–10). In particular, smoking frequency and duration, age at start and years after giving up smoking have previously been reviewed (11, 12). European studies involving older patients, have reported adjusted relative risks (RR) of 3.6 in 'moderate' smokers to RR = 9.4 in 'heavy' smokers with oral and pharyngeal cancer (13) and odds ratios (OR) = 3.0 for oral cancer in male current smokers (14) to OR = 20.7 for cancer of the oral cavity in cigar and pipe smokers (9). European data involving females with oral and oropharyngeal cancer have produced reduced OR = 0.7 in current smokers (14) and OR = 0.6 in smokers of 8–25 g of tobacco/day (15). Studies from the USA have produced similar data on risks, with OR = 9.7 in heavy long-term smokers (40 cigarettes a day for ≥20 years) (5). However, lower ORs have also been reported for tongue cancers with OR = 1.8 for smokers of between 16 and 25 cigarettes/day rising to OR = 2.1 for smokers of 35 or more cigarettes/day (16).

The role of alcohol is less clear, and inconsistent risks associated with alcohol consumption have been reported. A study by Brugere et al. found OR = 2.7 for those consuming 40–99 g of alcohol/day, increasing to OR = 13.1 with 100–159 g of alcohol/day and a more than 70-fold risk in consumers of more than 160 g of

alcohol/day (17). However, in a more recent study from Italy, reduced ORs were found for males consuming between 21–40 g of alcohol/day (OR = 0.7) and 81–120 g/day (OR = 0.6). An increased OR of only OR = 2.1 was found for those consuming in excess of 120 g of alcohol/day (15). Increased risks of OR = 3.4 and OR = 11.0 have been reported for females consuming 41 g of alcohol/day or in excess of 30 alcoholic beverages a week, respectively (5, 15). Multiplicative or super-multiplicative effects of alcohol and tobacco have been commonly asserted in studies involving older populations (4–6, 18).

Case–control studies have consistently shown that oral cancer patients have histories of diets low in fruit and vegetables (18–20). Research has confirmed that frequent consumption of vegetables, citrus fruit, fish and vegetable oils are the major features of a protective diet for cancer of the oral cavity after adjusting for smoking and alcohol intake.

Evidence from the few case series so far published, which involve small numbers of cases, suggests that there is an association between heavy smoking and alcohol abuse in younger patients (21–24). Recent evidence, however, suggests an absence of traditional risk factors in a significant proportion of younger patients, especially amongst females (25–32). Moreover, the time span for carcinogens such as tobacco and alcohol to exert a detrimental effect in these younger patients is relatively short. Thus, it has been suggested that oral cancer in the young may be a disease distinct from that occurring in older patients with a different aetiology and disease progression (1). However, the relative rarity of oral cancer occurring in relatively younger adults and the diversity in reporting age criteria, sites, stages and undisclosed aetiology, make comparisons between studies problematic.

A recent review of the literature (33) has demonstrated that there is a paucity of research examining risk factors for oral cancer among young people. It is now of importance to examine the potential risk factors, and likely protective factors such as diet, to provide a more thorough aetiological examination.

Thus, the purpose of this study was to identify the risk factors for oral cancer in recently diagnosed relatively younger patients.

Methods

Recruitment of cases

This multicentred study involved 14 hospitals in the southeast of England, UK. Between 1999 and 2001, participating consultants informed us of oral cancer cases of age 45 years or younger admitted to their respective units as potential recruits for the study. Cases were only included if diagnosed with a SCC of the lip (ICD-10 site code C00); intra-oral sites (ICD-10 C01–C06) or oropharynx/tonsil (ICD-10 C09 and C10). The salivary glands (ICD-10 C07 and C08), nasopharynx (ICD-10 C11) and hypopharynx (ICD-10 C12 and C13) were excluded. Patients were invited to participate in the study and a consent form was provided at initial contact. Non-responders were contacted on two further occasions. After consent was given, patients were contacted by the researcher and arrangements were made to visit the individuals either at home or at the treating hospital.

Recruitment of control subjects

Where feasible, two control subjects were recruited per cancer case, matched for sex, area of residence and within 2 years of the cases' age. Initially, recruitment was conducted by contacting the cases' general practitioner (GP, with their permission) and identifying, from their Practice Register, two suitable controls who had never had cancer. In situations where the GP of a known cancer case was unable or non-compliant in providing matched controls, GP's in the area local to the cancer case were contacted. Collection of data from control subjects was a mixture of postal returns and individuals completing the questionnaire at the time of visiting the doctor's practice, depending on the preference of the individual practice. Control subjects were given a pack consisting of an information letter, a consent form, a pre-paid envelope and a similar questionnaire to that provided for the cancer case, relating to their habits.

The questionnaire

The structured questionnaire contained questions pertaining to the main risk factors of tobacco habits and alcohol use at the time of cancer diagnosis. To account for the social habits among Asian ethnic minorities, additional questions on consumption of betel quid/pan or supari were included.

The amount of tobacco smoked per day was calculated by converting all tobacco consumed into cigarette equivalents. The following calculations were used: one bowl of pipe tobacco being (approximately) equivalent to 2.5 cigarettes, a small, medium and large cigar equivalent to 1.5, two and four cigarettes respectively. Twenty-five grams (1 oz) of roll-up tobacco was considered equivalent to 50 manufactured cigarettes. Ex-smokers were those who had given up smoking at least 12 months prior to answering the questions.

Regular alcohol consumption per week was recorded in units, 1 unit being equivalent to one small glass of wine; one bar measure of spirits or liqueurs; $\frac{1}{2}$ pint of regular beer/lager or cider. Half a pint of strong beer/lager or cider was considered to have 2 units of alcohol. Current UK government guidelines recommend that males consume ≤21 units of alcohol/week and females ≤14 units/week for health purposes (34).

Participants were also asked about the amount of fresh fruit and vegetables regularly consumed in the 10 years prior to diagnosis and typically consumed during childhood. In addition, demographic data concerning age, gender, cohabitation status, education and occupation was requested. Questions were based on current literature examining possible risk factors. A pilot interview study was conducted with 15 non-eligible head and neck cancer patients to test the acceptability and understanding of the questions. Ethical approval for this study was granted by the Multiple Research

Ethics Committee (MREC/98/7/04) and written consent was obtained from all participants.

Statistical analysis

Conditional logistic analyses were conducted using Cox's regressional procedures. The following predictor variables were categorical: smoking status; amount per day in cigarette equivalents; years smoked; main type of tobacco; diet and social class. Predictor variables of alcohol consumption, whether an individual chewed tobacco or betel quid, ever smoked (ex- and current smokers combined), age started smoking and drinking alcohol or having had a vegetarian diet were all dichotomous. Conditional analyses was conducted on male and female samples separately as well as combined. Secondary models were calculated with statistical adjustment for alcohol consumption (within recommended limits/over limits) and smoking (having ever smoked: yes/no). All regressional analyses were adjusted for social class (categorized as four groups: I and II, III manual and non-manual, IV and V and those non-classifiable or unemployed) and ethnicity (categorized as four groups: White UK, Black Caribbean/African/other, Asian/Indian, other). Ethnicity was collapsed into four broad categories because of the ethnic makeup of our sample of cases and controls. Pearson's correlation coefficients were conducted on continuous variables of units of alcohol consumed and cigarette equivalents. All tests of statistical significance were two-sided.

Statistical analysis was carried out with the statistical software package SPSS for Windows version 11.

Results

Study sample

Seventy cancer cases fulfilling the criteria for recruitment were identified by participating consultants. Four patients died prior to interview. Of the 66 patients eligible for participation, one patient declined, two patients were considered by the clinician to be too ill to contact and three patients did not attend further hospital appointments and were lost to follow-up. Fifty-three patients were interviewed giving an 80% participation rate.

The largest number of patients, $n = 20$ (38%) were diagnosed with SCC of the tongue. Ten had cancer of the floor of mouth and the rest were equally distributed among other intraoral sites.

Collection of controls

Thirty-eight cases (72%) were fully matched with two control patients and 15 (28%) were matched with only one case: therefore, a total of 91 controls (1.7:1) were collected (Table 1). Cases of oral cancer and controls were by study design similar in respect to age and gender.

Table 1 shows the distribution of age, ethnicity and social class of the cases and controls by gender. Fifty-three percent of the oral cancer cases recruited were male. The mean age of males at diagnosis was 37.9 years (SD 6.6) and 39.2 (SD 7.4) for females. Nine of the 53 cases (17%) were under the age of 30 years at diagnosis. The predominant ethnic group amongst cases was White UK (76%) with a further seven cases (13%) classified as White 'other'. The majority of cases (46%) were classified as social class III, viz. skilled non-manual and manual, with a further 29% in classes I and II. Most of the cancer cases (58%) lived in a city prior to diagnosis, with only 8% living in rural areas, and the majority (55%) resided with a partner. Twenty-three percentage were living alone at the time of diagnosis.

Analysis of exposure to risk factors

Tables 2–5 give the distribution of exposure to risk factors by sex and for the whole group under study.

Sixty-one percent of male cases and 44% of female cases were smoking at the time of diagnosis, compared with 29% of male controls and 24% of female controls. Only 25% of males but 40% of female cases had never smoked, with similar percentages of controls. Despite this difference in smoking patterns between cases and controls, the cancer risk from smoking was not found to be significant for variables of currently smoking or having ever smoked, after adjusting for alcohol consumption (Table 2). However, a significant reduction in risk from ex-smoking was evidenced for the sample as a whole [OR = 0.2; 95% CI: 0.5–0.8].

Fifty-seven % of males and 44% of female cases had smoked moderate (11–20 cigarettes/day) to heavy (≥21 cigarettes/day) amounts of tobacco compared with 35% of male and 24% of female controls. No dose–response relationship in the level of associated risk was found in the amount of tobacco smoked after adjusting for alcohol intake although a significant reduction in risk was shown for those smoking the equivalent of 10 or less cigarettes/day (OR = 0.2; 95% CI: 0.1–0.9).

A significant risk (OR = 7.2; 95% CI: 1.3–40.7) was associated with starting to smoke under the age of 16 years in the sample as a whole (alcohol-adjusted), which increased to OR = 19.5 (95% CI: 1.3–286.8) in males alone. No significant risk was found for females regarding this variable.

Univariate analysis revealed a significant risk for smoking over 21 years in duration (OR = 3.1; 95% CI: 1.0–9.5), however, this was not found significant when adjusted for alcohol.

Only three cases reported betel quid/pan or supari use, thus no risk was found. Reported cannabis use amongst cases (9%) was found to be smaller than amongst control patients (15%), although generally higher amongst males than females. No significant risks were found for the type of tobacco typically used even after adjustment with the amount of tobacco consumed and alcohol (Table 2).

Eighty-two percent of male cases and 68% of female cases regularly consumed alcohol. The majority (70%) of male drinkers consumed over the recommended units of alcohol per week (refer to Methods) in contrast to half of female drinkers (53%) who were consuming in excess of recommended amounts. Anecdotally, 10 cases mentioned that they considered themselves to abuse alcohol regularly. A significant increase in risk was

Table 1 Demographics of cases and controls by sex

	Males		*Females*		*Total*	
	Cases (n = 28) n (%)	*Controls (n = 45) n (%)*	*Cases (n = 25) n (%)*	*Controls (n = 46) n (%)*	*Cases (n = 53) n (%)*	*Controls (n = 91) n (%)*
Age (years)[a]						
18–30	5 (18)	8 (18)	4 (16)	8 (17)	9 (16)	17 (19)
31–40	11 (39)	18 (34)	5 (20)	8 (17)	16 (40)	34 (37)
41–45	12 (43)	22 (48)	16 (64)	30 (66)	28 (44)	40 (44)
Mean age (SD)[a]	37.9 (6.6)	38.7 (6.3)	39.2 (7.4)	39.6 (7.1)	38.5 (7.0)	39.2 (6.7)
Median age[a]	40	40	42	42	41	41
Ethnicity						
White UK	22 (79)	39 (87)	18 (72)	32 (70)	40 (76)	71 (78)
White other	3 (11)	1 (2)	4 (16)	3 (7)	7 (13)	4 (4)
Asian	1 (4)	2 (4)	3 (12)	3 (7)	2 (4)	5 (5)
Black	2 (8)	2 (4)	0 (0)	6 (13)	2 (4)	8 (9)
Other	0 (0)	1 (2)	0 (0)	1 (2)	0 (0)	2 (2)
Social class[b]						
I and II professional and intermediate	7 (25)	24 (53)	8 (32)	20 (44)	15 (29)	44 (49)
III skilled non-manual and manual	15 (54)	14 (32)	9 (36)	15 (33)	24 (46)	29 (32)
IV and V partly skilled and unskilled	5 (18)	6 (13)	3 (12)	8 (17)	8 (15)	14 (15)
Unemployed/house persons	0 (0)	1 (2)	5 (20)	3 (7)	5 (9)	4 (4)
Non-classifiable	1 (4)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)
Main residential location[c]						
City	17 (61)	20 (44)	14 (56)	24 (52)	31 (58)	44 (48)
Suburban area	10 (36)	18 (40)	8 (32)	17 (37)	18 (34)	35 (39)
Rural area	1 (4)	6 (13)	3 (12)	4 (9)	4 (8)	10 (11)
Living arrangements[d]						
Lived alone	10 (36)	6 (13)	2 (8)	5 (11)	12 (23)	11 (12)
With partner	12 (43)	29 (64)	17 (68)	30 (65)	29 (55)	59 (65)
With parents	5 (18)	2 (4)	0 (0)	2 (4)	5 (9)	4 (4)
Other	1 (4)	7 (16)	6 (24)	9 (20)	7 (13)	16 (18)
Total	28 (53)	45 (50)	25 (47)	46 (50)	53 (100)	91 (100)

[a]For cases, this is age at diagnosis.
[b]Since the 1911 census it has been customary, for analytical purposes, to arrange the large number of groups of occupational classification into a small number of broad categories called social classes I–V (48).
[c]Data missing from two cases.
[d]Data missing from one case.

shown for the sample as a whole consuming alcohol in excess of recommended amounts, after adjusting for smoking behaviour (OR = 5.5; 95% CI: 2.0–15.3), and a significant eightfold increase in risk was shown for males (OR = 8.1; 95% CI: 1.6–40.1) (Table 3). No significant risks were shown for females. The majority of cases and controls started to consume alcohol under the age of 18 years.

Fifty percent of male cases had smoked and also consumed excessive amounts of alcohol compared with 32% of female cases. Significant risks were evidenced for males (OR = 4.4; 95% CI: 1.1–17.7) who both smoked and consumed excessive amounts of alcohol. No significant risks were evidenced amongst females (Table 4). The amounts of tobacco smoked and alcohol consumed were correlated amongst cases ($r = 0.369$; $P = 0.008$). Thirty-six percent of females but only 18% of males reported no exposure to tobacco or excess amounts of alcohol.

A vegetarian diet was more common amongst females, and more female cases (12%) than controls (9%) were vegetarian. Both male and female cases consumed more portions of fresh fruit and vegetables during their childhood than controls, and female cases also reported consuming more portions in the 10 years prior to diagnosis than female controls.

A highly significant reduction in risk was shown for females who consumed at least three portions of fresh fruit and vegetables per day (OR = 0.08; 95% CI: 0.01–0.8). Male cases reported consuming less portions in the 10 years prior to diagnosis than controls, however, the risks were not elevated after adjusting for alcohol and tobacco use (Table 5).

Discussion

The primary aim of this case–control study was to evaluate and substantiate the major risk factors for oral cancer in people of age 45 years or younger. It is recognized that the cut-off age is arbitrary but consistent with reported studies. Fifty-three cases (80% recruitment rate) were recruited to the study from the Southeast of England. Compared with previously reported case-series on oral cancer among young adults, the current research involved a substantial number of cases interviewed for a single study.

Tobacco and alcohol have long been implicated in the aetiology of oral cancer in older adults (5, 18). Results

Table 2 Odds ratios (OR) and corresponding 95% confidence intervals (CI) for oral cancer in 53 newly diagnosed cases and 91 matched controls

	Cases 53 n (%)	*Controls 91 n (%)*	*OR[e] (95% CI)*	*OR[f] (95% CI)*	*Male cases, n = 28 (controls n = 45) OR[f] (95% CI)*	*Female cases, n = 25 (controls n = 46) OR[f] (95% CI)*
Tobacco						
Never smoked[a]	17 (32)	30 (33)	1	1	1	1
Ex-smoker	8 (15)	38 (42)	**0.3** (0.1–0.9)	**0.2 (0.5–0.8)**	0.1 (0.1–1.0)	0.4 (0.1–3.1)
Current smoker	28 (53)	24 (26)	2.4 (0.9–6.4)	1.2 (0.4–3.8)	1.0 (0.2–5.1)	0.8 (0.1–41.6)
Ever smoked	36 (68)	62 (68)	1.1 (0.5–2.5)	0.6 (0.2–1.6)	0.6 (0.1–2.4)	0.6 (0.2–1.6)
Amount per day[b,d] (cigarette equivalents)						
0[a]	17 (32)	30 (33)	1	1	1	1
≤10	8 (15)	31 (34)	0.4 (0.1–1.4)	**0.2** (0.1–0.9)	0.1 (0.1–1.4)	0.2 (0.1–3.0)
11–20	13 (25)	13 (14)	1.5 (0.5–4.6)	0.6 (0.2–2.3)	0.4 (0.1–6.5)	0.3 (0.1–7.9)
≥21	14 (26)	14 (15)	2.2 (0.7–6.7)	1.4 (0.4–5.5)	3.5 (0.2–59.8)	4.8 (0.2–129.3)
Age started smoking (years)						
≥16[a]	18 (34)	45 (49)	1	1	1	1
<16	18 (34)	16 (18)	**7.2** (1.3–40.7)	**19.5** (1.3–286.8)	**14.3** (1.1–178.8)	> 1000 (0 to > 1000)
Years smoked (prior to diagnosis)[c]						
< 1[a]	19 (36)	32 (35)	1	1	1	1
1–10	4 (8)	21 (23)	0.4 (0.1–1.4)	0.3 (0.1–1.2)	0.3 (0.1–2.6)	0 (0 to > 100)
11–20	8 (15)	21 (23)	0.9 (0.3–2.8)	0.5 (0.1–1.9)	0.3 (0.1–5.2)	0.5 (0.1–6.6)
≥21	22 (41)	17 (19)	**3.1** (1.0–9.5)	1.6 (0.4–6.4)	3.4 (0.4–31.6)	0.6 (0.1–6.0)
Main type of tobacco						
Filter cigarettes[a]	29 (55)	44 (48)	1	1[h]	1[h]	1[h]
Hand rolled cigarettes	3 (6)	4 (4)	0.3 (0.1–4.5)	0.1 (0.1–13.0)	0.1 (0.1–93.5)	–
Mixed	4 (8)	10 (11)	0.6 (0.1–3.8)	0.2 (0.1–80.1)	0.2 (0.1–725.7)	1.0 (0.1–16.0)
Cannabis smoker[d]	5 (9)	14 (15)	0.5 (0.1–1.7)	0.3 (0.1–1.8)[g]	0.3 (0.1–3.9)[g]	0.7 (0.1–184.9)[g]
Betel Quid/pan or supari habits	3 (6)	1 (1)	9.5 (0.6–149.0)	4.6 (0.3–77.0)[g]	1.4 (0.1–94.3)[g]	–

[a]Reference category.
[b]Refer to methods.
[c]'Years smoked' for controls based on age started until the age of diagnosis for their corresponding matched case.
[d]Some data are missing.
[e]Estimates from conditional regression analyses.
[f]Estimates from conditional regression analyses, adjusting for alcohol consumption.
[g]Estimates from conditional regression analyses, adjusting for alcohol and tobacco consumption.
[h]Estimates from conditional regression analyses, adjusting for alcohol and amount of tobacco consumed.
Bold type indicates significance at $P \leq 0.05$.

Table 3 Odds ratios (OR) and corresponding 95% confidence intervals (CI) for oral cancer in 53 cases and 91 controls

	Cases 53 n (%)	*Controls 91 n (%)*	*OR[c] (95% CI)*	*OR[d] (95% CI)*	*Males OR[d] (95% CI)*	*Females OR[d] (95% CI)*
Alcohol[e]						
Within recommended levels[a,b]	27 (51)	77 (85)	1	1	1	1
Over recommended levels	25 (47)	13 (14)	**4.6** (1.8–11.9)	**5.5** (2.0–15.3)	**8.1** (1.6–40.1)	3.8 (0.7–20.7)
Age started drinking (years)[e]						
≥18[a]	14 (26)	23 (25)	1	1	1	1
<18	27 (51)	47 (52)	1.1 (0.4–3.2)	1.1 (0.4–3.4)	4.4 (0.4–51.0)	0.5 (0.1–2.6)

[a]Reference category.
[b]≤14 units/week for females and ≤21 units/week for males.
[c]Estimates from conditional regression analyses.
[d]Estimates from conditional regression analyses, adjusting for having ever smoked (yes/no).
[e]Some data are missing.
Bold type indicates significance at $P \leq 0.05$.

from young people have produced mixed results as to their significance. Fifty-three percent of our sample was smoking at the time of diagnosis and the majority of females (60%) and males (75%) were ever smokers compared with 38–100% reported (33). Studies from India (29, 30) have reported lower percentages (16–25%) of ever smokers, but these populations are likely to be using unburned tobacco as part of betel quid use. Previous case–control studies have highlighted increased ORs from current smoking and smoking for 21 years and longer in young patients, and even higher ORs than in older patients (35, 36). However, we failed to find any increased risks from currently smoking or the amount of tobacco smoked. Extremely high ORs were found, however, for males starting to smoke under the age of 16 years.

Our analysis also revealed a significant reduction in risk for all ex-smokers, which represent a large health,

Table 4 Odds ratios (OR) and corresponding 95% confidence intervals (CI) for oral cancer in 53 cases and 91 controls

	Cases 53 *n (%)*	*Controls 91* *n (%)*	*OR*[b] *(95% CI)*	*Males* *OR*[b] *(95% CI)*	*Females* *OR*[b] *(95% CI)*
Ever smoked *plus* consumed *any* alcohol[c]	31 (58)	46 (51)	1.4 (0.6–3.2)	1.4 (0.4–4.4)	1.3 (0.3–6.7)
Ever smoked *plus* consumed *over* recommended limits of alcohol[a,d]	22 (42)	13 (14)	**3.9** (1.5–9.7)	**4.4** (1.1–17.7)	3.5 (0.8–15.2)

[a]≤14 units/week for females and ≤21 units/week for males.
[b]Estimates from conditional regression analyses.
[c]Not adjusted for exposure to tobacco; reference category are those who have never smoked, or smokers who never drink alcohol.
[d]Not adjusted for exposure to tobacco; reference category are those who have never smoked, or smokers who never or moderately drink alcohol.
Bold type indicates significance at $P \leq 0.05$.

Table 5 Odds ratios (OR) and corresponding 95% confidence intervals (CI) for oral cancer in 53 cases and 91 controls

	Cases *(n = 53)* *n (%)*	*Controls* *(n = 91)* *n (%)*	*OR*[b] *(95% CI)*	*OR*[c] *(95% CI)*	*Males* *OR*[c] *(95% CI)*	*Females* *OR*[c] *(95% CI)*
Vegetarian prior to diagnosis	3 (6)	7 (8)	0.8 (0.2–4.0)	0.5 (0.1–3.1)	0 (0–0)	1.3 (0.1–14.0)
Fresh fruit/vegetables during childhood[d]						
2 or less portions daily[a]	32 (60)	66 (73)	1	1	1	1
3+ portions per day	20 (38)	23 (25)	0.6 (0.2–1.3)	0.4 (0.2–1.2)	0.2 (0.1–1.2)	0.5 (0.1–2.6)
Fresh fruit/vegetables in 10 years prior to diagnosis[d]						
2 or less portions daily[a]	31 (58)	60 (66)	1	1	1	1
3+ portions per day	21 (40)	29 (32)	0.6 (0.2–1.6)	0.3 (0.1–1.1)	0.6 (0.1–3.0)	**0.08** (0.01–0.8)

[a]Reference category.
[b]Estimates from conditional regression analyses.
[c]Estimates from conditional regression analyses, adjusting for alcohol consumption and having ever smoked (yes/no).
[d]Some data are missing.
Bold type indicates significance at $P \leq 0.05$.

benefit from giving up smoking. However, ex-smokers may have been lighter smokers than those unable or unwilling to cease smoking. We propose tobacco cessation at the earliest opportunity is the most significant public health measure to control oral cancer at any age.

The majority of both males and females consumed alcohol regularly and 70% of males and 53% of females were regularly consuming in excess. Moreover, an approximate eightfold increase in risk was shown for males who consumed over the recommended amounts of alcohol, after adjusting for social class, ethnicity and smoking habits. These results compare with a growing literature implicating alcohol as the primary risk factor for the development of oral cancer, especially amongst males (37, 38).

The joint effect of alcohol and tobacco on the oral cavity evidenced in older patients (5, 10, 36) was found in males in this study (OR = 4.0).

Cannabis is the most commonly used illegal drug among both men and women in England and Wales but its use in our cases was low. A third of young men and over a fifth of young women in the population claim its use (34) and 31% of the United States population 12 years or older in 1992 had reported marijuana use (39). Recent studies implicate marijuana smoking in the development of head and neck cancer in the young (39).

Betel quid/pan or supari habits with or without the inclusion of tobacco have long been identified as major risk factors for oral cancer in Asian populations (40, 41). The number of patients reporting the habit was small, which is perhaps not surprising when the ethnic profile of our sample is examined.

The benefits of antioxidants derived from a diet rich in fruit and vegetables are consistently shown to give protection against cancer (19, 42). The literature reports consistent inverse associations between oral cancer risk and fruit and vegetable intake in adults, with relative risks commencing at 0.2 (43). Our results lend support, particularly amongst females, whereby a strong reduction in risk was evidenced for those who reported consuming at least three portions of antioxidants per day in the previous 10 years.

The present study has distinct advantages over previous research involving relatively younger patients. First, for a relatively rare disease in this age group, the study involved a substantial number of cases and matched control subjects. Secondly, regarding the generalizability and reliability of the results, cases were recruited when newly diagnosed with a response rate of 80%, eliminating the possibility of any skewed aetiology to those who survive. Thirdly, the controls were not a hospital sample but population-based and representative of the geographic areas where the patients were resident. One could argue that selecting controls from GP practices could introduce a bias towards sick patients but other alternatives such as using relatives of cancer cases could also bias the selection as they may share behavioural risk habits. The results were subject to robust conditional analyses, whereby each case was analysed against their matched counterpart and unlike

the majority of case–control analyses that fail to analyse risk factors by gender, our study showed quite clearly that the risk factors differed between males and females in this sample. Lastly, due to patients being recruited prospectively, the problems of recall bias were minimized. Unfortunately, most studies eliciting behavioural information direct from the patient are subject to 'social desirability effects' of certain responses. Our data were not derived from hospital records and thus probably more accurate.

The results have three important implications. Central, is the need for continued aggressive promotion of tobacco cessation and moderate alcohol use amongst the general public and young individuals and to emphasize the benefits of a diet rich in fresh fruit and vegetables. Particularly pertinent to our results are the increased risks associated with commencing smoking at an early age, thus the persistent targeting of adolescents not to start smoking as part of their educational programme is crucial. This also acts to raise people's awareness of oral cancer from an early age. Moreover, benefits of quitting were apparent in the ex-smoker groups. Finally, the pattern of oral cancer is changing and it can no longer be assumed by health care professionals that the stereotypical patient with oral cancer is an elderly male from a low social class reporting use of tobacco and excess consumption of alcohol. Although oral cancer amongst under 45 year olds is still relatively rare, our previous population data (44) also showed that oral cancer cannot be discounted in young patients who report no history of tobacco or alcohol use. Continued education amongst health care professionals such as general dental practitioners and general medical practitioners is imperative if oral cancer is to be diagnosed without delay.

In conclusion, the results of this case–control study indicated that risk factors present in patients of 45 years and younger were similar to older patients, compatible with previous studies (45). However, smoking and drinking alcohol are common lifestyle behaviours particularly amongst this younger age group hence the need for a case–control study design. Highest ORs were associated with starting to smoke under the age of 16 years and excessive alcohol consumption. These risk factors were skewed towards a male predominance and it is also in question whether exposures were of long enough duration to be considered aetiological agents of oral cancer. What is most interesting, is the distinct subsample of younger patients, particularly females, who reported little or no exposure to any of the major risk factors. This group has been noted previously in the literature (26, 27, 31) and warrants further investigation into whether other risk factors such as genetic predisposition or viral infections and sexual practices (46) can account for the development of oral cancer in these young people. Data from this present study on newly diagnosed young oral cancer cases in Southern England (1999–2001) support our previously reported findings from an analysis of 116 cases extracted from the cancer registry (1990–1997) in the same region (47).

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Acknowledgements

This study was funded by the NHS Executive London (NHSE-LRO), Research & Development, Responsive Funding Programme. A grant received from The Ben Walton Trust is gratefully acknowledged. The authors would like to thank the North Central Thames Primary Care Research Network (NoCTeN), the South Thames Research Network (StaRNet) and GP's in the London area for their assistance with the collection of control patients. Authors also thank Dr Caroline Sabin (University College London, UK) for statistical advice and all the patients who took part in the study and the consultants and staff at the recruiting hospitals.