Association between Human papillomavirus and oral cancer in Iranian clinical samples: a meta- analysis review

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Abstract

Background: Oral squamous cell carcinoma (OSCC) is one of the most common malignancies and is a serious problem worldwide. The role of HPV in oral cavity squamous cell carcinoma has beenstudied in several researches.

Objective: The aim of the present review and meta-analysis was to investigate the relation between human papillomavirus (HPV) and oral cancer.

Study design: Relevant studies were found using online international databases and suitable studies were selected and assessed by two independent researchers. The quality of all papers were determined by a checklist. Heterogeneity assay among the primary studies was evaluated by Cochran's Q test and I2 index. The statistical analyses were done using Stata SE, V.11 software. Trim and Fill method was applied to confirm the validity of the results.

Results: This meta- analysis consists of 8 primary studies on the incidence of HPV infection in Iranian patients with oral diseases. The odds ratio between HPV infection and risk of oral cancer was 4.00 (95%CI: 2.31, 6.93).

Conclusion: This meta- analysis showed associations between prevalence of HPV infection and oral cancer among Iranian patients. The chance of developing oral cancer among HPV positive patients was higher than that in HPV negative patients.

Introduction

Oral squamous cell carcinoma (OSCC) is among the most common cancers and is a serious problem that causes 2 -3% of all malignancies [1, 2]. Oral disease generally involves cancers of lip, buccal mucosa, tongue, gingiva, floor of the mouth, soft palate, and hard palate and their incidence and mortality are growing in many regions around the world[1, 3] [4]. Squamous cell cancers of head-and-neck occur in the oral cavity, nasopharynx, larynx, oropharynx, and hypopharynx. The mortality and morbidity rates of head and neck squamous cell cancer vary around the globe but they reported to be the highest in South-East Asia and eastern Europe[5].

Human papillomaviruses (HPV) belong to papillomaviridae family [6]. Papillomaviruses (Pvs) comprise a group of DNA viruses that cause warts and condylomas. The virion particles of HPV consist of a double-stranded circular DNA (dsDNA) with 8,000 bp in size, and approximately 55 nm in diameter. The genome of HPV structure is composed of early genes (E) and late genes (L) which encode E1 to E7 proteins and L1, L2 proteins, respectively[7]. The L1 and L2 proteins form the viral capsid and E1 to E7 proteins are necessary for viral replication, virion synthesis, release, and also cell transformation[8]. So far, more than 200 different types of HPV have been recognized. HPV was first hypothesized as a risk factor for oral cancer in 1983[9]. HPV types that infect the mucusa are divided into two categories based on their potantial to induce malignancy: low-risk (LR-HPV) genotypes, including 6 and 11 that were detected in genital warts and high-risk (HR-HPV) such as 16 and 18 leading to cervical dysplasia which can also cause cervical cancer [10, 11]. In investigations on the role of HPV in particular subgroups in oral cavity cancer HPV16 was detected as the most frequent type in head and neck cancer [3, 12].

Evidence suggests that some behaviors such as the use of alcohol and marijuana alter antitumor immunity, and play a role in shifting HPV infection to HPV-related malignancies [13]. Among young people with multiple sexual

partners, oral sex (genital or anal) may help the virus reach the oral cavity and cause neoplasia in the oropharyngeal area [14].

There are different results on the associations between oral cancer and HPV. So, systematic review and meta-analysis methods can evaluate the quality of studies and solve this problem[15]. In this article, we will investigated the relationship between HPV and oral cancer based on studies extracted from electronic databases.

Materials And Methods

2.1 Search strategy

Two independent researchers searched online international databases, including Science direct, ISI, Pubmed, Scopus, Embase, and Google scholar, to determine relevant studies published between 2000 and Jan 2020. Appropriate keywords were used: “Human papilloma virus”, “Oral cancer”, “Iran”, and “Oral squamous cell carcinoma” which were combined with and/or/not. In addition, to improve the search sensitivity, we examined the references of these studies. Two other researchers assessed the search approach at random and confirmed that all appropriate studies had been detected. Moreover, additional efforts have been made to identify unpublished studies.

2.2 Study selection

During the advanced search, full texts or abstracts of all articles were reviewed. First, duplicate papers were excluded from the study. Then, irrelevant papers were deleted after analyzing the titles, abstracts, and full texts.

2.3 Quality assessment

In order to assess the quality of the studies the STROBE statement was used. The statement is a checklist of 22 items covering all components of the methodology, including sample size, type of study, methods and instruments for data collection, variables, aims, study objectives, study population, results presentation, and statistical analysis. In current study, the lowest and highest scores were 0 and 44, respectively. The studies were divided into three groups, based on the quality analysis: low quality (< 15.5), average quality (15.5- 29.5), and high quality (30-44).

2.4 Inclusion criteria

All papers that passed the above assessment phases for high quality scores were selected if meeting the following conditions: 1) Case- control studies published in English and 2) Case-control studies on the prevalence of HPV infection in patients with oral cancer.

2.5 Exclusion criteria

The following studies have been ruled out: 1) Case reports or case series. 2) Articles with no access to the full-text. 3) Duplicated studies. 4) Conference abstracts with no full-text publication available. 5) Studies published in languages other than English. 6) Studies with low and average quality scores.

2.6 Data extraction

After selection of suitable studies, the following data were extracted: name of authors, year of publication, place where the study was conducted, study size, number of cases and controls, source of samples, total infection prevalence among oral cancer patients, and type of HPV.

2.7 Statistical analysis

In this study, the degree of heterogeneity in studies results was measured using Cochran's Q test and I2 index. The odds ratio of the oral cancer was estimated based on a random-effect model. Also, sensitivity analysis was used for detection of heterogeneity. We also designed forest plots for estimation of odds ratio of oral cancer according to the results of primary studies with 95% confidence intervals (crossed lines). Each box in a forest plot indicated the weight of the study. For measuring the publication bias, the Funnel plot was used by subjective judgment in each study. In this study Trim and Fill method was used to confirm the validity and reliability of the results. All statistical analyses were performed in Stata SE, V.11 software.

Results

In current study, 4927 articles were detected at the starting process. The number of studies were reduced to 308 following limitation of the search strategy and exclusion of duplicates. In next step, 153 irrelevant studies were excluded after reviewing the titles and abstracts, and 147 documents were removed after reviewing the full texts. Ultimately, the meta-analysis included 8 qualifying studies (Fig. 1). Interestingly, no cohort research was established regarding the subject of the study. Accordingly, this analysis focused on case-control studies, which have recruited 879 people, of whom 487 had oral cancer. All case-control studies reviewed in this paper had reported higher rates of HPV in patients with oral cancer than controls (Table 1).

In this case control study the prevalence of HPV infection was more common in cases than controls (Table 1).Heterogeneity was not observed in this meta-analysis (Q=4.69, P=0.697; I2=0.0%) and developing of oral cancer among people with and without HPV infection using random and fixed models were estimated 4.00 (95%CI: 2.31–6.93) (Fig. 2).

In addition, sensitivity analysis was carried out to determine the reliability and stability of this meta-analysis. According to Fig. 3 there was no significant difference between these studies. The funnel plots in Fig.4 ((β=1.07, P=0.076)) confirmed significant publication bias among eight studies.

Trim and fill analysis was performed to evaluate the number of missing studies, by which three articles were found. According to the missing studies and eight primary studies, the odds ratio of oral cancer was 3.34 (95%CI: 1.98-5.63), indicating no significant difference between final studies included in the meta-analysis (Fig. 5).

Discussion

The present study showed that among 487 patients with oral cancer, 110 were positive for HPV infection. The odds ratio for developing oral cancer between people with and without HPV infection was 4.00 (95%CI: 2.31–6.93).

The prevalence of HR-HPV in oral cavity cancers vary across different regions. High rates of HPV positivity among patients with oral cancer were detected in Asia (33.77%) followed by America and Europe (19.65%and 16.19%, respectively and the lowest prevalence was reported in Australia (6.84%)[16]. Prevalence of HPV among patients

with OSCC is seen in various geographic locations. As reported, the prevalence of HPV in Asian countries, including India, Japan, China, Taiwan, and Iran, are 36.6%, 36%, 23.5%, 19.7%, and 19.2%, respectively. In America, the infection rate of HPV is detected from 14.8% in the United States to 23.9% in Colombia Mexico. Also in Europe, HPV has the highest incidence rate in Hungary (47.7%). Erythroplakia, leucoplakia, and oral submucous fibrosis (OSMF) are the most common premalignant lesions in Asian countries and 3–8.1% of premalignant oral lesions are reported to transform to oral cancer [17]. The incidence of HPV among oral cancer patients in Asia indicates that HPV infection combined with other cofactors is a significant risk factor for increasing rate of oral cancer[16].

Zarei et al. reported that the rate of HPV among OSCC patients was 60% [18]. In a case-control study in Shiraz (South-central Iran), the prevalence of HPV was 14% among 50 cases and no one in the control group was positive for HPV [19]. Other studies suggested that the High and low prevalence of HPV infection was seen among SCC patients in Sari (North of Iran) and Ahvaz (south east Iran) (13.25% and 3.9%, respectively) [2] [20]. On the other hand, in other research studies HPV DNA was not detected among patients [21].

Differences between these results may have been associated with small sample sizes and low levels of sensitivity of the assays [18]. In almost all studies reviewed here, HPV DNA sequencing had been detected by PCR specific primers. The present study showed that the prevalence of HPV-16 infection in OSSC samples was higher than other types. This is consistent with a study in Australian patients, that observed the significant role of HPV-16 in development of OSCC [22]. Similarly, a study done by PCR among 36 Korean patients with early oral tongue SCC and 25 normal tongue mucosa showed that the prevalence of HPV was 36% and 4%, respectively. In these cases, the most prevalent genotypes were HPV-16 (85%) [23]. Likewise, Villiers et al. found similar results [24]. On the other hand, a research in Chinese patients with tonsillectomy and SCC, HPV-16 and 18 were not found to be associated with oral HPV[25] [26]. According to current findings, HR-HPV infection plays a significant role in oral cavity carcinogenesis and is highly linked with increased risk of oral cancer among Iranian patients.

There are some limitations in our study, including the small number of participants in some groups. Also, the relation between specific genotypes of HPV and oral cancer was not investigated.

Suggestion

Further research with large sample size using more developed techniques for HPV genotyping are needed to clarify the role of HPV in the development of odontogenic lesions and tumors. Cohort studies on HPV in OSCC region could be of great benefit in determining the HPV persistence in normal cases and patients. Also, knowledge about the etiologic factors of odontogenic cysts could provide new approaches in preventing oral cancers and treatment of precancerous lesions.

Declarations

Competing interests

Author declares that no conflict of interest.

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Table

Table 1. Primary studies (case-control) included in the meta-analysis

nce	First author	Publication year	Publication language	Case (N)		Control (N)		Type of HPV		Source of sample	OR (95%)
				Event	Total	Event	Total	Case (%)	Control (%)		
	Ashraf	2017	English	7	50	0	50	Not detected	Not detected	SCC	17.41 (0.97, 313.73)
	SahebJamee	2009	English	10	22	5	20	6,11(30) 6 (60) 18(10)	6,11(20) 16(80)	SCC	2.50 (0.67, 9.31)
	Saghravanian	2015	English	18	155	0	18	6,11 (83.33) 16,18 (16.66)	Not detected	SCC, VCs, LPs	4.98 (0.29, 86.12)
	Rahbarnia	2019	English	3	30	0	30	Not detected	Not detected	OSCC	7.76 (0.38, 157.14)
	Mokhtari-Azad	2006	English	32	100	5	50	6 (31.6) 11 (12.5) 16 (12.5) 31 (3.1) 6,16(6.3)	Not detected	ameloblastoma	4.24 (1.53, 11.69)
	Tabatabai	2015	English	17	39	0	27	16,18(12.8) 16 (30.7)	Not detected	OSCC	42.78 (2.44, 751.32)
	Khodayari Namin	2003	English	20	50	9	50	6(40)	Not detected	ameloblastoma	3.04 (1.21, 7.60)
	Saghravanian	2011	English	3	41	0	18	16,18(7.3)	Not detected	LPs, VCs	3.36 (0.17, 68.56)
d estimate (random model)				110	487	19	263				4.00 (2.31, 6.93)

Figures

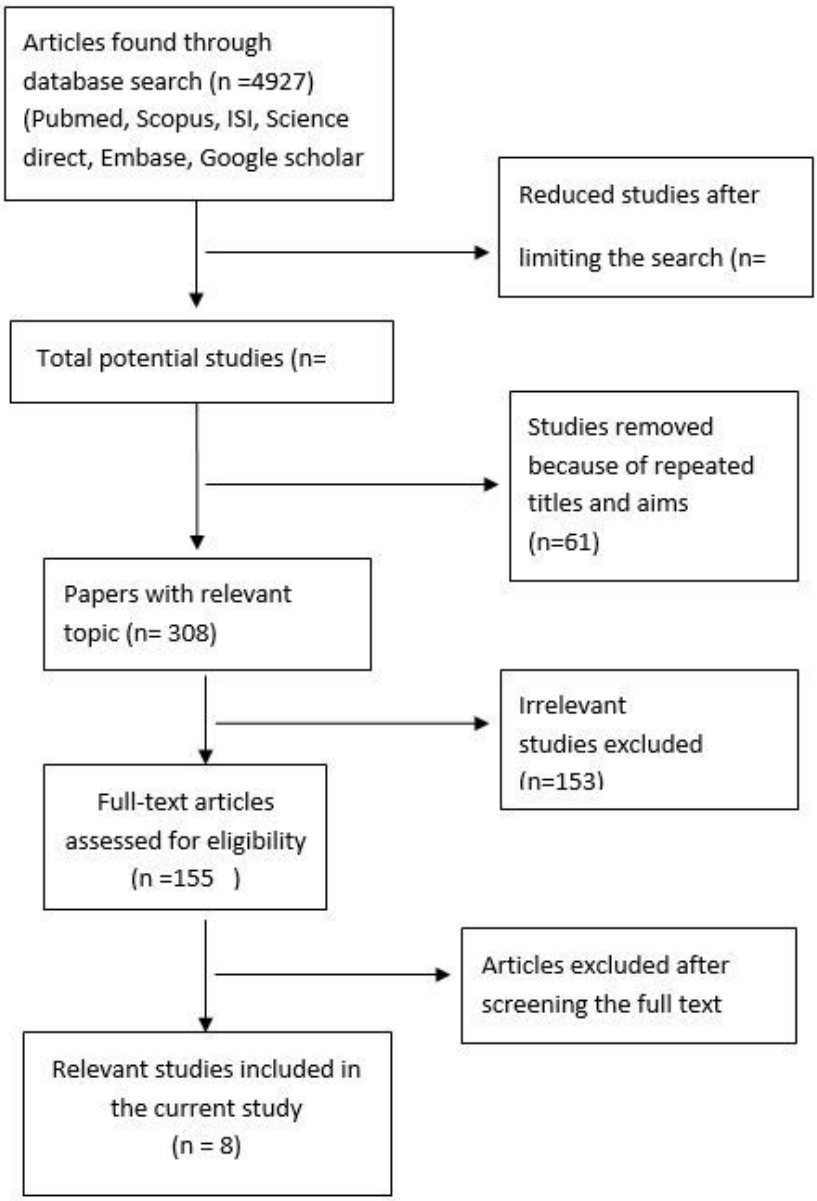

Figure 1

Literature search and review flowchart for selection of primary studies

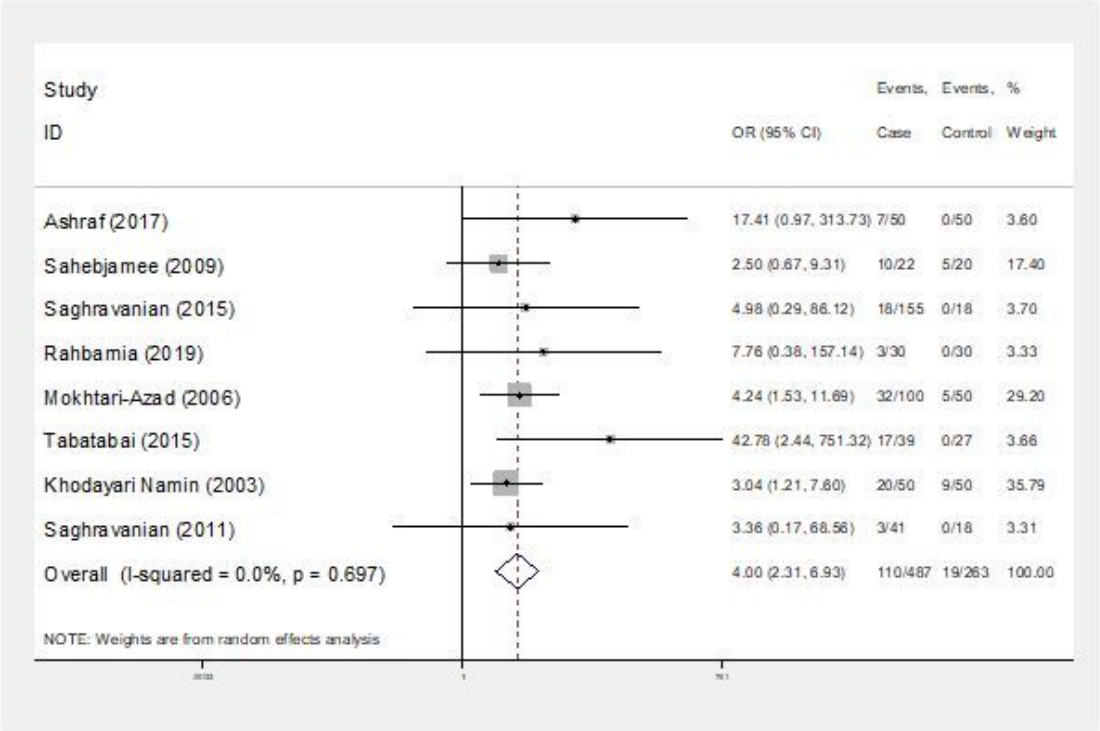

Figure 2

Forest plot. Odds ratio of oral cancer according to the results of primary studies and its overall estimation

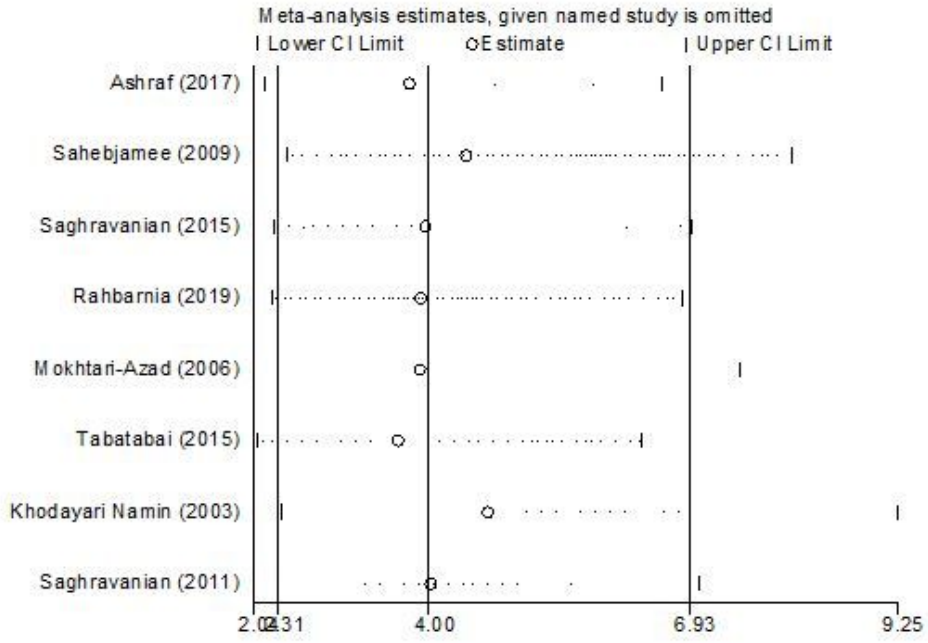

Figure 3

Sensitivity analysis of the studies included in this meta-analysis.

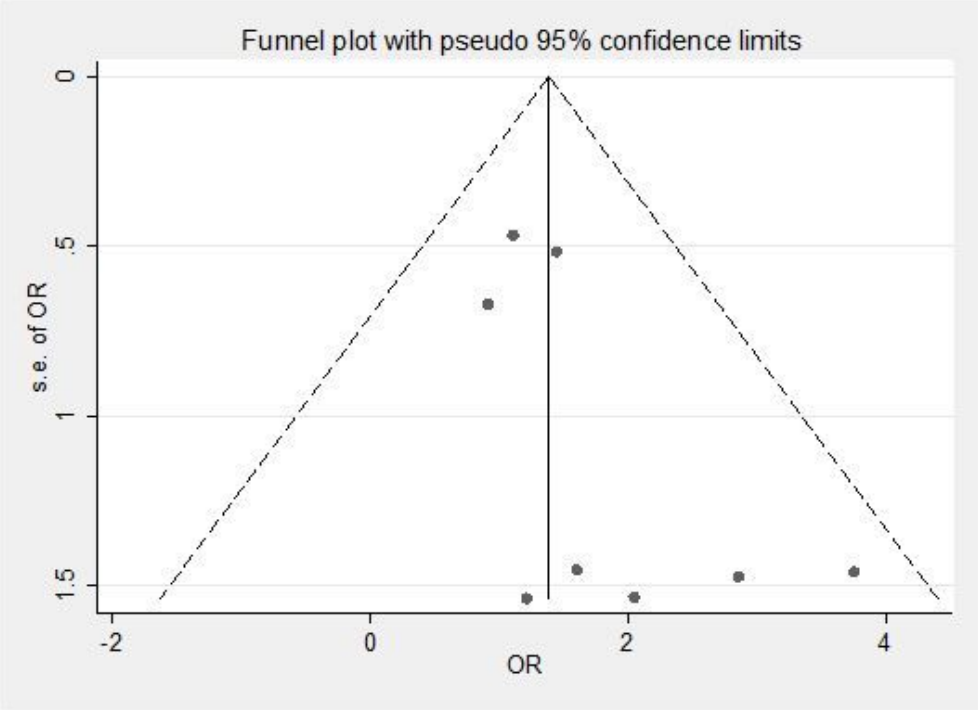

Figure 4

Publishing bias based on Funnel plot

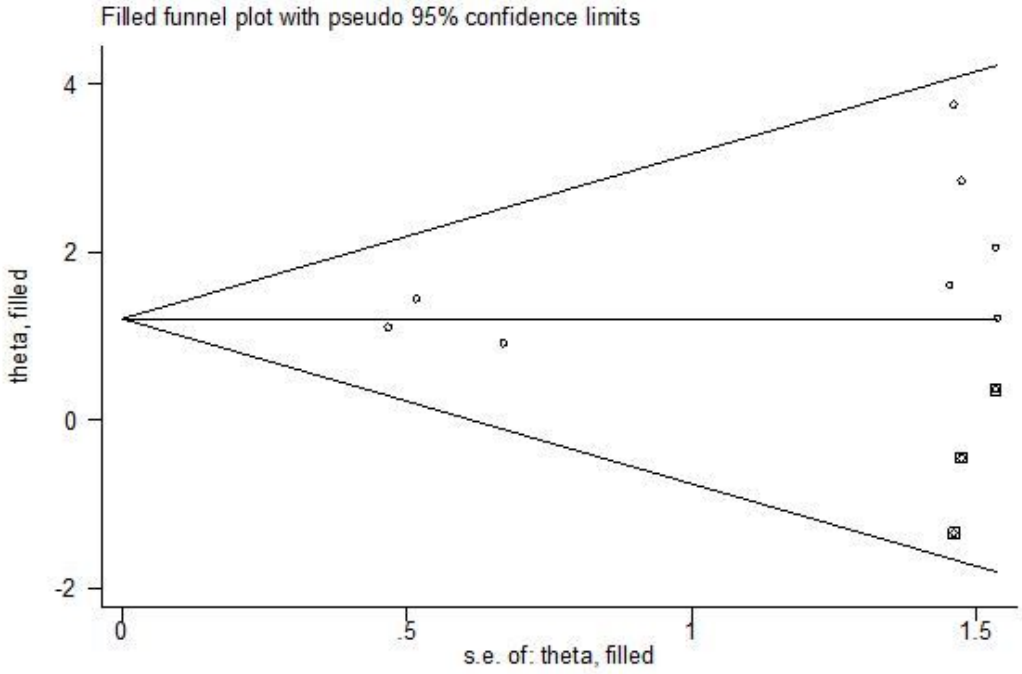

Figure 5

Trim and Fill method analysis for missing studies