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Meta-Analysis

Relevance of Epstein–Barr virus infection in the oral squamous cell carcinoma: A meta-analysis

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Abstract

Objectives: The objectives of the study were to assess the main risk factors related to Epstein–Barr virus (EBV) infection on oral squamous cell carcinoma (OSCC) and the influence on its biological behavior. **Methodology:** A search for articles on EBV infection and mouth neoplasms was performed in the next electronic databases: PubMed (MEDLINE, Cochrane Library), Web of Science, and Spanish Medical Index (IME). From 600 potentially eligible articles, 575 were excluded for several reasons: Articles without full-text availability (201), studies on hairy leukoplakia (256), studies in patients without OSCC (42), studies on malignant salivary gland neoplasms (19), studies in HIV+ or immunocompromised patients (14), and studies with non-usable data (43). Finally, 25 studies were included in this meta-analysis. The statistical software RevMan 5.3 (The Cochrane Collaboration, Oxford, UK) was used to analyze the data. For dichotomous outcomes, the estimates of effects of an intervention were expressed as odds ratio (OR) using the Mantel-Haenszel method with 95% confidence intervals. **Results:** About 46.3% of oral cancers were infected with EBV. Oral cancer patients had more than triple the risk of being infected with EBV than controls (OR: 3.48, P = 0.01). In contrast, age (>60 years), gender (women), tumor location (tongue-floor of the mouth), tumor differentiation degree (well differentiated), or tumor stage (III and IV) were parameters without significant influence ($P > 0.05$) in oral cancers infected with EBV. **Conclusion:** EBV infection may be an important risk factor in oral cancer. **Clinical Significance:** Specific treatment of EBV infection can improve the biological behavior of oral cancers toward less aggressive tumors.

Keywords: Epstein–Barr virus infections, herpesvirus 4 human, mouth neoplasms, oral manifestations, prognosis, risk factors

Introduction

Oral cancer has the ninth largest prevalence in males worldwide, being oral squamous cell carcinoma (OSCC) the most common histologic type with approximately 90% of cases. The main risk factors for OSCC remain the consumption of tobacco and/or alcohol and, above all, the combined consumption of both. Other proposed etiological factors are infectious agents such as human papillomavirus (HPV), *Candida* species superinfection, or Epstein–Barr virus (EBV).[1]

EBV is a gamma-herpesvirus that infects both B lymphocytes and oral epithelial cells. Once the infection occurs, the subject is infected for life, and the host may be asymptomatic as the virus is in a dormant state. It is responsible for common benign processes such as infectious mononucleosis and is also associated with different types of malignancies such as lymphomas (Burkitt and Hodgkin) or carcinomas (nasopharyngeal, etc.).[2]

The real role of EBV infection in the development of OSCC remains unclear. The poor detection of EBV-DNA in OSCC compared to control groups could be explained by the so-called "hit and run theory," where viral DNA would only act as an initiator and would decrease with the malignant transformation of cells. In this same sense, the expression of the latent membrane protein (LMP) of the EBV 1, the main oncoprotein of this virus is essential for the transformation of cells, but unnecessary in already transformed cells.[3]

EBV is in a latent status in all malignancies related to this virus. Viral latency allows sustained expression of viral oncogenes, remaining undetected by the host immune system. EBV infection may induce epigenetic changes and inheritable changes in gene expression that do not result from DNA mutations, in lymphoid and epithelial cells.

Epidemiological studies have revealed highly variable rates of EBV infection in OSCC, probably conditioned by

geographic and ethnic differences. EBV-positive OSCCs have been shown to have a worse tumor differentiation degree. EBV infection delays epithelial differentiation and promotes a more invasive phenotype of epithelial cells. Moreover, the delayed differentiation and the greater invasive capacity were maintained in epithelial cells even after the loss of EBV, indicating that stable epigenetic reprogramming followed EBV infection. Thus, EBV infection could contribute to the pathogenesis of OSCC by epigenetic reprogramming of infected neoplastic cells.[4] This study aimed to assess the main risk factors related to EBV infection on OSCC and the influence on its biological behavior.

Methodology

A search of studies on oral cancer and EBV was performed in the following databases: PubMed (MEDLINE, Cochrane Library), Web of Science (WoS), and the Information and Documentation of Science in Spain (InDICEs-CSIC) that include the Spanish Medical Index (IME). Search strategies included terms from Medical Subjects Headings (MeSH) and free text words such as "Epstein–Barr virus infections" OR "Epstein–Barr virus" AND "mouth neoplasms" OR "oral cancer." A total of 1588 articles were located (548 in PubMed, 1038 in WoS, and 2 in IME) between February 1964 and May 2018, 988 of them duplicates for having the same title and abstract, which left 600 articles for review. The titles and abstracts of the studies were independently examined by two authors (ARA and KL) to evaluate eligibility, and subsequently, the possible discrepancies were resolved jointly. No restrictions regarding the sample size or the EBV detection method were established. Exclusion criteria were as follows: (a) Articles without full-text availability ($n = 201$), (b) studies on hairy leukoplakia ($n = 256$), (c) studies in patients without OSCC ($n = 42$), (d) studies in malignant salivary gland neoplasms ($n = 19$), (e) studies in HIV-positive or immunocompromised patients ($n = 14$), and (f) studies with non-usable data ($n = 43$). Finally, 25 studies were incorporated to this meta-analysis [Figure 1].

Statistical analysis

For the meta-analysis, the data were processed with the RevMan 5.3 program (The Cochrane Collaboration, Oxford, UK). For dichotomous outcomes, the odds ratio (OR) was used with the Mantel-Haenszel Chi-square formula, and for the continuous ones, the inverse of the variance (IV) was used for the mean differences, both with 95% confidence intervals (95% CI). Heterogeneity was determined according to P values and the Higgins statistic (I^2). The random effect model was applied in cases of high heterogeneity (I^2>50%). $P < 0.05$ was considered as the minimum level of significance.

Results

Twenty-five studies[5-29] analyzed the prevalence of EBV detection in patients with oral cancer from 14 different countries [Table 1]. About 46.3% of oral cancer patients (722/1559) were infected with EBV, with frequencies ranging from 8.0% in India[26] in 2013 to 82.5% in Taiwan[18] in 2009. Regarding

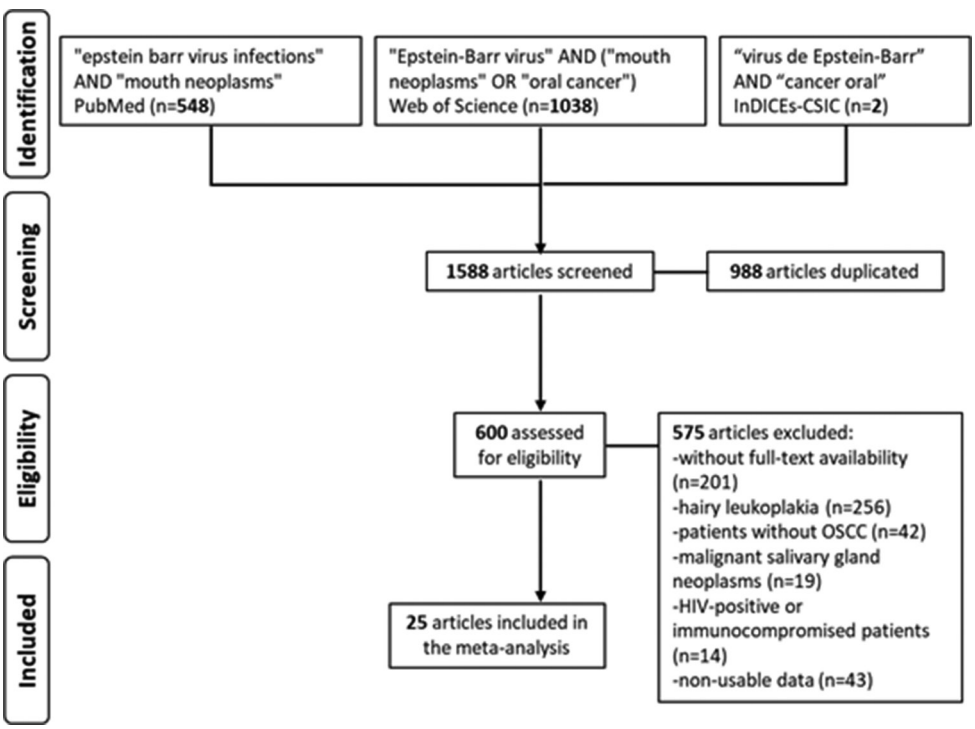

Figure 1: Study flow diagram

Table 1: Studies on the prevalence of Epstein–Barr virus (EBV) in patients with oral cancer

First author	Year	Country	Study type	EBV detection method	EBV+n/N (%)
van Heerden *et al.*[5]	1995	South Africa	C-C	PCR	13/48 (27.1)
Cruz *et al.*[6]	1997	Netherlands	C-C	PCR	18/36 (50.0)
D'Costa *et al.*[7]	1998	India	C-C	PCR	25/103 (24.3)
Maeda *et al.*[8]	1998	Japan	CS	PCR	29/45 (64.4)
Tsuhako *et al.*[9]	2000	Japan	CS	PCR	62/102 (60.8)
Gonzalez-Moles *et al.*[10]	2002	Spain	CS	PCR	15/78 (19.2)
Higa *et al.*[11]	2002	Japan	CS	PCR	39/54 (72.2)
Sand *et al.*[12]	2002	Sweden	C-C	PCR	11/29 (37.9)
Shimakage *et al.*[13]	2002	Japan	C-C	PCR	15/29 (51.7)
Szkaradkiewicz *et al.*[14]	2002	Poland	CS	PCR	8/14 (57.1)
Bagan *et al.*[15]	2008	Spain	C-C	PCR	6/11 (54.5)
Shamaa *et al.*[16]	2008	Egypt	C-C	IMH	18/22 (81.8)
Kis *et al.*[17]	2009	Hungary	C-C	PCR	48/65 (73.8)
Yen *et al.*[18]	2009	Taiwan	CS	PCR	47/57 (82.5)
Jalouli *et al.*[19]	2010	Sweden	C-C	PCR	69/217 (31.8)
Nola-Fuchs *et al.*[20]	2012	Croatia	C-C	PCR	11/24 (45.8)
Acharya *et al.*[21]	2015	Thailand	C-C	PCR	41/91 (45.1)
Jiang *et al.*[22]	2015	China	C-C	PCR	4/25 (16.0)
Polz-Gruszka *et al.*[23]	2015	Poland	CS	PCR	24/92 (26.1)
Bagan *et al.*[24]	2016	Spain	C-C	PCR	7/12 (58.3)
Kikuchi *et al.*[25]	2016	Japan	C-C	PCR	78/150 (52.0)
Reddy *et al.*[26]	2017	India	C-C	IMH	2/25 (8.0)
Shahrabi-Farahani *et al.*[27]	2018	Iran	CS	PCR	68/94 (72.3)
Rahman *et al.*[28]	2019	Thailand	C-C	IMH	22/36 (61.1)
Sharma *et al.*[29]	2019	India	C-C	PCR	42/100 (42.0)
Total					722/1559 (46.3)

C-C: Case–control study; CS: Cross-sectional study; PCR: Polymerase chain reaction; IMH: Immunohistochemistry

EBV detection methods, 22 studies[5-15,17-25,27,29] (88%) used the polymerase chain reaction (PCR), and 3[16,26,28] (12%) used immunohistochemistry (IMH) techniques.

Table 2 presents the analysis of the main risk factors in OSCC patients infected with EBV.

Nineteen studies[5-7,10,12-17,19-22,24-26,28,29] examined the presence of EBV in OSCC patients and controls without the disease. OSCC patients had 3.51 times more likely to be infected with EBV, with statistically significant differences (OR = 3.51; 95% CI: 1.49–8.23; $P < 0.01$).

Eight studies[6,9,11,13,15,20,23,24] investigated the role of age on the risk of EBV infection, showing a slightly higher risk in subjects older than 60 years, although no statistically significant relationship was found (OR = 1.05; 95% CI: 0.66–1.55; $P = 0.85$). Other 10 studies[6,8,9,11,13,15,18,20,24,27] analyzed gender, confirming a higher probability of EBV infection in women than in men. However, no statistically significant association was observed (OR = 1.20; 95% CI: 0.77–1.86; $P = 0.42$).

Table 2: Risk factors related to Epstein–Barr virus infection in patients with oral squamous cell carcinoma

Risk factor	*n*	Reference value	OR	[95% CI]	I^2 (%)	*P*-value
EBV detection	19	OSCC	3.51	[1.49–8.23]	91	<0.01*
Age	8	>60 yr	1.05	[0.66–1.65]	24	0.85
Gender	10	Female	1.20	[0.77–1.86]	0	0.42
Tumor location	11	T-FM	1.14	[0.78–1.67]	22	0.49
Tumor differentiation	6	WD	1.39	[0.88–2.19]	0	0.16
Tumor stage	5	III-IV	1.11	[0.68–1.83]	0	0.67

n: Number of studies; yr: Years; T-FM: Tongue-floor of mouth; WD: Well differentiated; OR: Odds ratio; [95%CI]: 95% confidence interval; I^2: Higgins statistic for heterogeneity; *statistically significant

Eleven studies[6,8,9-11,13,15,18,20-22] evaluated the location of the tumor lesion. A greater number of EBV-infected tumors located

on the tongue or the floor of the mouth were reported, although without statistically significant differences (OR = 1.14; 95% CI: 0.78–1.67; $P = 0.49$).

Six studies[6,8,9,11,13,27] examined the possible influence of EBV infection on the tumor differentiation degree, finding a higher percentage of well-differentiated EBV-positive tumors. Nevertheless, a statistical significance was not reached (OR = 1.39; 95% CI: 0.88–2.19; $P = 0.16$). Five studies[9,11,13,20,27] analyzed the tumor stage, highlighting more EBV-infected tumors in more advanced stages (III-IV) but with no statistically significant relationship (OR = 1.11; 95% CI: 0.68–1.83; $P = 0.67$).

Discussion

Data from 25 studies have been included in the present meta-analysis on the potential role of EBV infection in OSCC.

In the present study, the mean percentage of EBV detection in OSCC patients was 46.3%, a similar percentage to that found by de Lima *et al.*[30] with 45.37% and much lower than that observed by Kis *et al.*[17] with 73.08% detection of the virus in patients with oral cancer. The EBV detection rates were highly variable in the different studies, probably due to differences in methodologies or applied techniques (PCR, nested PCR, IMH, *in situ* hybridization, etc.) to detect EBV in OSCC samples. Fresh/frozen tissues showed a higher positivity rate to EBV than that expressed by paraffin-embedded tissues, although detection of viral DNA is easier and simpler in the latter.[3]

In this study, OSCC patients were 3.51 times more likely to be infected with EBV than controls with very significant statistical differences ($P < 0.01$). Fourteen studies[6,7,10,12-17,21,22,24,28,29] agreed with our results, observing a higher detection of EBV in patients with oral cancer, which could highlight a possible relationship between EBV and OSCC.

Once infected, EBV remains transcriptionally active, expressing so-called "latent genes." This group of latent genes includes EBV-encoded RNAs, Epstein–Barr nuclear antigens (EBNAs), and LMPs.[4] Furthermore, EBV is capable of encoding some oncogenic proteins, especially the EBV LMP-1 and the EBNA-2, which are essential for cell transformation and have a fundamental role in cell immortalization.[4] LMP-1 is an oncoprotein that plays a crucial role in cellular transformation through the inhibition of the differentiation of epithelial cells, favoring oral malignancy. LMP-1 is considered the most important gene because it increases the expression of anti-apoptotic proteins in infected B cells, protecting them from p53-mediated apoptosis. It increases the expression of IL-10, which stimulates the proliferation of B cells and inhibits the local immune response.[4]

In contrast, four studies[5,19,20,25] disagreed with our findings, not evidencing a higher detection of EBV in patients with oral cancer, suggesting a lack of relationship. Some studies observed a higher expression in severe dysplastic lesions than in OSCCs,[25] others were carried out in population groups with very specific characteristics and with particular habits that do not allow the results to be extrapolated to the general population.[5,19] Finally, others pointed out that the presence of EBV in oral cancers could be a coincidental event rather than an etiological factor, especially if there is no coinfection with other viruses, such as the HPV.[20]

This study also analyzed the possible influence of epidemiological parameters (age and gender) on EBV infection in OSCC patients. Although a higher prevalence of EBV was observed in subjects older than 60 years and women, the results were not statistically significant ($P = 0.85$ and $P = 0.42$, respectively). The true influence of age on EBV infection is controversial with disparate results in different studies. Six studies[6,9,11,15,23,24] observed more EBV infections in those older than 60 years and, in contrast, another four,[9,11,13,20] in subjects younger than this age.

If with increasing age, the probability of having cancer increases, it seems logical that also at older age, greater probability of EBV infection. However, it should also be borne in mind that EBV is responsible for infectious mononucleosis, a characteristic disease of the young patient.[24]

The same occurs with gender, where the results were conflicting. Some studies[8,9,11,13,18,20,27] indicated a higher frequency in women and others[6,9,15,24] indicated a predilection for males. The carcinogenic effect of EBV in cancer patients is likely similar regardless of their gender.[27] Other factors involved in oral carcinogenesis should also be considered, such as tobacco and alcohol consumption, which, in principle, is higher in men.[24]

In the present study, the location of the tumor was also evaluated by comparing the locations with the highest risk (tongue/floor of the mouth) for their ability to spread with the rest of the oral locations. Although more EBV-positive tumors were located in these higher risk locations, no statistically significant differences were observed (P=0.49). As happened on previous occasions, the findings are very different. Six studies[9-11,13,18,22] indicated a greater location in the tongue and the floor of the mouth and another six,[8,9,11,15,20,21] indicated the rest of the oral locations as the most prevalent in EBV-positive tumors. These highly variable results are likely conditioned by the selection of patients with oral cancer. The most common oral cancer location is the lateral borders of the tongue and, in the case of oropharyngeal cancer, the tonsils, and the base of the tongue. Coinfection of HPV and EBV could explain this predilection for lingual location.[22] However, Acharya *et al.*[21] found the gingiva as the main location of EBV-positive tumors. This study was conducted in a group of patients who, in addition to the harmful habits of tobacco and alcohol consumption, were betel quid chewers. These authors observed a statistically significant relationship ($P = 0.02$) between virus infection and betel quid chewing, suggesting that EBV detection may be increased in OSCC patients.[21]

The possible influence of EBV infection on some tumor histopathological parameters such as the tumor differentiation degree and tumor stage was also analyzed in our study. Although a greater number of EBV-positive tumors were well-differentiated

and in more advanced stages (III-IV), statistical significance was not reached ($P = 0.16$ and $P = 0.67$, respectively).

These findings are highly conditioned by the different geographical areas where the studies were carried out the kind of job and the habits of these populations.[11] Another factor influencing differentiation and tumor staging is EBV and HPV coinfection. Infection with the latter virus is closely linked to orogenital sex practices. HPV-infected oral tumors tend to have better differentiation and a higher survival rate.[20]

New studies to determine the real influence of all these factors on EBV-infected oral tumors are needed.

Some limitations must be taken into account in the present study. First, the results of this meta-analysis, especially regarding the prevalence of EBV in patients with OSCC and controls, should be interpreted with caution due to the high heterogeneity observed. The differences between studies may be conditioned by the type of design and analysis, the different EBV detection techniques, or the particular characteristics of the study populations. Second, other sources of potential bias are the different techniques and methodologies used to EBV detection, the possible interlaboratory variability even if they use the same tests, the histological classification of tumor samples, or the use of different tissues as control samples. Third, studies with small sample sizes tend to overestimate their results and decrease their precision. Fourth, in some studies, there is little information on the characteristics of the control groups and others did not adequately evaluate different confounding factors (age, gender, harmful habits, etc.).

Conclusion

In this study, the mean EBV detection rate in patients with oral cancer was 46.3%. Oral cancer patients had more than 3 times greater risk of being infected with EBV than controls (OR: 3.51; $P < 0.01$). On the other hand, age (>60 years), gender (women), location (tongue-floor of mouth), degree of tumor differentiation (well differentiated), or tumor stage (III and IV) were parameters without significant influence ($P > 0.05$) in EBV-infected oral cancers.

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