Original Article on Oral Pre-cancer and Cancer

Assessing the potential association between Epstein-Barr virus and oral squamous cell carcinoma: a systematic review and meta-analysis

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Background: This study aims to qualitatively and quantitatively review the association between Epstein-Barr virus (EBV) and oral squamous cell carcinoma (OSCC).

Methods: PubMed, Scopus, and Web of Science databases were searched using the keywords "EBV or Epstein Barr virus and Oral cancer or Oral squamous cell carcinoma" for published case-control studies in the English language upto August 2019.

Results: The search yielded 985 articles out of which 966 articles were excluded by screening their titles and abstracts as they were irrelevant or duplicates. Based on the full-text assessment of the remaining 19 articles, only 7 satisfied the inclusion criteria and were included in the qualitative analysis, out of which only 4 were compatible to be included in the meta-analysis. The diagnostic modalities used included immunohistochemistry, *in situ* hybridization and polymerase chain reaction. The diagnostic targets included latent membrane protein (LMP)-1, EBV determined nuclear antigen-1, EBV-encoded small non-polyadenylated RNA-2. The meta-analysis showed that there is an association between the EBV and OSCC.

Conclusions: Determining the association of EBV with OSCC is highly tedious due to the contrasting data obtained from individuals' studies which in turn is due to the wide variations in the sensitivity and specificity of the diagnostic modalities used and diagnostic targets selected. Although the meta-analysis revealed an association between EBV and OSCC, the number and the quality of the studies included in the meta-analysis are limited, thus the association requires further validation for any conclusive inference.

Keywords: Epstein-Barr virus (EBV); meta-analysis; oral squamous cell carcinoma (OSCC)

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Introduction

Oral squamous cell carcinoma (OSCC) is a multifactorial disease, whose risk factors have been well documented in the past. The most well-established risk factors of OSCC include tobacco and alcohol (1-5). There are independent risk factors in that they can cause oral cancer on their own and together (alcohol and tobacco) have a synergistic effect augmenting the overall cancer risk (4-6). The World Health Organisation (WHO) and other health agencies around the globe have constantly implemented regulations to prohibit the use of these known risk factors of oral cancer. Despite strict regulations on known risk factors, the incidence of OSCC has not been curbed (7,8). The cause of the persisting high OSCC incidence can largely be attributed to the potential risk factors. Unlike tobacco, and alcohol the causal nature of potential risk factors including environmental agents (e.g., household air pollution), infections (e.g., HPV, EBV, candida); immune status, etc. to oral cancer remains controversial (9-15). Studies have shown contrasting results which in turn is largely attributed to the variations in the sensitivity and specificity of the diagnostic tools used. Among microbial factors, much importance is given to HPV high-risk types 16 and 18 (14) and candida, including non-candida albicans species (13). Other microbial agents including EBV have been relatively less explored in OSCC. Most EBV based studies are on nasopharyngeal carcinoma wherein the causal nature is well-established. Similar to HPV, the carcinogenic potential of EBV remains controversial with respect to the oral cavity. Although several studies have isolated EBV from OSCC and oral potentially malignant tissues (OPMDs), many of these studies have significant methodological flaws including a lack of control group; sampling of saliva or exfoliated oral cells for detecting EBV; use of different sampling methods between study and the control groups; lack of potential confounder (age, gender and habit, etc.) matching between the comparison groups (16-34). In addition, even the diagnostic targets have often varied between the studies. In EBV based studies the most commonly assessed targets include latent membrane protein (LMP)-1 (an EBV associated protein implicated in activating EBV associated signaling pathway), Epstein-Barr virus (EBV)-encoded small non-polyadenylated RNA (EBER)-2, and EBV determined nuclear antigen (EBNA)-1 (implicated in regulating genetic expression) (17,21,23,25,27-31,34). Most EBV based studies on OSCC have assessed only one of these targets using modalities with different sensitivity and specificity, thus causing further discrepancies in the results obtained. The present manuscript attempts to assess the association between EBV and OSCC by systematically reviewing the literature for published case-control studies investigating the prevalence of EBV in OSCC tissues. Apart from the qualitative and quantitative assessment of EBV associations to OSCC, the present review also focuses on addressing the methodological flaws in the published studies.

Methods

Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) protocol was strictly adhered in the systematic review.

Inclusion criteria

(I) Case-control observational studies in English language.
(II) The control samples must be clinically assessed to have normal oral mucosa (NOM).
(III) The OSCC samples must be histopathologically confirmed cases.
(IV) The samples must be conventional (incisional or excisional) tissue biopsies.

Exclusion criteria

(I) Narrative review, systematic review, meta-analysis, case reports/series, letter to the editor, conference papers.
(II) Articles in languages other than English.
(III) Microbes other than EBV.
(IV) Cancers other than OSCC.

Focused question

"Is there an association between EBV and OSCC?

The framework of the population (P), intervention (I), comparison (C), outcome (O), studies (S) were used for this focused question. P represents histopathologically confirmed cases of OSCC; I represent the presence of Epstein Barr virus (EBV); C represents clinically determined cases of NOM, O represents the prevalence of EBV in OSCC compared to NOM, S represents case-control observational studies.

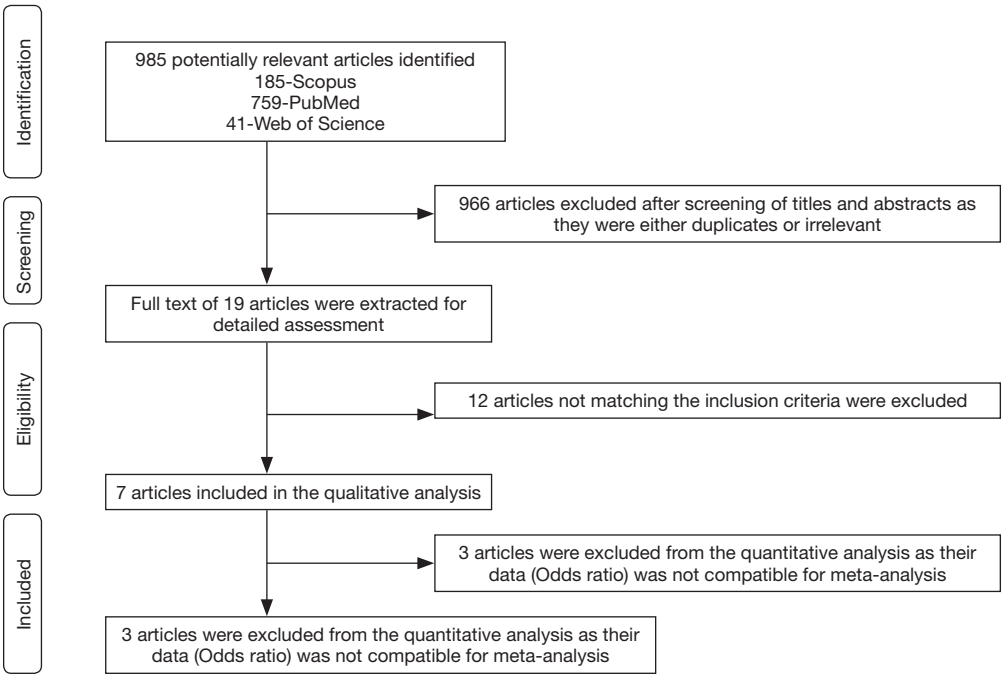

Figure 1 Summary of the search strategy employed.

Search strategy

Data mining was done using Web of Science, Scopus and PubMed databases. The search included articles published until August 2019. The following keywords were used for data mining "EBV or Epstein Barr virus and Oral cancer or Oral squamous cell carcinoma".

Studies selection and data extraction

Two reviewers (SS and ATR) used the above selection criteria to select the cases for this systematic review independently. Two steps were involved in this selection process. First, the reviewers screened the titles and abstract of the identified articles to remove potential duplicates and irrelevant articles. In the second step, the full text of the articles selected in the first step was assessed by the two reviewers using the inclusion criteria.

Risk of biased assessment

Newcastle Ottawa scale (NOS) was used to score the quality of the articles such as selection outcome/exposure and comparability. The maximum score for selection was 4, comparability was 2, and outcome/exposure was 4. Thus, a total of 10 points can be given for a single study. A score above 7 was considered good.

Statistical analysis

As they were two reviewers, potential inter-observer bias was assessed by the Kappa coefficient. Confidence interval (CI) and odds ratio (OR) was calculated for each of the studies included in the meta-analysis. WinPepi version 11.38 was used for generating the forest plot from the estimated CI and OR.

Results

Study selection

Using the keywords "EBV or Epstein Barr virus and Oral cancer or Oral squamous cell carcinoma", a total of 985 articles were identified (185-Scopus, 759-PubMed, 41-Web of Science). A total of 966 articles were excluded after screening the titles and abstracts as they were irrelevant and/or duplicates. The full text of the remaining 19 articles was assessed using the inclusion criteria. Out of the 19 articles, only 7 satisfied the selection criteria and were included in the systematic review (17,21,23,28-31). *Figure 1* summarizes the search strategy of the review in the form of a PRISMA flowchart. Kappa coefficient between

Table 1 Summary of the data extracted from the studies included in the systematic review

S.no	First authors name/ year/country (reference number)	Nature of the tissue sample examined	Sample size (n)		Parameters matched between the comparison groups	Diagnostic modality/ diagnostic target	Results-positive cases (n)	
			OSCC	NOM			OSCC	NOM
1	Reddy SS/2017/ India (28)	FFPE	25	25	Age, gender, tobacco chewing habit were matched	IHC/LMP-1	2	2
2	Kikuchi K/2016/ Japan (23)	FFPE	150	30	Matching details were not provided	PCR/EBNA-2 (EBV DNA)	78	25
						PCR/LMP-1	16	7
3	Sand LP/2002/ Sweden (30)	FBS placed in 99% alcohol for 24 hours at room temperature, followed by storage at –20 ℃	29	67	Only 12 of the 67 controls were age and tobacco habit matched	PCR/EBV DNA	11	4
4	Bagan JV/2008/ Spain (17)	FBS frozen at –80 ℃	11	5	Age and gender were not matched	PCR/EBV DNA	6	0
5	Gonzalez-Moles/2002/ Spain (21)	FFPE	78	50	Age and gender were matched	PCR/EBV DNA	15	0
						IHC/LMP-1	12	0
						ISH/EBER (EBV RNA)	0	0
6	Rahman R/2019/ Thailand (29)	FFPE	36	10	Matching details were not provided	IHC/LMP-1	21	3
7	Talacko AA/1991/ UK (31)	FBS frozen at –70 ℃	20	18	Matching details were not provided	ISH/EBV DNA	0	0

All included articles were case-control observational studies. All case and control samples were biopsied oral cancer and normal oral mucosal tissues. OSCC, oral squamous cell carcinoma; NOM, normal oral mucosa; EBNA, Epstein-Barr virus determined nuclear antigen; LMP, latent membrane protein; EBER, Epstein-Barr virus-encoded small non-polyadenylated RNA; FFPE, formalin-fixed paraffin-embedded samples; FBS, fresh biopsy specimens; UK, The United Kingdom; DNA, deoxyribonucleic acid; RNA, ribonucleic acid.

the two reviewers (SS and ATR) for the first and second steps of the review was 0.98 and 1 respectively. *Table 1* summarizes the data extracted from the included studies.

Study characteristics

All the included articles were case-control observational studies. Two studies were from Spain (17,21), one each from India (28), Sweden (30), Japan (23), Thailand (29), and The United Kingdom (31). The diagnostic modality used in the studies ranged from immunohistochemistry (IHC), *in situ* hybridization (ISH) to polymerase chain reaction (PCR). The tissue samples were either formalin-fixed paraffin-embedded (FFPE) tissues or frozen biopsy specimens, except for one study (30) wherein the biopsy specimen was placed in 99% alcohol for 24 hours at room temperature, followed by storage at –20 ℃.

Newcastle-Ottawa scale

In the included studies matching details of confounding factors (age, gender, associated habits, etc.) between the comparison groups (OSCC and NOM) were assessed. Reddy *et al.* (28) matched for age, gender and habit history, while only age and habit history was matched by Sand *et al.* (30) for a small portion of the control sample. Gonzalez-Moles *et al.* (21) matched only age and gender. In the remaining studies either matching was not done or the matching information was not provided. Of the 7 included studies, only Gonzalez-Moles *et al.* (21) used more than 1 diagnostic

Table 2 New Castle Ottawa scale for studies included in the systematic review

First author (reference number)	Selection				Comparability		Exposure				Total score
	Case definition	Case representativeness	Control selection	Control definition	Matching known confounding factor	Matching potential confounding factor	Secure patient records	Interviewer blinded to cases and control	Similarity in case and control ascertainment	Non-response rate	
Reddy SS (28)	1	1	0	1	1	0	1	0	1	0	6
Kikuchi K (23)	1	1	0	1	0	0	1	0	1	0	5
Sand LP (30)	1	1	0	1	0	0	1	0	1	0	5
Bagan JV (17)	1	1	0	1	0	0	1	0	1	0	5
Gonzalez-Moles (21)	1	1	0	1	0	0	1	0	1	0	5
Rahman R (29)	1	1	0	1	0	0	1	0	1	0	5
Talacko AA (31)	1	1	0	1	0	0	1	0	1	0	5

Vital details including that blinding information on cases and controls were not provided in the manuscript. Thus, without confirmation, score of 0 was rendered in such studies.

modality to 3 diagnostic targets ((PCR-EBV DNA, IHC-LMP-1 and ISH- EBER). Kikuchi *et al.* (23) used one diagnostic modality (PCR) for assessing two markers (EBNA-1 and LMP-1). The rest of the studies assessed only one diagnostic target using one diagnostic modality. The highest sample size was noted in Kikuchi *et al.* study (150 OSCC and 30 NOM cases) followed by Gonzalez-Moles *et al.* (78 OSCC and 50 NOM cases), Sand *et al.* (29 OSCC and 67 NOM cases), Reddy *et al.* (25 OSCC and 25 NOM cases), Rahman *et al.* (36 OSCC and 10 NOM cases), and Talacko *et al.* (20 OSCC and 18 NOM). The lowest sample size was noted in Bagan *et al.* (11 OSCC and 5 NOM cases). The Newcastle-Ottawa scores for the studies included in the systematic review are in *Table 2*.

Prevalence of EBV in OSCC compared to the NOM

The prevalence of EBV in OSCC in the included studies ranged from 0 to 58.3%. The vast differences in the estimates were due to the variations in the sensitivity and specificity of the diagnostic modalities used and the type of diagnostic targets investigated. While the diagnostic modalities included PCR, IHC, and ISH, the targets included EBNA-1, EBER, LMP-1. In order to estimate an overall EBV prevalence, the studies were subjected to meta-analysis for which the confidence interval and odds ratio were calculated for the included studies individually. Four (23,28-30) out of the 7 studies in the qualitative analysis had no EBV prevalence in controls, thus their odds ratio was arriving at infinity and were excluded from the meta-analysis. The confidence interval and odds ratio of the remaining 4 studies are shown in *Table 3*. *Figure 2* shows the forest plot depicting the overall estimate of the EBV association with OSCC from the 4 included studies. The meta-analysis (forest plot) shows an association between EBV and OSCC, although, the number and the quality of studies (based on the Newcastle-Ottawa scale) contributing to the meta-analysis data are below par.

Discussion

The most common and well-established risk factors for OSCC are tobacco and alcohol (1-6). Most of the remaining risk factors in OSCC are designated the term potential risk factor to indicate that there is a lack of conclusive evidence for causal inference. Cases of OSCC presenting with no history of known risk factors have often been attributed to these potential risk factors ranging from environmental

Table 3 Odds ratio and confidence interval of individual study included in meta-analysis

Study	Odds ratio	95% confidence interval
Individual study		
Rahman R *et al.*, 2019 (29)	3.27	0.60–22.22
Reddy SS *et al.*, 2017 (28)	1	0.07–14.89
Kikuchi K *et al.*, 2016 (23)	0.22	0.06–0.62
Sand LP *et al.*, 2002 (30)	9.63	2.41–45.19
All the studies	1.61	0.22–11.72

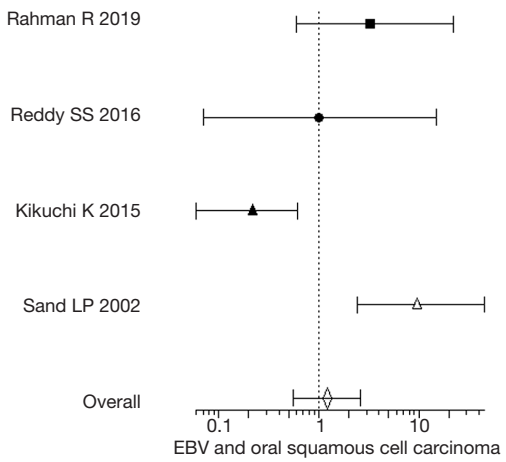

Figure 2 Forest plot for studies included in the meta-analysis.

factors such as household air pollution to infections, immune status, genetic profile, etc. (9-15). Among this much importance is being given to microbial agents as they have shown to possess the carcinogenic potential (presence of oncogenes) and have shown to have a causal association with other forms of carcinoma including HPV with cervical and oropharyngeal cancer and EBV with nasopharyngeal cancer (35-38). Despite years of research, establishing microbial etiology for OSCC as an independent risk factor has been largely controversial (14).

The major reason for the lack of conclusive evidence is due to both the multi-factorial nature of the disease and that most OSCC cases included in studies carry a history of known risk factors such as tobacco and alcohol. Even in studies including only OSCC cases with no known risk factors, there seem to be large scale variations in the sensitivity and specificity of the diagnostic tools used. In addition to the varying diagnostic modalities used, there also seems to be variations in the diagnostic targets. While some studies have focused on identifying the presence of the microbe in the tissue sample (EBV DNA/RNA), others have largely focused on assessing the presence of surrogate markers (LMP-1) which could implicate a causal association for the agent in question (17,21,23,28-31). Very few studies have investigated both the presence of the microbial entity and its nature of association with the disease. In the present systematic review, only 2 (21,23) of the 7 included studies assessed the presence of more than one diagnostic target.

Another major factor to be considered is the samples to be collected. Several studies were excluded in the present systematic review as they had collected samples from saliva and exfoliated oral cells. This due to the fact that specific populations irrespective of the presence or absence of the disease might be microbial carriers. Thus, in such cases, the presence of the microbial agents in saliva or exfoliated cells would not be related to the OSCC. Identifying the microbe within the oral cancer tissue would be relatively more specific (39). Thus, only studies using biopsied tissue specimens were included in the review. Further several studies were also excluded as they failed to provide a comparison control group. Within those studies providing the control groups, there were several major limitations including use of alternative sample collections between the OSCC and the control specimens. While the OSCC cases were subjected to biopsy, samples from the controls (NOM) subjects were often collected through saliva or exfoliated oral cells/brush biopsy. Thus, the present review only included those studies which had analyzed the biopsied tissues from both the OSCC and the NOM groups.

As with many case-control studies, it is vital that the comparison groups (OSCC and NOM) are matched with respect to potential confounders such as age, gender and in cases of oral cancer, the associated habit history. Although the lack of matching would reduce the overall quality of the study, it was not considered as an exclusion criterion in the present systematic review. Apart from defining the inclusion and exclusion criteria one major factor determining the relevance of the case-control study is the sample size, which in the included studies varied significantly from 180 (150 OSCC cases and 30 NOM) to 16 (11 OSCC cases and 5 NOM). Thus, in such cases, the CI of the odds ratio also varied largely between the studies as shown in *Table 3*. The forest plot in *Figure 2* was based on the calculated OD and

CI from the included studies.

Based on the meta-analysis (forest plot) there is an association between EBV and OSCC. The association has to be viewed carefully as both the number and the quality of the studies (based on the Newcastle-Ottawa scale) contributing to the meta-analysis is below par. Further, there were large scale discrepancies between the included studies ranging from sensitivity and specificity of the diagnostic modalities used, diagnostic targets selected, sample size and potential confounder matching between the comparison groups.

Conclusions

The aim of the present systematic review was to answer the focused question: Is there an association between EBV and OSCC? According to the meta-analysis, there is an association between EBV and OSCC. The significance of the meta-analysis data obtained depends on the quality and the number of individual studies (their sample size) contributing to the data. The systematic review included only seven studies, out of which only four studies were compatible with the meta-analysis. Even within the limited number of studies included, there were major limitations. Two out of the 4 studies failed to provide information on matching between the OSCC and the NOM groups, while 1 study matched only age and habit for small proportion of the control samples. Further only one of the 4 studies assessed more than one diagnostic target. Thus, given the several major limitations of the included studies, the association noted between the EBV and OSCC in the present meta-analysis would require further validation for any conclusive inference.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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