

REVIEW

Malignant Salivary Gland Tumors and Epstein-Barr Virus (EBV) Infection: A Systematic Review and Meta-Analysis

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Abstract

Background: Salivary gland tumors are rare head and neck tumors with lymphoepithelial carcinoma (LEC) as a particularly infrequent variant. This study was an evaluation of the incidence of EBV infection in malignant salivary gland tumors with the emphasis on tumor type and geographical area. **Methods:** Five databases (PubMed, ScienceDirect, Scopus, Web of Science and Cochrane library) were searched for data on the prevalence of EBV in malignant salivary gland tumors. A random-effects meta-analysis was conducted with Comprehensive Meta-Analysis software version 2.0 (CMA 2.0) using the event rate (ER) for estimation of the incidence of EBV in the salivary gland tumor patients. Publication bias was lacking as assessed through funnel plot analysis with the Begg's and Egger's tests ($P>0.05$). **Results:** Out of 618 studies searched in databases, 19 reported the prevalence of EBV in malignant salivary gland tumors and were included in the present meta-analysis. The pooled ER of all studies was 44% [95%CI=21.5-69.2%] with extreme heterogeneity that for the studies in America was 44.2% [95%CI=4.1-93.6%], in Asia (249 patients) was 70% [95%CI= 33.4-91.6%] and in Europe was 11.8% [95%CI=7.4-85.5%] with extreme heterogeneity for three subgroups. The pooled ER for patients with undifferentiated carcinoma was 86.7% [95%CI=71.5-94.4%] compared with 6.6% [95%CI=2.5-16.5%] for other carcinomas. **Conclusions:** The incidence of EBV infection in malignant salivary gland tumors in Asia was greater than in Europe and America and the higher presence of EBV infection in LEC cases implies that EBV may be a major factor in its etiology or pathogenesis. Genetic, environmental and other geographic factors may also be involved.

Keywords: Salivary gland- malignant tumor- Epstein-Barr virus

Asian Pac J Cancer Prev, **18 (5)**, 1201-1206

Introduction

Benign and malignant salivary gland tumors belong to rare head and neck tumors, which most of them are benign and only 20% are malignant (To et al., 2012). The incidence of these tumors is more in men and the most common location of them is the parotid gland (Rezaei et al., 2016). Lymphoepithelial carcinoma (LEC) or the preferred term, lymphoepithelioma-like carcinoma is a rare malignancy (Terada, 2013; Schneider and Rizzardi; 2008). It occurs mainly in East Asia population and only rarely in western countries (Terada, 2013), accounting for less than 1% of all salivary gland tumors (Schneider and Rizzardi;2008). Morphological features are similar to undifferentiated nasopharyngeal carcinoma and most of the cases have been reported in South China and Eskimos (Iezzoni et al.,1995). Epithelial malignancies of the head and neck region such as undifferentiated nasopharyngeal carcinoma and LELC of the salivary gland have been linked to EBV infection (Iezzoni et al.,1995).

Epstein-Barr virus (EBV) is detected by EBER in-situ hybridization (ISH) and by polymerase chain reaction (PCR) to detect latent membrane protein-1 (LMP-1) gene with formalin-fixed, paraffin-embedded tissues (Kuo and Tsang, 2001). The aim of this study was to assess the incidence of EBV infection in malignant salivary gland tumors with emphasis on tumor type and geographical area.

Materials and Methods

Search strategies and Study criteria

The studies were searched in five databases (PubMed, ScienceDirect, Scopus, Web of Science and Cochrane library) from 1980 to 2016 for publications with English abstract using the keywords Epstein Barr virus or Epstein-Barr virus or EBV and salivary gland and tumor or carcinoma.

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Study selection

One author (M.S) searched the articles and then the second author (M.R) blinded to the first reviewer. If there was any disagreement between two reviewers, third reviewer (H.R.M) resolved the problem. All studies were searched for evaluation of the prevalence of EBV in salivary gland tumors. The inclusion criteria for the studies selected were as follows: I) studies reporting the prevalence of EBV based on ISH or PCR; II) studies including only malignant salivary gland; III) studies reporting only the prevalence of EBV in salivary gland; IV) only studies with English-language abstract could be included; The exclusion criteria: I) reporting both malignant and non-malignant salivary gland; II) reporting the prevalence of EBV in salivary gland and other oral areas; III) data from case reports, incomplete reports (not sufficient information), and letters were not eligible for this study.

Data Extraction

The name of author, year of publication, country of region, number of patients, tumor type, method of viral detection and number of patients with EBV infection were the relevant data extracted from every study.

Statistical analysis

A random-effects meta-analysis was used by Comprehensive Meta-Analysis software version 2.0 (CMA 2.0). The event rate (ER) of the studies was calculated for estimation of the incidence of EBV in the salivary gland tumor patients. Heterogeneity between estimates was assessed by the Q and I2 statistic that for the Q statistic, heterogeneity was considered for P<0.1. Confidence interval (CI) was 95% and 2-sided p-value<0.05 was considered to be statistically significant in this meta-analysis study. The I2 statistic yields results

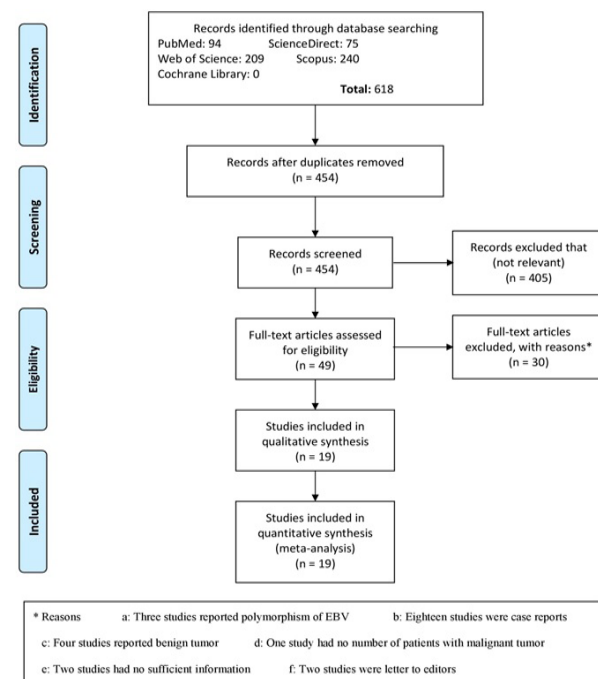


Figure 1. The Flow Chart of Study

ranging from zero to 100% (I2: 0 to 25%, no heterogeneity; I2: 25 to 50%, moderate heterogeneity; I2: 50 to 75%, large heterogeneity; I2: 75 to 100%, extreme heterogeneity) (Egger et al., 1997). Also, the publication bias was assessed through funnel plot analysis with the Begg's and Egger's tests.

Results

Out of 618 studies searched in databases, 49 studies were evaluated for eligibility. Of 49 studies, three studies reported polymorphisms of EBV, eighteen were case report study, four reported benign tumors, one didn't report the number of patients, two studies didn't have sufficient information and two were the letter to editor study that excluded from the study (Figure 1). Therefore, 19 studies reported the prevalence of EBV in malignant salivary gland tumors and included in the meta-analysis study (Table 1).

Study characteristics

The characteristics of 19 studies included in meta-analysis have been shown in Table 1. All studies

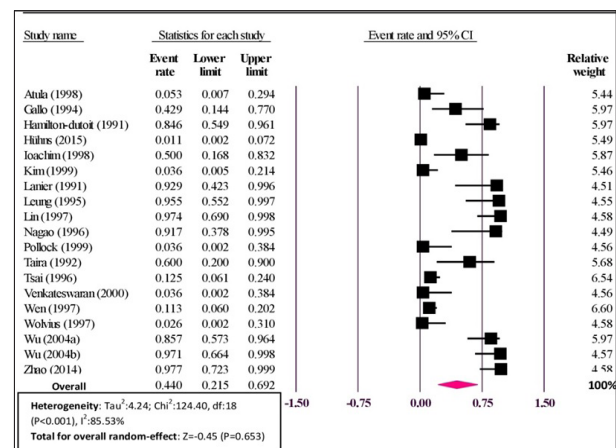


Figure 2. Forest Plot of the Incidence of EBV in Malignant Tumors of Salivary Gland

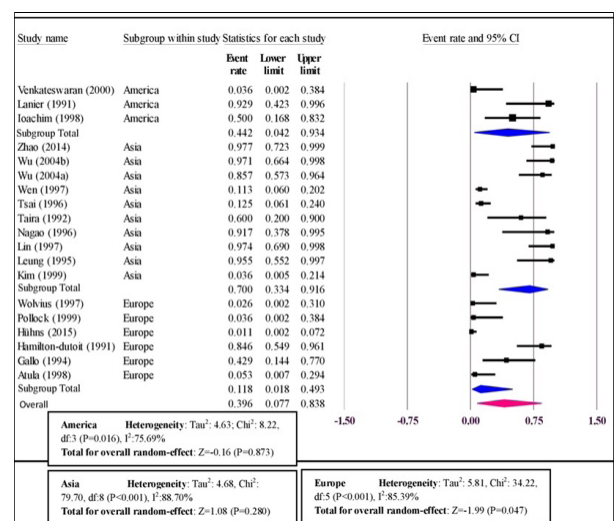


Figure 3. Forest Plot of the Incidence of EBV in Malignant Tumors of Salivary Gland Based on Geographical Areas

Table 1. The Characteristics of Studies in Meta- Analysis (n=19)

Study (year)	Country	Number of patients (N)	Tumor type of salivary gland	Method of detection of EBV	Number of EBV+ patients (N)
Hamilton-dutoit (1991)	Denmark	13	Lymphoepithelial carcinomas	ISH	11
Lanier (1991)	Alaska	6	Lymphoepithelial carcinoma	ISH	6
Taira (1992)	Japan	5	Mucoepidermoid carcinomas	PCR	3
Gallo (1994)	Italy	7	Undifferentiated carcinomas	ISH	3
Leung (1995)	China	10	Lymphoepithelial carcinomas	ISH	10
Nagao (1996)	Japan	5	Undifferentiated carcinoma with lymphoid stroma	ISH	5
Tsai (1996)	Taiwan	56	Mucoepidermoid carcinomas: 14; Adenoid cystic carcinomas: 13; Malignant mixed tumors: 7; Adenocarcinomas: 4; Salivary duct carcinomas: 4; Acinic cell carcinomas: 2; Undifferentiated carcinomas without lymphoid stroma: 2; Lymphoepithelioma-like carcinomas: 7; Squamous cell carcinomas: 2; Small cell carcinoma: 1	ISH	7
Wen (1997)	Japan	80	Undifferentiated carcinomas: 6; T-cell lymphomas: 3; B-cell lymphomas: 3; Mucoepidermoid carcinomas: 15; Adenoid cystic carcinomas: 20; Acinic cell carcinomas: 15; Carcinomas in pleomorphic adenoma: 8; Adenocarcinoma: 5; Squamous cell carcinomas: 3; Papilloadenocarcinomas: 2	ISH	9
Lin (1997)	China	18	Lymphoepithelial carcinomas	PCR/ISH*	18
Wolvius (1997)	Netherlands	18	B-cell lymphoma	ISH	0
Ioachim (1998)	USA	6	B-cell lymphoma	ISH	3
Atula (1998)	Finland	19	Acinic cell carcinomas: 4; Lymphomas: 4; Squamous cell carcinomas: 3; Mucoepidermoid carcinomas: 3; Adenocarcinomas: 2; Adenoid cystic carcinoma: 1; Epithelial-myoepithelial carcinoma: 1; Myoepithelial carcinoma: 1	PCR/ISH*	1/0
Kim (1999)	Korea	28	Mucoepidermoid carcinoma: 13; Adenoid cystic carcinoma: 8; Malignant mixed tumor: 2; Acinic cell carcinoma: 2; Cystadenocarcinoma: 1; Poorly differentiated carcinoma: 1; Lymphoepithelial carcinoma: 1	ISH	1
Pollock (1999)	Ireland	13	Mucoepidermoid carcinoma: 2; Salivary duct carcinoma: 2; Non-Hodgkin's lymphoma: 2; Acinic cell carcinoma: 2; Adenocarcinoma arising in PSA: 2; Polymorphous low grade adenocarcinoma: 1; Undifferentiated carcinoma: 1; Epithelial-myoepithelial carcinoma: 1	ISH	0
Venkateswaran (2000)	USA	13	Mucoepidermoid carcinoma: 7; Rhabdomyosarcoma: 3; Acinic cell carcinoma: 2; Malignant fibrous histiocytoma: 1	ISH	0
Wu (2004a)	China	14	Lymphoepithelial carcinomas	PCR/ISH*	12/14
Wu (2004b)	China	16	lymphoepithelial carcinomas	ISH	16
Zhao (2014)	China	21	Primary lymphoepithelioma-like carcinomas	ISH	21
Hühns (2015)	Germany	93	Mucoepidermoid carcinoma: 17; Adenoid cystic carcinoma: 16; Adenocarcinoma NOS: 10; Salivary duct carcinoma: 9; Acinus cell carcinoma: 7; Adenoid basal-cell carcinoma: 5; Squamous cell carcinoma: 5; Nonkeratinized squamous cell carcinoma: 4; Keratinized squamous cell carcinoma: 4; Oncocytic carcinoma: 2; Lymphoepithelial carcinoma: 2; Micropapillary carcinoma: 2; Myoepithelial carcinoma: 5; Pseudo sarcomatoid carcinoma: 1; Polymorphic low-grade carcinoma: 1; Undifferentiated carcinoma: 1; Cystadenocarcinoma: 1; Malignant melanoma: 1	ISH	1

ISH, in situ hybridization; NOS, not otherwise specified; PCR, polymerase chain reaction. * in two methods, we used the number of the most detection of EBV in meta-analysis.

were published from 1991 to 2015. One study was done in Denmark (Hamilton-Dutoit et al.,1991), one study in Alaska (Lanier et al.,1991), three studies in Japan (Taira et al.,1992; Nagao et al.,1996; Wen et al.,1997), one

study in Italy (Gallo et al.,1994), five studies in China (Leung et al.,1995; Lin et al.,1997; Wu et al.,2004a; Wu et al.,2004b; Zhao et al.,2014), one study in Taiwan (Tsai et al.,1996), one study in Netherlands (Wolvius et

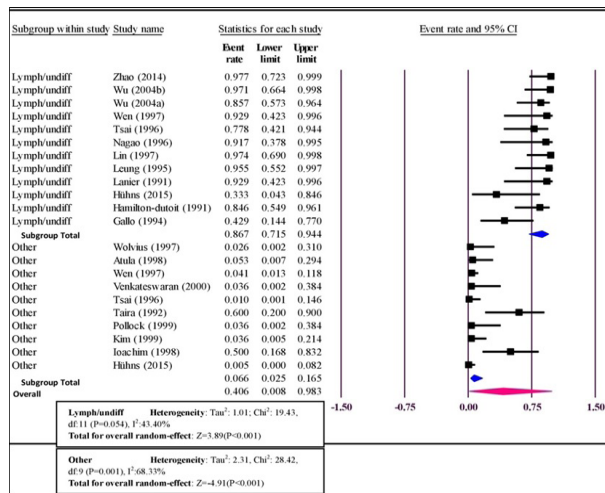


Figure 4. Forest Plot of the Incidence of EBV in Malignant Tumors of Salivary Gland Based on Tumor Type (Lymphoepithelial (-like) or Undifferentiated Carcinomas Versus other Carcinomas (Lymph/undiff versus other))

al., 1997), two studies in the USA (Ioachim et al., 1998; Venkateswaran et al., 2000), one study in Finland (Atula et al., 1998), one study in Korea (Kim et al., 1999), one study in Ireland (Pollock et al., 1999) and one study in Germany (Hühns et al., 2015). Four-hundred and forty-one patients were included in the meta-analysis that 127 (28.8%) patients had EBV positivity. The tumor type and method of detection of EBV have been shown in Table 1. One study (Wen et al., 1997) was short communication that had sufficient information and therefore we selected it for meta-analysis study.

EBV infection and all malignant tumors

The incidence of EBV in malignant tumors of salivary gland has been reported in Figure 1 by the ER. Pooled ER of the studies (441 patients) was 44% [95%CI=21.5-69.2%] with extreme heterogeneity [I²=85.53%; P<0.001].

EBV infection and geographical area

The incidence of EBV in malignant tumors of salivary gland based on geographical areas has been shown in Figure 2. Three studies were in America (Lanier et al., 1991; Ioachim et al., 1998; Venkateswaran et al., 2000), ten studies in Asia (Taira et al., 1992; Nagao et al., 1996; Wen et al., 1997; Leung et al., 1995; Lin et al., 1997; Wu et al., 2004a; Wu et al., 2004b; Zhao et al., 2014; Tsai et al., 1996; Kim et al., 1999) and six studies in Europe (Hamilton-Dutoit et al., 1991; Gallo et al., 1994; Wolvius et al., 1997; Atula et al., 1998; Pollock et al., 1999; Hühns et al., 2015). Pooled ER of the articles for the incidence of EBV in malignant tumors of the salivary gland in America (25 patients) was 44.2% [95%CI=4.1-93.6%] with extreme heterogeneity [I²=75.69%; P=0.016], in Asia (249 patients) was 70% [95%CI= 33.4-91.6%] with extreme heterogeneity [I²=88.70%; P<0.001] and in Europe (167 patients) was 11.8% [95%CI=7.4-85.5%] with extreme heterogeneity [I²=85.39%; P<0.001].

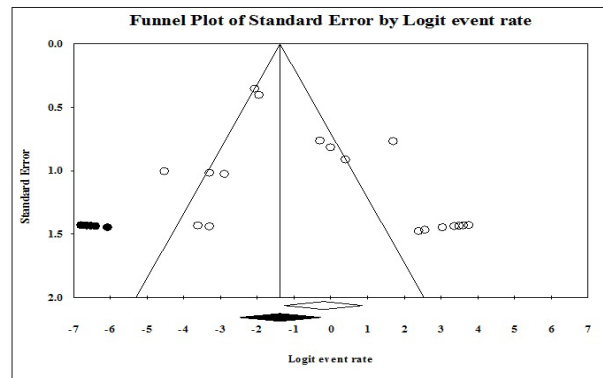


Figure 5. Funnel Plot of Random Effect of the Studies for the Incidence of EBV in Malignant Tumors of the Salivary Gland

EBV infection and tumor type

Figure 4 shows the incidence of EBV in malignant tumors of salivary gland based on tumor type (LEC/LELC or undifferentiated carcinoma versus other carcinomas). Pooled ER for the patients with undifferentiated carcinoma (128 patients) was 86.7% [95%CI=71.5-94.4%] with moderate heterogeneity [I²=43.40%; P=0.054] and for other carcinomas (313 patients) was 6.6% [95%CI=2.5-16.5%] with large heterogeneity [I²=68.33%; P=0.001].

Publication bias

The funnel plot analysis of random effect of the studies in meta-analysis has been shown in Figure 5. The Begg's and Egger's tests didn't show publication bias (P=0.327 and P=0.068, respectively).

Discussion

This study reported that the incidence of EBV infection in malignant tumors of salivary gland was 45.1% that this incidence in American patients was 44.2%, Asian patients 70% and European patients 11.8%. Also, this incidence in the patients with undifferentiated carcinomas was 86.7% compared with 6.6% for other carcinomas. Because nasopharyngeal lymphoepithelioma has been demonstrated to be strongly associated with EBV infection, the role of EBV in LELC of salivary glands has also been investigated (Zhao et al., 2014). EBV has been studied as an etiologic agent in adult salivary gland tumors (Venkateswaran et al., 2000). The oncogenic role of EBV is elicited by its products that among these, LMP-1 has a driving role (Lu et al., 2006). The expression of this protein was observed only in few EBV-linked salivary LELC from Asian patients in some studies. We know that different strains of EBV could be involved in the pathogenesis of salivary LELC in different geographic areas (Jen et al., 2003). Ampinder et al., (1994) indicated that EBV does not have a role in most of the tumor types, but the PCR method showed that EBV is strongly associated with lymphomas. Also, Hühns et al., (2015) indicated that infection with EBV does not play a major role in salivary gland neoplasm. One study in China (Wu et al., 2004a), showed that EBV plays an important role

in the pathogenesis of LEC of salivary glands in Sichuan Chinese. The EBV has been studied as an etiologic agent in adult salivary gland tumors and was demonstrated that EBV infection in LELC of the salivary gland in certain ethnic groups with a striking racial and geographic predilection affecting the Greenland Eskimos, Alaskan natives, and Asian patients (Hamilton-Dutoit et al., 1991; Nagao et al., 1996; Sheen et al., 1997). The EBV infection does not appear to play a major role in the pathogenesis of pediatric salivary gland tumors (Venkateswaran et al., 2000). The results of two studies reported that that EBV infection could have some relationship with the genesis of malignant lymphoepithelial lesions (Lanier et al., 1991; Lin et al., 1997). Two studies (Ioachim et al., 1998; Nadal et al., 1994) reported that non-Hodgkin lymphoma and precursor lymphoproliferative lesions of the salivary glands in immunocompromised individuals also have a strong association with EBV infection. Therefore, the racial/genetic, environmental or geographic factors may impact on the incidence of EBV in malignant salivary tumors, especially undifferentiated carcinomas.

Limitations

1) The number of patients in most studies was low. 2) The method of detection of EBV was different in the studies. 3) The tumor type and number of patients for each tumor type were different. 4) The heterogeneity between the studies was high.

In conclusions, the incidence of EBV infection in Asian patients with malignant salivary gland tumors was more than European and American patients and the higher presence of EBV infection in LEC cases implies that EBV may be a major factor in the etiology or pathogenesis of LEC and also genetic, environmental or geographic factors may be involved in the etiology or pathogenesis.

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