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Oral infections and dental factors in relation to oral cancer: a Swedish case–control study

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We investigated the role of oral infections, dentition and dental X-rays for oral cancer in a north Swedish population. This case–control study consisted of 410 cases with oral cancer for the period 1980–89 and 410 matched controls. All subjects received a mailed questionnaire. The response rates were 96% and 91% for cases and controls, respectively. The univariate analysis showed a statistically significant increased risk for oral cancer among individuals reporting problems with recurrent clinical oral infection (odds ratio (OR) 3.8). Separate analyses were made for groups with a clearly stated HSV-1 infection (OR 1.9) and highly suspected HSV-1 infection (OR 3.3) as reported by the subjects. Odds ratios were also calculated for infections in relation to tobacco and alcohol habits. For individuals reporting recurrent infection problems an increased risk was observed in every combination category. Dental factors such as different fillings, dentures and fixed prostheses showed no increased risks. Dental X-ray did not produce an increased OR either. A multivariate analysis suggested that the most important risk factors were oral infections followed by liquor consumption and active smoking.
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Key words: Case–control study, dental factors, dental X-ray, HSV-1, oral cancer, oral infections.

Introduction

Oral cancer is a disease with increasing incidence and mortality in most western countries (Boyle *et al*, 1995). Data from several European countries show a general increase in mortality rates of oral cancer among men, with particularly marked increases in young and middle-aged males. Only in Scandinavia (Norway and Sweden) is the mortality approximately stable, and in Finland the trend is downwards (La Vecchia *et al*, 1992). With the exception of lip cancer, however, the incidence of oral cancer has increased also in Sweden (Östman *et al*, 1995).

Oral cancer has been regarded as preventable to a large degree because of its relation with tobacco and alcohol consumption, which is described in many epidemiological studies (Blot *et al*, 1988; Franceschi *et al*, 1992; Mashberg *et al*, 1993; Bundgaard *et al*, 1995). When scrutinizing several studies in the field, however, the results are, in fact, rather contradictory and inconclusive, even regarding cigarette smoking, with some studies showing no correlation, as reviewed by Smith *et al* (1990). Unlike the situation for lung cancer, there

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has not been an increase in incidence corresponding to the increase in cigarette smoking during most of this century (Smith *et al*, 1990). Therefore, it is important to study other potential risk factors, among which oral infections, dental factors and iron deficiency have come into focus. Convincing evidence from *in vitro* studies implicate infections by herpes simplex virus type 1 (HSV-1) with oral cancer, especially studies on HSV antibodies, as reviewed by Scully (1983). It may also be noticed that some case reports suggest an association between herpes of the lip and carcinoma (Wyburn-Mason, 1957; Kvasnicka, 1964; Gecht, 1980). Even more interest has been devoted to the possible oral carcinogenicity of human papilloma virus (HPV), which now is accepted as causative in cervical cancer, and as a suspected carcinogen in different other malignancies (Gissman, 1992). Recent research, *eg* the detection of HPV DNA in oral carcinomas, indicates that HPV may be involved in the aetiology of some benign and malignant oral lesions (Lakshmi *et al*, 1993).

Regarding bacterial infections, the only described association has been known from the early decades of this century, *ie* between late stage syphilis and lingual carcinoma, as reviewed by Clemmesen (1965). It is possible, however, that various preparations of arsenicals and heavy metals used in the treatment of that disease may have acted as the most important carcinogenic agents (Smith *et al*, 1990).

Chronic candidiasis has been suspected as an oral carcinogen based on the fact that it causes leukoplakias, and therefore must be regarded as having premalignant potential (Cawson and Binnie, 1980). Furthermore, the leukoplakias caused by candida often have a speckled character especially likely to show epithelial dysplasia or carcinoma (Pindborg *et al*, 1963). Thus, it seems likely that chronic candidiasis may be a precancerous condition, although the possibility that candidal invasion may occur as a superimposed infection has been discussed (Cawson and Binnie, 1980).

Thus, today there is quite an impressive amount of evidence relating different infectious agents with oral cancer based on experimental research, but few epidemiological studies have focused on clinical infections (Maden *et al*, 1992).

Some epidemiological studies report that poor dentition, indicated by missing teeth, bad oral hygiene and bad condition of dentures, are risk factors for oral cancer independent of smoking and drinking habits (Zheng *et al*, 1990; Graham *et al*, 1997).

To our knowledge, no study has reported any relation between dental X-rays and oral cancer. This exposure has been shown to increase the risk for tumours of the parotid gland in one study (Preston-Martin *et al*, 1985) and also thyroid cancer (Wingren *et al*, 1993; Hallquist *et al*, 1994).

Iron has an ability to favour neoplastic cell growth with possible implications for different type of tumours, as described in a recent review (Weinberg, 1996). However, regarding oral cancer, as well as cancers in the pharynx and oesophagus, iron deficiency connected with Plummer–Vinson syndrome is related to an increased risk, which has been known since the 1930s (Ahlbom, 1937). Increased risks for pharyngeal and lingual cancer were also indicated in an American cohort of white males with pernicious anaemia, possibly related to dysplastic changes related to this disease (Brinton, 1989).

The present report is part of a case–control study conducted in Sweden. Results of the analyses regarding tobacco and alcohol demonstrate a quite moderate risk increase for these factors (Schildt *et al*, 1998). We thus suspect that other aetiological agents are involved in many cases of oral cancer in Sweden. This study was designed to specifically investigate the role of oral infections, dentition, iron deficiency, and dental X-ray investigations.

Material and methods

This population-based case–control study included all histopathologically verified squamous cell oral cancer cases (ICD-7 codes: 140 = lip, 141 = tongue, 143 = floor of mouth, 144 = gingiva, 145 = tonsil/mesopharynx) diagnosed and reported to the Cancer Registry in the four most northern counties in Sweden; Norrbotten, Västerbotten, Jämtland and Västernorrland, during 1980–89.

Cases

Out of 419 identified patients one was excluded because of a wrong coding of diagnosis and there were eight fewer cases owing to a lack of relatives. Thus, the study comprised, in total, of 410 cases, distributed as described in Table 1. The mean age was 72.3 years for women and 69.6 years for men.

Controls

For each of the 175 living cases one living control was drawn from the National Population Registry. The person closest in age, *ie* the one with the closest personal identification number, with the same sex and living in the same county was used. For each of

Table 1. Number of the interviewed women and men, cases and controls, before and after excluding of incomplete pairs

	Initially Included	Women	Men	Refusers	Remaining after exclusion	Women	Men
Cases	410	134	276	18	354	117	237
Alive	175	53	122	11	143	43	100
Deceased	235	81	154	7	211	74	137
Controls	410	134	276	38	354	117	237
Alive	175	53	122	21	143	43	100
Deceased	235	81	154	17	211	74	137

the 235 deceased cases one deceased control was selected from the National Registry for Causes of Death. The same matching criteria were used and furthermore, deceased controls were matched on year of death.

Assessment of exposure

All the 350 living subjects received a mailed questionnaire. To obtain information concerning deceased persons, the questionnaire was sent to the next-of-kin defined in the order of husband or wife, child, parent, sibling or other. The specific nature of the investigation was not disclosed, and there was no reference to the disease under study. Instead, the general information given was that different factors of potential importance for health were studied. The questions concerned different exposure factors of possible interest for oral cancer. In this paper, the following exposure factors were taken into account.

Oral infections. The subjects were asked if and when they have had infections in the oral cavity or on the lips, and if so, they were asked to describe the localization and type of infection, and if the infection was chronic or intermittent.

Dental factors. The subjects were asked questions about their use of removable dentures and fixed prostheses, their number of dental X-rays, and if they had tooth fillings with dental amalgam, gold or plastic material. They were also asked if they have had caries, tooth loss or dental calculus.

Iron supplements. The subjects were asked if they took an iron supplement, and if so, for what reason and for how long.

If the questionnaire was incomplete or a question was obviously misunderstood the subject was contacted by telephone by a specially trained interviewer who did not know whether the person under investigation was a case or a control, and the data were supplemented according to written instructions. Some persons, or next-of-kin, did not answer the questionnaire, but accepted a full telephone interview.

After the questionnaire had been completed by the interviewer, the front page including name, personal identification number and address was removed, thus enabling a blind coding of the answers.

Specific considerations in data analysis

Because of the suggestion that oral infections might be a tumour related problem, it was decided to exclude all subjects with exposure to an infection within a year before tumour diagnosis. For controls the year of diagnosis of the matched case was used. Regarding other exposure factors no latency period was used.

Concerning dental care, a specific category was constructed with all subjects who reported either fillings or removable denture/fixed prosthesis, in order to evaluate if care about dental health affected the risk for oral cancer. This category is denominated 'ever dental care' in this paper.

Statistical methods

All exposure factors were investigated with univariate conditional logistic regression analysis. The calculations were performed using the EGRET program (Epidemiological Graphics Estimation and Testing package, SERC, Seattle, USA). The variables were expressed in categoric forms and the results are presented as the odds ratio (OR) and 95% confidence interval (CI) in every particular category compared with the reference category. It was decided that exposure factors showing a statistically significant increased risk in this univariate

analysis, should also be analysed in a multivariate test including tobacco and alcohol, as previously analysed (Schildt *et al*, 1998). This multivariate conditional logistic regression was also performed using the EGRET program.

Results

Out of 410 cases, 11 living subjects and seven next-of-kin to deceased persons refused to participate. Corresponding numbers of refusers for controls were 21 living subjects and 17 next-of-kin to deceased persons. This gave a response rate of 96% and 91% for cases and controls, respectively. Since we used a matched study design, the 56 refusers and their counterparts were excluded from further analysis, which thus deals with the remaining 708 subjects or 354 matched pairs distributed as described in Table 1.

Univariate analyses

The univariate analysis revealed that oral infections were a strong risk factor for oral carcinoma with an OR of 3.8 (CI 2.1–6.9) (Table 2). Several individuals reported recurrent herpes infection (HSV-1) as the specific type. This motivated a sub-analysis of HSV-1 infections only, which turned out to be a non-significant risk factor, with an OR of 1.9. Furthermore, in 27 subjects the oral infection was highly suspected to be HSV-1, but was not stated specifically. When these were included in the group of certain HSV-1, and reanalysed, the risk increased to OR 3.3, which was statistically significant (Table 2).

Table 2. Odds ratio (OR) and 95% confidence interval (CI) for infections according to ICD codes and type of infection: univariate analysis

Exposure factor	Cases/controls	OR	CI (95%)
All localizations (ICD 140, 141, 143–145)			
Total	57/19	3.8	2.1–6.9
HSV-1			
certain	16/10	1.9	0.7–4.5
certain + probable	39/14	3.3	1.6–6.5
Infections NUD	18/5	4.2	1.4–13
Lip (ICD 140)			
Total	28/7	4.5	1.8–11
HSV-1			
certain	7/4	2.3	0.6–9.1
certain + probable	24/6	4.6	1.7–13
Infections NUD	4/1	4.0	0.4–36

Because of the usual localization of HSV-1 on the lip we made a subanalysis according to localization, which showed an increased OR for both certain (OR 2.3) and probable (OR 4.6) HSV-1 infections (Table 2).

Eight cases but not controls stated a rubbing removable denture in relation to infections, but for this obviously increased risk no OR could be calculated because of no controls with such exposure.

Regarding dental factors, neither different types of fillings nor dentures or fixed prosthesis were associated with increased risks (Table 3). For the group 'ever dental care', no decreased risk was seen (OR 1.4). The specific teeth conditions investigated were not related to oral cancer.

Although the OR for dental X-ray was 1.0, a slight trend of increasing risk was observed when dividing the subjects according to the number of X-ray investigations, as shown in Table 3.

Multivariate analysis

Two separate multivariate analysis were performed to evaluate any interactions between different factors of interest.

Firstly, infections were analysed with regard to each of the factors smoking, oral snuff and alcohol habits. Regarding smoking and oral snuff, a division was made according to present or former use. In this analysis, infection remained an important risk factor of about the same magnitude in all categories (Table 4).

Secondly, oral infections, oral snuff, smoking and liquor consumption were all included in a multivariate analysis (Table 5). This analysis revealed that oral infections were an independent risk factor,

Table 3. Odds ratios (OR) and 95% confidence interval (CI) in relation to different exposure factors, all localizations (ICD 140, 141, 143–145): univariate analysis

Exposure factor	Cases/controls	OR	CI (95%)
Dental factors			
Removable denture	258/241	1.3	0.9–1.9
Fixed prosthesis	44/54	0.8	0.5–1.3
Dental amalgam	153/164	0.8	0.5–1.2
gold	72/78	0.9	0.6–1.3
plastic	15/19	0.8	0.3–1.6
'Ever dental care'	338/334	1.4	0.6–3.2
X-ray, ever	119/119	1.0	0.6–1.5
1–5	50/65	0.8	0.5–1.3
6–15	34/29	1.2	0.6–2.2
> 15	35/25	1.4	0.8–2.6
Caries	305/299	1.5	0.7–3.3
Tooth loss	53/56	0.9	0.6–1.5
Dental calculus	72/70	1.1	0.6–2.1
Iron supplement	52/59	0.8	0.5–1.4

Table 4. Odds ratios (OR) and 95% confidence interval (CI) for infections, all localizations (ICD 140, 141, 143–145), in relation to tobacco and alcohol habit. Multivariate analysis with interaction term

Exposure factor	Cases/controls	OR	CI (95%)
Infection*			
Never smoked	29/11	4.0	1.7–9.2
Active smoker	15/5	4.2	1.4–13
Ex-smoker	13/3	5.5	1.5–20
Infection†			
Never used snuff	49/16	3.6	1.9–6.8
Active snuff user	5/2	3.4	0.6–19
Ex-user of snuff	3/1	2.7	0.2–27
Infection‡			
Never used alcohol	21/7	5.6	1.9–16
Reporting alcohol use	35/11	5.0	2.3–11

*Reference category: no infection and never smoked.
†Reference category: no infection and never used snuff.
‡Reference category: no infection and never used alcohol.

Table 5. Odds ratios (OR) and 95% confidence interval (CI) for different exposure factors, univariate and multivariate outcome

	Univariate analysis		Multivariate analysis	
Exposure factor	OR	CI (95%)	OR	CI (95%)
Oral snuff				
Ex-use	1.4	0.7–2.8	1.7	0.8–3.5
Active use	0.6	0.3–1.1	0.6	0.3–1.1
Smoking				
Ex-smoking	1.0	0.6–1.5	0.8	0.5–1.4
Active smoking	1.7	1.0–2.6	1.5	0.9–2.5
Liquor	1.6	1.1–2.3	1.5	1.0–2.3
Infections	3.7	2.0–6.8	3.8	2.0–7.0

together with liquor consumption. Increased risk was also found for active smoking, although not significant. For oral snuff use no pattern of an association was found.

Discussion

This investigation gives strong support to experimental studies indicating infectious agents to be involved in the carcinogenesis of oral cancer. In particular, our findings concerning reported HSV-1 infections are in line with the existing evidence regarding antibodies against HSV-1 in oral cancer tissue (Scully, 1983).

Despite some case reports on the association between herpes infection localized on the lip and lip cancer (Wyburn-Mason, 1957; Kvasnicka, 1965; Gecht, 1980), no earlier case–control study has addressed this issue. The OR of 4.6 of suspected cases with HSV-1 indicates this to be an important risk factor to be considered in relation to protective measures against oral cancer.

Other infections, which were not possible to identify, also showed a statistically significant increased risk. This group may consist of HSV-1, HPV and/or candida infections, all of which are suspected to be involved in oral cancerogenesis.

Sweden is a country with quite a long history of general socialized dental health care. As early as 1938, the Swedish government instituted community responsible dental health care, especially for children and young people. As a result, dental health improved in all aspects (Hugosson *et al*, 1991). In this material the group 'ever dental care' consisted of the great majority of all cases and controls which made it impossible to trace any possible protective effect by dental care. Thus, the important risk factor for oral cancer in this population must be other factors.

Removable dentures were not found to be a risk factor in this study and this finding is consistent with several other epidemiological studies (Franco *et al*, 1989; Kabat *et al*, 1989; Zheng *et al*, 1990; Marshall *et al*, 1992), but the finding that eight cases but no controls reported a rubbing denture in relation to infection is suggestive.

In several other studies tooth loss has been associated with increased risk for oral cancer. In our study we could not verify this finding, possibly due to too few subjects with this disease which could be explained by the general socialized system of dental care for the whole population in Sweden.

Prompted by findings in other studies showing an association of dental X-rays with tumours of the parotid gland (Preston-Martin *et al*, 1985) and the thyroid (Wingren *et al*, 1993; Hallquist *et al*, 1994) we included a question on this exposure. We did not find an increased risk related to dental X-ray, but the weak trend observed when dividing the material according to number of X-ray investigations (Table 3) may be noteworthy. Whether this finding reflects a carcinogenic effect or a confounding caused by poor dentition requiring frequent X-rays could not be ascertained, however.

True iron deficiency is not very common in men or postmenopausal women in Sweden mainly because of the use of enriched wheat flour, and therefore, Plummer–Vinson is not a common condition in this country. It is very likely that many people taking iron supplements do so without having a true deficiency, sometimes on their own initiative, and

sometimes wrongly prescribed because of a low total serum iron reflecting some chronic disease. In this study we investigated the reason and the length of iron supplement, but a great number of subjects could not give specific answers to this question, which may support the hypothesis of a rather weak relation between true iron deficiency and supplement. Thus, it is not surprising that no relation was found between iron supplement and oral cancer.

In conclusion, this study strongly indicates HSV-1 as an independent causative agent in oral cancer, especially when localized on the lip. This relation ought to be investigated in other studies.

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