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Papers

A Quantitative Evaluation of the Aetiological Role of Betel Quid in Oral Carcinogenesis

Steven Thomas and Andrew Wilson

Computer aided search and review of bibliographies of published papers and monographs revealed 17 case control studies of oral cancer and betel quid chewing from 1933 to 1990. Studies were assessed and site specific risk of oral cancer associated with chewing betel quid with and without tobacco in the quid among smokers and non-smokers was computed. Tobacco smoking and chewing betal quid containing tobacco arose as important risk factors for oral cancer, betel quid without tobacco significantly increased risk in only one study. Heterogeneity in estimates of risk among studies was reduced by restricting analysis to those with more exact definition of exposure and site of the cancer. Variation in risk among studies reflects bias in selection and inadequate definition of exposure and tumour site and an inability to control effectively for confounding. Further studies, addressing these issues are advised, to clarify the role of betel quid without tobacco as a carcinogen, alone and in combination with tobacco smoke.
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INTRODUCTION

THERE HAVE been relatively few case–control studies of betel chewing and oral cancer, most have been undertaken in India. The objectives of this quantitative review were to assess from published studies, the risk of oral cancer following exposure to betel quid alone and with tobacco among smokers and non-smokers and to examine how this risk may vary according to the site of the oral cancer.

The term betel quid can be confusing since it indicates a combination of ingredients in the form of a chew. Usually it refers to the seed of the "betel-nut palm" *Areca catechu* Linn. combined with the leaf, stem or inflorescence of *Piper betle* Linn. and calcium hydroxide. About 50 species of areca palm are found from India to the Solomon Islands, the seeds of the *Areca catechu* being the species commonly included in the quid [1]. The nuts are used at various stages of maturity and are chewed raw or after either curing or drying. Calcium hydroxide, obtained from coral, shells or limestone, is used after mixing with water as a paste in Asia [2] or as a free flowing dry powder in Melanesia. In most of Asia the leaf of the male vine is used to produce wrapped quids which contain areca nut, lime and often tobacco and other spices and resins [2]. In contrast, in Melanesia the quid is always unwrapped. It is formed by chewing the areca nut and adding powdered lime directly to the chew using the moistened inflorescence of the female vine. No tobacco is added in Melanesia [3].

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MATERIALS AND METHODS

In compiling this review, all case–control studies of oral cancer published in English which document exposure to betel quid have been included (Tables 1 and 2). These studies were selected from a number of sources including a MEDLINE search and bibliographies in previously published reviews [4]. The medical subject headings used in this computer search were: areca, betel, neoplasia, carcinoma, leukoplakia, oral and mouth.

The betel quid (BQ) is defined as a combination of the following.

—The seed of the "betel-nut palm *Areca catechu* Linn. which is included in the subfamily Areceae of the family Palmae.

—The leaf, stem or inflorescence of *Piper betle* Linn.

—Calcium hydroxide (slaked lime).

In addition to the above ingredients betel quid often contains tobacco, defined in this respect as betel quid plus tobacco (BQ + T). A variety of other ingredients are included according to culture and personal preference [2], these are not defined in most studies. Smoking (S) refers to any type of tobacco smoking and is assumed to be current smoking unless stated otherwise.

Oral cancer is defined as squamous cell carcinoma (SCC) affecting the sites described by oral tongue and mouth (ICD 9-

Table 1. Characteristics of cases and controls

Country, Region principal investigator year of publication (Ref.)	No. of cases	No. of controls	Site of cancer	Diagnostic criteria	Origin of controls	Selection factors
India, South Orr 1933 [21]	100	100	Buccal 33%, oral* 52%, tongue 15%	Histology not stated	Not stated	Not stated
India, Bombay Sanghvi 1955 [18]	492	288	Buccal 24%, oral* 35%, tongue 41%	Histology confirmed	Hospital based	Not stated
India, Assam Sarma 1958 [5]	238	4000	Oral* 14% + pharynx larynx and oesophagus	Histology not stated	Hospital based inpatients + visitors	Age >20 years
India, Bombay Khanolkar 1959 [22]	95	288	Buccal 100%	Histology not stated	Not stated	Not stated
India, Madras Shanta 1959 [9]	246	278	Buccal 84%, anterior tongue 16%	Histology confirmed	Not stated	Age, sex
India, Madras Shanta 1963 [10]	551	400	Lip 3%, buccal 81%, anterior tongue 16%	Histology confirmed	Non-random population based + hospital based	Age, sex, socioeconomic status
India, Chittaranjan Chandra 1962 [19]	450	500	Buccal 100%	Histology not stated	Hospital based attendants of patients	Age, sex
India, Agra Wahi 1965 [11]	821	1916	Buccal 52%, oral* 19%, tongue 27%, tonsil 2%	Histology confirmed	Hospital based	Age, sex, religion, socioeconomic status
India and Sri Lanka Hirayama 1966 [20]	725	440	Buccal 75%, palate 5%, anterior tongue 20%	Histology not stated	Hospital based	Age, sex
India, Bombay Jussawalla 1971 [23]	826	2005	Buccal 24%, oral* 21%, tongue 55%	Histology confirmed	Population based	Age
India, Varanasi Khanna 1975 [12]	256	100	Buccal 28%, oral* 45%, tongue 27%	Histology not stated	Hospital based	Age, sex, birthplace
Pakistan, Karachi Jafarey 1976 [6]	1192	3562	Buccal 27%, oral* 31%, tongue 24%, pharynx 17%	Histology confirmed	Population based	Age, sex
Thailand, Changmai Simarak 1977 [13]	88	1113	Mouth† + oropharynx	Histology for 50%	Hospital based	Age, sex
India, Bombay Notani 1988 [17]	278	215 Hospital 177 Community	Tongue, gum, floor of mouth, unspecified mouth	Histology confirmed	Hospital based + separately defined community based	Hospital, religion, sex, State, socioeconomic class Community—urban, religion, socioeconomic class
India, South Sankaranarayanan 1989 [14]	228	453	Tongue + floor of mouth	Histology confirmed	Hospital based	Matching included in the analysis for age, sex and religion
India, South Sankaranarayanan 1989 [16]	109	895	Gingiva	Histology confirmed	Hospital based	Unmatched
India, South Sankaranarayanan 1990 [15]	250	895	Buccal + labial	Histology confirmed	Hospital based	Unmatched

*Any combination of the following sites, palate, alveolus, lip, floor of mouth. †Undefined oral cavity.

Table 2. The definition of study factors, cancer sites, study quality scores and proportions of non-betel quid chewers among cases and controls

Exposure	Orr 1933 [21]	Sanghvi 1955 [18]	Sarma 1958 [5]	Khanolkar 1959 [22]	Shanta 1959 [9]	Shanta 1963 [10]	Chandra 1962 [19]	Wahi 1965 [11]	Hirayama 1966 [20]	Jussawalla 1971 [23]	Khanna 1975 [12]	Jafarey 1976 [6]	Simarak 1977 [13]	Notani 1988 [17]	Sankaranarayanan 1989 [14]	Sankaranarayanan 1989 [16]	Sankaranarayanan 1990 [15]
BQ+T+S	–	+*	–	–	–	–	+	–	+	–	–	+	–	–	+‡	+‡	+‡
BQ+S	–	–	–	–	–	–	–	–	+	–	–	+	–	–	–	–	–
BQ+T	–	+*	–	–	–	–	+	–	+	–	–	+	–	–	+‡	+‡	+‡
BQ	–	–	–	–	–	–	+	–	+	–	–	+	–	–	–	–	–
BQ (undefined)+S	–	–	–	+	–	–	–	+†	–	+	–	–	–	+	–	–	–
BQ (undefined)	–	–	–	+	–	–	–	+†	–	+	–	–	–	+	–	–	–
S	–	+	–	+	–	–	+	+	+	+	–	+	–	+	+‡	+‡	+‡
S (chewing status undefined)	–	–	–	–	+	+	–	–	–	–	–	–	+	–	–	–	
BQ+T (smoking status undefined	+	–	–	–	+	+	–	–	–	–	+		–	–	–	–	–
BQ (smoking status undefined)	–	–	+	–	+	+	–	–	–	–	–	–	–	–	–	–	–
Site and exposure defined	–	+	–	+	+	+	+	–	+	–	–	–	–	–	+	+	+
Study score	7.5	14.5	7	11.5	13	16	15.5	13	16.5	20	7.5	19	13.5	21	21	21	21
% non chewing cases	2	34.3	3.4	26.3	5.3	7.3	41.1	8.8	12.4	43.1	39.3§	33.6	25	38.7	25.4	10.2	8.9
% non chewing controls	34	70	21	67.4	35.7	39.6	66.6	26.7	38.6	66.7	75§	69.9	53.5	46.9‖ 75.4¶	47.7	40.2	40.2

BQ = betel quid, i.e. areca nut, slaked lime, piper betel. T = tobacco added to the quid and chewed. S = smoking tobacco. *Tobacco commonly added. †Includes chewers of tobacco and lime alone as well as with BQ. ‡Non-smokers, non-chewers, smokers of 'bidi' cigarettes and chewers of betel quid with tobacco defined. §BQ+T only calculated. ‖Hospital control group. ¶Community control group. + = Reported. – = Not reported.

Table 3. Odds ratios for oral cancer and 95% confidence intervals for studies where exposure is clearly defined

Principal author	S		BQ+T+S		BQ+T		BQ+S		BQ	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Sankaranarayanan, 1989, 1990 [14–16]	4.1	2.6, 6.4	13.0	8.7, 19.6	8.8	6.1, 12.7				
Jafarey, 1976 [6]	5.5	4.2, 7.2	20.3	15.3, 27.4	13.7	10.7, 17.8	21.0	15.9, 28.4	3.6	2.4, 5.3
Hirayama, 1966 [20]	3.5	2.1, 6.1	14.2	8.9, 24.1	9.1	5.9, 15.0	3.3	1.6, 6.8	1.2	0.6, 2.6
Sanghvi, 1955 [18]	2.9	1.8, 5.2	8.4	5.1, 15.1	10.0	5.9, 18.4				
BD χ^2 homog. of OR*	5.48		8.82		4.71		23.47		24.15	
P value	0.14		0.032		0.194		< 0.001		< 0.001	

S = Smokers only, BQ + T + S = betel quid + tobacco + smoking, BQ + T = betel quid + tobacco, BQ + S = betel quid + smoking, BQ = betel quid only, *Breslow–Day test for homogeneity of odds ratios.

141, 143-5, 149). Base of tongue was considered to be part of the oropharynx and where identified was not included in the analysis [9, 10, 20, 22]. Four studies included oropharyngeal SCC which could not be separately identified [5, 6, 11, 13] and one study included pharyngeal, laryngeal and oesophageal SCCs (ICD 9-146, 148, 150) [5], only one of these studies [6] was included in the more detailed analysis.

Studies were assessed independently, using a written protocol to rank studies according to scores based on subject selection, exposure measurement, control of confounding and external validity. Studies were given a score for each of 10 criteria (defined in Appendix 1). In order to create a comparable outcome for all studies, exposures were classified as chewing, irrespective of smoking status, with a reference category of non-smoker, non-chewer. Crude odds ratios (OR) and 95% confidence interval (CI) were calculated [7] and a Breslow–Day test for heterogeneity of odds ratios was computed [8]. For ease of comparison, point estimates and their 95% CI are presented graphically in ranked order. Where individual studies showed large discrepancies from the average effect of all the studies they were re-examined for evidence of bias and confounding.

In five studies [9–13] data was presented as percentages of the totals, thus estimates of numbers in categories may not be exact. Three simultaneous studies [14–16] in which the cases differed by intra-oral site although the controls appeared to be selected from the same pool of 895 patients, were included as a single study by summation of the cases and utilising the full control set. While it is probable that the aetiology differs for individual intra oral sites, the pooled data for anatomical sites were used from all other studies. Notani's data [17] uses two separate control groups, a community group and a hospital group. Crude data for each control group is presented here. Only daily smokers and chewers, contributed to the crude estimates of risk, in Notani's [17] and Sankaranarayanan *et al.*'s data [14–16], and for the latter only "bidi" smokers were analysed.

More detailed definition of exposures was available for only five studies [6, 14–16, 18–20]. The data of these studies were analysed separately to produce odds ratios and 95% CI [7] and within each exposure category. Non-chewing, non-smoking was the reference category for all comparisons.

RESULTS

Seventeen case–control studies examining betel quid chewing as a risk factor for oral cancer were assessed [5, 6, 11–23]. A quarter of the studies were published prior to 1960 and only three involved non-Indian populations. All the studies found an increased risk of oral cancer associated with betel quid chewing although the estimated risk varies considerably. The characteristics of cases and controls are shown in Table 1. The samples range in size from 88 to 1192 cases. All the studies recruited their cases from hospital clinic populations although one included hospital records [20]. Two studies recruited community controls exclusively and one used separately defined community and hospital controls. In most of the other studies it was difficult to define how representative the controls were of the source population. Most studies after 1960 selected controls matched by age and sex although only one included matching in the analysis [14]. All the studies included males and females. The period of recruitment of cases ranged between 1 and 12 years. In 7 of the 17 studies the informant for the data was not stated and the interview method was described in 13 of the 17 studies. Histological confirmation of the diagnosis was not stated in seven studies, and in one other study was only available for half the cases. In seven studies, no age range of cases was given, and the remainder ranged from 14 to 80 or more years.

The prevalence of betel quid use in the control group, shown in Table 2 along with other exposure details, varied substantially among studies from 21 to 79%. Only two studies clearly define the exposure to betel quid with and without tobacco among smokers and non-smokers.

Figure 1 shows the odds ratios and 95% confidence intervals for exposure to betel quid ranked according to the study score. Variation in estimates of effect among studies is clear. With decreasing scores the point estimates of risk show increased variability from 3.4 to 75.9 and the confidence intervals broaden. The χ^2 value for heterogeneity is highly significant ($\chi^2 = 233.34$, df = 15, $P < 0.0001$).

Of the five studies providing data comparing chewing betel quid with tobacco among smokers and non-smokers, one includes only buccal carcinomas. When the analysis is restricted to the four studies in which all intra oral sites were included and exposure was specified, the overall heterogeneity on crude estimates is considerably reduced and is no longer significant ($\chi^2 = 5.96$, df = 3, $P = 0.113$). However, there is still significant heterogeneity in three out of five exposure categories. Only two of these studies provided data on the effect of smoking among those who chewed betel quid without tobacco. In the presence of significant heterogeneity within exposure categories pooled estimates of effect were not appropriate and therefore are not presented.

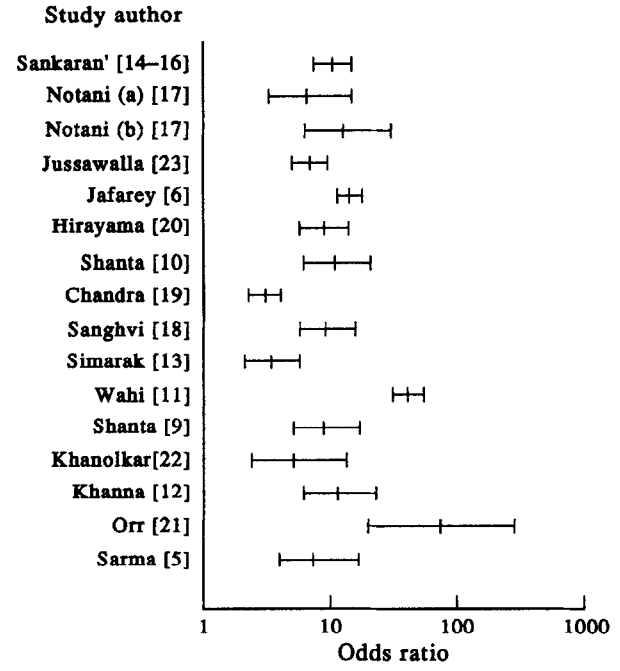

Fig. 1. Crude odds ratios and 95% confidence limits plotted for betel quid chewing regardless of smoking status, ranked according to study score. Notani (a) = hospital controls; Notani (b) = community controls.

Four studies showed that the risk of oral cancer associated with chewing betel quid with tobacco in the quid was markedly higher than that for betel quid alone and smoking among non-chewers was associated with a considerably higher risk than chewing without tobacco. Smoking also increased the magnitude of risk among chewers. In Jafarey and Zaidi's study [6], among those who chewed betel without tobacco, smoking resulted in a 6-fold increase in risk of oral cancer but by only 1.3 times among those who included tobacco in the quid. However, this smoking effect among chewers without tobacco was not observed in the only other study presenting comparable data [20].

A possible further factor contributing to the heterogeneity is the failure to differentiate among oral sites and exposures. Nine studies discriminated between intra-oral sites of the primary cancer [9, 10, 14–16, 19, 20] of which one study included only buccal carcinomas [19]. Six studies documented exposure to smoking or chewing but did not define these exposures as being separate or combined. In only three studies was it possible to distinguish between sites and examine individual exposures [14–16, 18, 20] (Table 4). The overall heterogeneity of the crude estimates among these three studies was very small ($\chi^2 = 0.36$, df = 2, $P = 0.836$). However, for buccal cancers there was still considerable variation in the point estimates of effect for betel with tobacco chewing, possibly due to unstated differences in site definition. Betel quid without tobacco appeared to increase risk for buccal cancers but not for cancers on the anterior two thirds of the tongue. The estimate for smoking from Chandra's data is inexplicably in the opposite direction to the other studies. It is not possible to define whether risk varies according to exposure and intra-oral site because even among the studies where these factors are defined, there is still considerable heterogeneity of effect.

DISCUSSION

Betel quid chewing with tobacco and smoking was associated with an increased risk of oral cancer in all published case–control studies reviewed here and in a large Indian cohort study [24]. However, among the 17 case–control studies there was great variation in the point estimate of effect and in most cases very broad confidence intervals. This analysis suggests that a large part of this variation in apparent effect is due to misclassification of exposure, failure to distinguish exposure in relation to tumour site and the effects of biases due to study design and analysis.

There is potential for ambiguous findings particularly when the review spans a period of fundamental change in design and analytic technique such as occurred in case control methodology since Orr's innovative study in 1933 [21]. The structured review is the best approach to systematically identifying such ambiguity and to separate real variation in effect, from those due to study design factors. Like any secondary analysis this process is dependent on the quality of the original data [25]. The criteria used for scoring the study methods was meant to be indicative of aspects of the case–control methodology which are linked to the likely validity of the result. The weights given to the criteria were generally based on our assessment of the relative importance of each criterion. The earliest investigations were not formerly designed as case–control studies,

Table 4. Odds ratios and 95% confidence intervals for studies where exposure and site is clearly defined

Site	Principal author	BQ+T+S OR	BQ+T+S 95% CI	BQ+T OR	BQ+T 95% CI	S OR	S 95% CI	BQ OR	BQ 95% CI
Buccal	Sanghvi, 1955 [18]	6.3	3.3, 13.8	9.6	5.0, 21.0	1.3	0.6, 2.8		
Buccal	Chandra, 1962 [19]	4.2	2.8, 6.7	4.3	3.0, 6.2	0.9	0.5, 1.5	1.3	0.8, 1.9
Buccal	Hirayama, 1966 [20]	32.0	16.2, 84.4	22.0	11.3, 57.0	5.3	2.4, 14.6	2.2	0.7, 7.0
Buccal + lip	Hirayama, 1966 [20]	33.5	17.0, 88.3	23.7	12.2, 61.5	5.5	2.5, 15.1	2.9	1.0, 8.8
Buccal + lip	Sankaranarayanan, 1989 [15]	20.5	12.1, 38.5	13.9	8.5, 25.3	4.0	2.0, 8.2		
Tongue ant 2/3	Hirayama, 1966 [20]	7.2	3.9, 15.4	2.7	1.4, 5.7	1.7	0.8, 4.1	0.5	0.1, 1.7
Tongue ant 2/3 + floor of mouth	Sankaranarayanan, 1990 [14]	6.6	3.8, 12.3	5.5	3.2, 9.8	4.8	2.6, 9.0		
Gingiva	Hirayama, 1966 [20]	13.9	4.8, 107.9	12.8	4.7, 97.9	8.1	2.6, 63.6	3.5	0.6, 29.9
Gingiva	Sankaranarayanan, 1989 [16]	17.2	8.6, 41.4	11.9	6.2, 28.0	4.2	1.7, 11.1		

BQ + T + S = betel quid + tobacco + smoking, BQ + T = betel quid + tobacco, S = smokers only, BQ = betel quid without tobacco.

however they are retained for their historical importance in the development of the hypothesis and methods.

The quality of study design varied considerably and the ranking of studies according to quality of design was related to the variability in estimates of effect. Definition of the study base is a major issue in all case–control studies [26]. In these studies case ascertainment was predominantly hospital-based and the control group taken either from the hospital or in two studies by an unspecified selection from the general community. Selection bias may occur if major referral hospitals receive essentially all the cases from the immediate area and also cases distant from it, and controls are selected from a population with a different referral pattern. It is unclear in most of these studies how representative the controls were of the case base. For instance, rural as opposed to urban residence may have an important bearing on subjects' exposure to the study factors. Similarly, acculturation may affect a decision to present to hospital and also be related to study factors. Such effects could be strong confounders as is suggested by the substantial variation in the proportion of non-chewers between cases and controls within and among studies. This is clearly demonstrated by Notani [17]; 75% of the predominantly urban community controls were non-chewers compared with only 46% of the hospital control group which contained rural and urban residents.

Even when the case base is clearly identified, controls from the general population are more expensive and logistically more difficult to obtain, particularly in the countries where oral cancer is a public health issue. Despite these constraints sampling strategies in some studies were well considered, for instance, Jafarey and Zaidi [6] selected controls randomly from a pool of nearly 11 000 healthy subjects from Karachi and then matched for age, sex and place of birth. Notani's study [17] is also important as an illustration of the marked variation between possible control groups.

It is clear from studies in non-betel using populations that smoking tobacco is an independent risk factor for oral cancer at all sites, therefore, its effects must be controlled for when considering carcinogenic effects of betel quid. A clear definition of separate exposures is lacking in the majority of these studies. Only three studies clearly distinguished between all possible combinations of tobacco and betel use, and only one of these showed a significant independent increased risk of oral cancer for betel quid without tobacco. However, when stratified by site, Hirayama's data [20] also shows an increased risk for buccal, lip and gingival cancers, but not tongue. In Jafarey and Zaidi's study [6], which ranked high on quality, there was evidence of a multiplicative increase in risk for betel chewers without tobacco who smoke. Moreover, smoking tobacco increases risk across all categories of chewing and among non-chewers in the other studies where these were defined.

While 70% of oral cancers occur in approximately 20% of the oral mucosa in both betel quid chewing and non-chewing populations, the predominant site is markedly different. In populations not exposed to betel quid, tumours commonly occur in a crescentic area in the floor of the mouth whereas in betel chewing areas the buccal mucosa is the most common site [27]. Oral cancer is associated with exposure to tobacco smoking in all countries where it has been studied, implying the difference in localisation of the tumours may be due to other factors such as betel quid or alcohol. The most obvious explanation for the site distribution in betel chewing regions is contact with components of the betel quid. This hypothesis is supported by the observation of an association between cancer site and usual location of the quid or its components [27]. Only one study [14–16] clearly distinguishes among sites and exposures, ranks high on study design, and showed independent effects of chewing betel quid with tobacco and smoking tobacco on risk of cancer at all sites.

These investigations were undertaken during a period of development of case control techniques and with few exceptions were done with limited resources. The size of the problem of oral cancer and the remaining doubt about the risk of chewing betel quid without tobacco suggest that further case–control studies are required addressing the issues discussed here. Because of the possible differences in aetiology, the importance of precise documentation of the site of the oral cancer has been recognised [14–16], although this must be combined with precision in the definition and measurement of exposure in carefully selected populations. Even on available evidence, it would appear that a public health strategy of excluding tobacco from the quid may have little effect in reducing oral cancer rates unless combined with a vigorous anti-smoking campaign, particularly given the recent trends indicating an increase in smoking related cancers in India [28].

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APPENDIX

Protocol for scoring studies

(A) Description of study type, a case control study with a well defined study base (3 points), a case control study with a poorly defined study base (1 point).

(B) Assembled study subjects, well defined study base with appropriate selection of cases and controls (2 points), well defined base however, selection of cases and controls inappropriate (1 point). Poorly defined study base (0 points).

(C) Ascertainment of cases, complete enumeration (4 points), registry based (3 points), hospital based (2 points), case finding or not specified (1 point).

(D) Ascertainment of controls, sampled randomly from the general population (3 points), non-random community sample (2 points), hospital based (2 points), not specified (1 point).

(E) Outcome factor, outcomes assessed and clearly defined (1 point), outcomes assessed but not clearly defined (0.5 point), outcomes considered not defined (0 points).

(F) Study factor definition, study factors appropriately defined (2 points), study factors not clearly defined (1 point).

(G) Confounding factors, all potential confounders considered and taken account of in the design or analysis (3 points), some important potential confounders overlooked or not dealt with adequately (1 point), potential confounders not considered (0 points).

(H) Study size adequate to answer relevant clinical and social questions, narrow confidence intervals (2 points), clinical or social relevance unclear, wide confidence intervals (1 point).

(I) Combined site/exposure definition. Intra oral site defined and exposure defined (4 points), intra oral sites only included, or also includes extra oral sites but defines exposure (2 points), site is undefined (1 point).

(J) External validity. Characteristics of the study population (study base) clearly defined and study groups representative of the same underlying population (3 points), clearly defined study population however insufficient information to assess whether study groups representative of the same underlying population (2 points), study subjects drawn from a poorly defined study population however the characteristics of the study subjects documented (1 point), characteristics of study subjects not specified (0 points).