JBUON 2020; 25(2): 1107-1115
ISSN: 1107-0625, online ISSN: 2241-6293 • www.jbuon.com
Email: editorial_office@jbuon.com

ORIGINAL ARTICLE

Do smoking and human papilloma virus have a synergistic role in the development of head and neck cancer? A systematic review and meta-analysis

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Summary

Purpose: *Head and neck squamous cell carcinoma (HNSCC), arising from the squamous epithelium, is the most common head and neck cancer (HNC). Smoking and alcohol are well known risk factors for HNSCC, while some high-risk human papilloma virus (HPV) subtypes were specifically identified as a high-risk factors for developing oropharyngeal squamous cell carcinoma (OPSCC). In this study, we have conducted a systematic review and meta-analysis in order to investigate the possible synergistic role of smoking and HPV in the development of HNSCC.*

Methods: *We conducted a systematic search in two online databases PubMed and Cochrane Library, searching for studies published between 2010-2018. Sixteen studies met the inclusion criteria; a total of 2161 patients were included, comprising 1470 HPV-negative and 691 HPV-positive, respectively.*

Results: *The number of smokers between HPV-positive HNSCC patients (group A) and HPV-negative HNSCC patients (group B) was compared. We have found that smokers in HPV-positive group were statistically significantly less than smokers in HPV-negative group (OR=0.33 with 95% CI 0.18, 0.61). The test for overall effect was Z =3.61 (p=0.0003).*

Conclusion: *Smoking is less common in HPV positive group than in HPV negative group, and so probably smoking does not play a major role in the pathogenesis of HPV-positive HNSCC as in the pathogenesis of HPV-negative HNSCC.*

Key words: *human papilloma virus, head and neck squamous cell carcinoma, oropharyngeal squamous cell carcinoma, smokers, smoking, HPV*

Introduction

Head and neck cancers (HNCs) are among the most prevalent malignancies, with a worldwide annual incidence around 500,000 new cases [1]. HNCs can arise from the oral cavity, the pharynx and the larynx [2]. The most common HNC is the squamous cell carcinoma (HNSCC), arising from the stratified squamous epithelium [3]. Smoking and alcohol consumption increase the risk of developing HNSCC [1]. Also, high-risk human papilloma virus (HPV) subtypes were identified as independent risk factors for developing oropharyngeal squamous cell carcinoma (OPSCC) [4-6]. The HPV-related OPSCC cancers differ from the HPV-unrelated OPSCC cancers at molecular level, while, the prognosis of HPV-related cancers is better [7,8]. So, the 8th edition of the American Joint Committee on Cancer (AJCC) has distinguished the staging algorithm for HPV-related OPSCC from the HPV-unrelated OPSCC [9].

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Received: 08/02/2019; Accepted: 20/01/2020

In 2012, Sinha et al published a review, where they investigated the possible effect of smoking in HPV infection and in HPV-related HNSCC [10]. In the retrieved articles, there had been a controversy if smoking is associated with HPV in the development of HNSCC; eight articles had not found any synergistic role, contrary to four articles, which reported an interaction between smoking and HPV. Even though the authors did not conduct a meta-analysis of the data retrieved, they concluded that probably smoking interacts with HPV infection in the development of HNSCC.

Our review and meta-analysis tried to enrich our knowledge about the association of smoking and HPV infection in HNSCC. It is important for the prevention to elucidate if there is a synergistic role of smoking and HPV infection in the development of HNC.

Methods

Databases search

We conducted a systematic search in two online databases PubMed and Cochrane Library, searching for studies published between 2010-2018 which investigated the possible effects of smoking in HPV-associated HNC. For our research we use the terms "Head and Neck Cancer", "smoking", "Human Papilloma Virus" and all possible combination of them. References cited in retrieved articles were also evaluated. Eligible articles had to: 1) include the necessary data of the smoking habit of HPV-positive and HPV-negative HNSCC; 2) use molecular assays for HPV detection (such as conventional PCR, Real Time PCR, *in situ hybridization* assay, immunotherapy); 3) have more than 50 participants/ patients in the HNSCC group; and 4) be written in English language. The evaluation of articles was performed based on their relevance of the title, abstract and manuscript review. In order to minimize the risk of bias, the evaluation of the articles was performed by two reviewers, independently.

Statistics

In order to determine possible association between smoking and HPV status, we have compared the number of current smokers between HPV-positive and HPV-negative group of patients with HNSCC. Many studies have categorized the participants in current and non-current smokers, but they did not clarify if the non-current smokers group included former smokers too. For the computation of the odds ratio we made 2 groups, current smokers and non-current smokers; the non-current smokers group included the non-current smokers group (in studies which categorized patients in current smokers/non-current smokers) and never smokers without former smokers (in studies which categorized patients in smokers/former smokers/never smokers). The computations were done by the program Review Manager (RevMan). Version 5.3. Copenhagen: The Nordic Cochrane Centre, the Cochrane Collaboration, 2014. The z-test depicted the statistical significance of method and values of $p<0.05$ were considered as statistically significant. Values of $I^2>75\%$ were regarded as high heterogeneity and random effects model was used in these cases.

Results

Articles selection

From the 2943 abstracts reviewed, 105 were relevant with the scopus of the present study. A total of 35 full-text articles were evaluated and among them 16 articles met the inclusion criteria. Reasons for the exclusion of 19 articles were that they did not use molecular assay for HPV detection, they did not present data concerning smoking and HPV infection status or they had categorized the smoking status according to pack-years. The main characteristics of the included studies are presented in the Table 1. Table 2 presents the smoking habits and the HPV status of participants in each of the studies included. We note that, in Table 2 there are 4 categories for smoking according to the retrieved data of the studies: current smokers (patients who were smoking), former smokers (patients who had quitted smoking), never smokers (patients who had never smoked) and non-current smokers (patients who were never smokers or former smokers).

Results of the studied articles

Ang et al demonstrated that 63.8% of patients with oropharyngeal cancer (OPC stage III/IV) were HPV-positive. HPV-positive OPC was more common in non-smokers than in smokers. The HPV-positive patients had better 3-year rate of overall survival ($p<0.001$). Smoking was also associated with survival and each pack-year statistically significantly increased the risk of death [11].

Maxwell et al examined the effect of the tobacco on recurrence among HPV-positive patients with OPC, and they found that the current smokers had statistically significantly higher risk of recurrence than the never smokers (hazard ratio 5.1, $p=0.03$). The prevalence of HPV was 82.3%. HPV-negative patients had significantly shorter time of recurrence ($p=0.02$) and shorter survival ($p<0.001$) compared to HPV-positive patients [12].

Smith et al had found that smoking increased the risk of HNSCC in both HPV-positive and HPV-negative patients. The prevalence of HPV-VLP (virus like particles) antibodies against 16,18,31 and 33 subtypes was 46% in patients and 40% in the control group. The risk of HNC in patients who were smoking, consumed alcohol or smoking and alcohol, showed little difference regarding the HPV VLP status. As far as HPV anti-VLP antibody status

Table 1. The main characteristics of the included studies

Authors	*Country*	*Date of data sampling*	*Cases of patients*	*Number of patients (vs controls)*	*Mean age of patients (vs controls)*	*Number of HPV tested patients (vs controls)*	*HPV detection method*	*HPV tested subtypes*
Ang et al; 2010	USA	2002 - 2005	Patients of the RTOG 0129 study with OPSCC III or IV	433	HPV+: 53.5y HPV-: 57.0y	323	HPV in situ hybridization	HR HPV: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68
Maxwell et al; 2010	USA	1999 - 2007	Patients with SCC of Oroharynx stage III or IV	124	57.2y	124	Quantitative real-time PCR	HR-HPV: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68 LR-HPV: 6, 11
Smith et al; 2010	USA	2001 - 2004	Adult patients with a primary HNC and control who were seeking routine medical care, routine screening or prescription	201 (vs 324)	59.6y (vs 59.6 y)	191 (vs 0)	PCR-amplified with MY09 and MY11 primers	N/A
Zhao et al; 2012	USA	2002 - 2006	Patients with HNSCC except nasopharynx	143	57y	143	HPV in situ hybridization	HR-HPV: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 66
Lako et al; 2012	Czech Republic	2000 - 2010	Patients diagnosed with OSC and OPSCC	92	Smokers: 58y Non- Smokers: 63y	92	PCR amplification with primers GP5+/ GP6+ and Linear HPV Genotyping Test	HR-HPV: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68 LR-HPV: 6, 11, 40, 42, 54, 55, 6, 62, 67, 69, 70, 71, 72, 81, 83, 84, CP6108 Probable HR-HPV: 26, 53, 73, 82, IS39
Hoffman et al; 2013	Germany	2004 - 2009	Patients with histo-pathologically confirmed HNSCC and controls with clinically normal mucosa of the aerodigestive tract and were treated for non-malignant diseases.	54 (vs 19)	58y (vs N/A)	54 (vs 0)	HPV type 3.5 LCD-Array and/ or multiplex HPV genotyping (MPG) assay	N/A
Gavid et al; 2013	France	2007- 2010	Adult patients with newly diagnosed HNSCC	200	61.3y	199	PCR with the HPV Consensus kit	HR-HPV: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68 LR-HPV: 6, 11, 40, 42, 43, 44, 54, 61, 62, 70, 71, 72, 81, 83, 84, 85, 89 Probable HR-HPV: 26, 53, 73, 82
Stephen et al; 2013	USA	1986- 2003	Patients with primary HNSCC	80	N/A	80	Real-Time quantitative PCR system	HR-HPV: 16

Continued on the next page

Authors	*Country*	*Date of data sampling*	*Cases of patients*	*Number of patients (vs controls)*	*Mean age of patients (vs controls)*	*Number of HPV tested patients (vs controls)*	*HPV detection method*	*HPV tested subtypes*
Hong et al; 2013	Australia	1987- 2006	Patients with SCC of the tonsil	411	HPV +: 55.0 y HPV -: 60.4 y	403	E6-based multiplex tandem PCR assay and semi quantitative immuno-histo-chemistry.	HR-HPV: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68 LR-HPV: 6, 11, 70 Probable HR-HPV: 26, 53, 73, 82
Melcane et al; 2014	France	2007 - 2009	Patients diagnosed or treated for an OPSCC	133	59y	133	TaqMan PCR	HR-HPV: 16, 18, 31
Saito et al; 2015	Japan	2004 - 2012	Patients diagnosed with OPSCC	150	64 y	150	In situ Hybridization method and/or Real-time PCR with TaqMan Probe	HR-HPV: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68
Shay et al; 2015	USA	2010- 2013	US veteran patients with HNSCC	150	64.6 y	134	DAKO panHPV immuno-histo-chemical staining detection	HR-HPV: 16, 18, 31, 33, 51, 52, 56, 58 LR-HPV: 6 11 42
Singh et al; 2015	India	2013- 2015	Clinically and histologically proven cases of OSCC	250	47.6y	250	Real time PCR, Conventional PCR, HPV 16/18 genotyping	HR-HPV: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68
Descamps et al; 2016	Belgium	N/A	Patients diagnosed with HNSCC who underwent concomitant chemo-radiotherapy	218	58y	213	TaqMan-based real-time PCR	N/A but 18 HPV types tested
Tsimplaki et al; 2017	Greece	2013- 2015	Adult patients with newly diagnosed histologically primary HNSCC, and adult control group being seen for benign conditions in the department of Oto-laryngology	172 (vs 91)	59.0y (vs 50.4y)	172 (vs 91)	PapilloCheck HPV genotyping assay	HR-HPV: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56,58, 59, 68, 73, 82 LR-HPV: 6, 11, 40, 42, 43, 44, 55, 70 Probable HR-HPV: 53, 66
Tsea et al; 2018	Greece	2010- 2014	Patients who had undergone surgery for HNSCC and control individuals with clinically normal mouth mucosa	90 (vs 206)	61y (vs N/A)	90 (vs 206)	Quantitative real-time PCR	HR-HPV: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68 LR-HPV: 6, 11

HNSCC: Head and Neck Squamous Cell Carcinoma, HNC: Head and Neck Cancer, OPSCC: Oropharyngeal Squamous Cell Carcinoma, OSCC: Oral Squamous Cell Carcinoma

is concerned, the patients with positive PCR for HPV16 and HPV18 were at greater risk for seropositivity (OR=4.4) [13].

Zhao et al investigated the correlation between p16 and survival in HNC. A proportion of 9.7% (14/143) of patients with HNC was HPV-positive. Oropharyngeal cancers and HPV-positive cancers had stronger p16 staining compared to other tumors. There was no significant difference in age, gender, smoking status, T stages and clinical stages between different staining groups. The survival rate was significantly different between staining groups. There was no significant difference in overall survival (OS) or progression-free survival (PFS) between the HPV-positive and HPV-negative group (p= 0.50 and 0.43, respectively) [14].

Lako et al have found that 15% of patients with OSCC and 80% with OPSCC were positive for HPV. The HPV-negative cancers were found more frequently in oral cavity (p<0.001), were more frequently associated with recurrence (p<0.05) and with tumor-related death (p=0.003). Smoking had no significant difference in HPV-negative and HPV-positive groups [15].

Hoffman et al investigated the role of secretory leukocyte protease inhibitor (SLPI) in HPV infection in HNC. HPV DNA was detected in 33.3% of HNSCC cases. SLPI expression showed an inverse

Table 2. HPV and smoking habits

Authors	*HPV status*	*Smoking habits*			
		*Non- current smoker***	*Current smoker*	*Former smoker*	*Never smoker*
Ang et al; 2010*	HPV+		24	110	59
	HPV-		32	54	14
Maxwell et al; 2010	HPV+		23	46	33
	HPV-		16	6	0
Smith et al; 2010*	HPV+		42		9
	HPV-		96		43
Zhao et al; 2012*,**	HPV+	3	13		
	HPV-	9	110		
Lako et al; 2012**	HPV+	21	21		
	HPV-	25	25		
Hoffman et al; 2013*	HPV+		9		4
	HPV-		32		1
Gavid et al; 2013**	HPV+	8	15		
	HPV-	8	168		
Stephen et al; 2013*	HPV+		20	12	7
	HPV-		19	15	3
Hong et al; 2013	HPV+		56	76	53
	HPV-		144	65	9
Melcane et al; 2014	HPV+		19	28	40
	HPV-		26	17	3
Saito et al; 2015**	HPV+	19	32		
	HPV-	15	84		
Shay et al; 2015*	HPV+		32	22	14
	HPV-		34	24	7
Singh et al; 2015**	HPV +	11	12		
	HPV -	117	110		
Descamps et al; 2016*	HPV+		26	11	6
	HPV-		100	51	18
Tsimplaki et al; 2017**	HPV+	12	10		
	HPV-	57	93		
Tsea et al; 2018**	HPV+	17	21		
	HPV-	22	30		

*Some demographic data are missing. ** In these studies it was not clear if non-current smokers were former smokers or non-ever smokers.

correlation with HPV status; low SLPI expression was associated with HPV presence, while high SLPI expression seemed to prevent HPV infection. Also, elevated SLPI expression correlated with fewer metastases and with smoking [16].

Gavid et al stated that the prevalence of HPV infection in the biopsy samples of HNSCC was 11.5%, and was statistically significantly higher in OSCC than in other anatomical sites (91.3% vs 27.3%, p<0.0001) and in non-smoker patients (65.2% vs 95.4%, p<0.0001). HPV DNA was not detected in any laryngeal or hypopharyngeal carcinoma. The most common HPV subtype was HPV-16. The 3-year OS rate for HPV-infected patients was 67% versus 39.9% for non-HPV-infected patients [17].

Stephen et al investigated the significance of p16 among HPV-positive and HPV-negative HNSCC. The p16 expression was different across sites (p<0.001) and was more frequent in oropharynx (OP) than non-OP sites (p<0.0001). The p16 was significantly associated with marital status and smoking. There was no association of HPV-16 with gender, age, marital status and smoking. The p16-positive patients had better OS for all sites than p16-negative patients. HPV 16-positive and p16-positive patients had the best survival compared to the HPV 16-negative and p16-positive, while HPV 16-positive/p16-negative and HPV16-negative/p16-negative had the worst survival [18].

Hong et al found that the prevalence of HPV in tonsillar squamous cell carcinoma was 45.9%, with HPV-16 being the most prevalent subtype (94.6% of the HPV-positive cases). The HPV-positive patients were significantly younger, more likely to have lower T classification, higher N classification and higher grade cancer; there was significantly difference in smoking habits (more smokers in HPV-group) but not in alcohol intake between HPV-negative and HPV-positive groups. The effect of smoking on loco-regional recurrence and survival outcomes was not statistically significant, and there was not significant evidence that the effect of smoking status on these outcomes was modified by HPV status; smoking decreased the OS regardless of HPV status [19].

Melcane et al stated that the prevalence of HPV in patients with OSCC was 65% (HPV-16 was found in 89% of the HPV-positive patients), while the percentage of p16 was 50%. Both p16 and HPV-positivity were significantly related to the absence of smoking and alcohol, lymphoid localization and poor tumor differentiation. Patients with p16-positive/HPV 16-positive had the best survival; patients with p16-negative/HPV-negative had worse overall survival [20].

Saito et al studied the expression of p16 in patients with OPC. In oropharyngeal carcinoma the prevalence of HPV was 34% and the percentage of p16-positive was 39%. Low tobacco/alcohol consumption, and tonsil/base of tongue localization were associated with patients who were HPV-positive/p16 positive. The OS of patients with p16-positive/HPV-positive and p16-positive/HPV-negative was statistically significantly better compared to patients with p16-negative/HPV-negative. The p16 expression was an independent factor regarding the prognosis of patients. Smoking was statistically significantly more common in HPV-negative patients (p=0.002) [21].

Shay et al found that the prevalence of HPV in US veterans with HNSCC was 46%. Tumor location differed significantly between HPV-positive and HPV-negative groups, with a predominance of HPV positivity in the oropharynx (75% HPV-positive, p<0.001). The HPV-positive patients had better prognosis than HPV-negative patients. Smoking and alcohol did not influence significantly the mortality rate of HPV-positive or HPV-negative patients. Smoking did not differ significantly between HPV-positive and -negative groups [22].

Singh et al stated that HPV prevalence in the studied population of oral squamous cell carcinoma (OSCC) patients was 9.2%, with a predominance of HPV-16 (30.4% among all the HPV-positive cases). In HPV-positive cases, 91.3% had taken tobacco in any form. The survival of HPV-positive patients was better, but not statistically significant than that of HPV-negative patients. Lastly, p16 and smoking were not associated with the presence of HPV (p=0.54 and p=0.73, respectively) [23].

Descamps et al had studied risk factors associated with survival of advanced HNSCC patients. HPV prevalence in their study group was 20%. HPV status did not play a significant role in response to therapy; patients who consumed tobacco and alcohol had a statistically significant worse prognosis than those who did not (p=0.03 and p=0.003, respectively). HPV status had not a significant relation with gender, smoking status and alcohol status [24].

Tsimplaki et al found that the overall HPV prevalence in patients with HNSCC was 12.8% versus 2.2% in the control group. High-risk HPV infection increased the risk of oropharyngeal cancer (OR=20.3) and laryngeal cancer (OR=22.8), but not the risk of oral cancer. Also, HPV infection was associated with poorly differentiated tumors (OR=2.8), but was not associated with demographic characteristics (age, gender, tumor grade, tobacco or alcohol) [25].

In our previous study, we have studied the HPV epidemiology in HNSCC in Greece. HPV prevalence

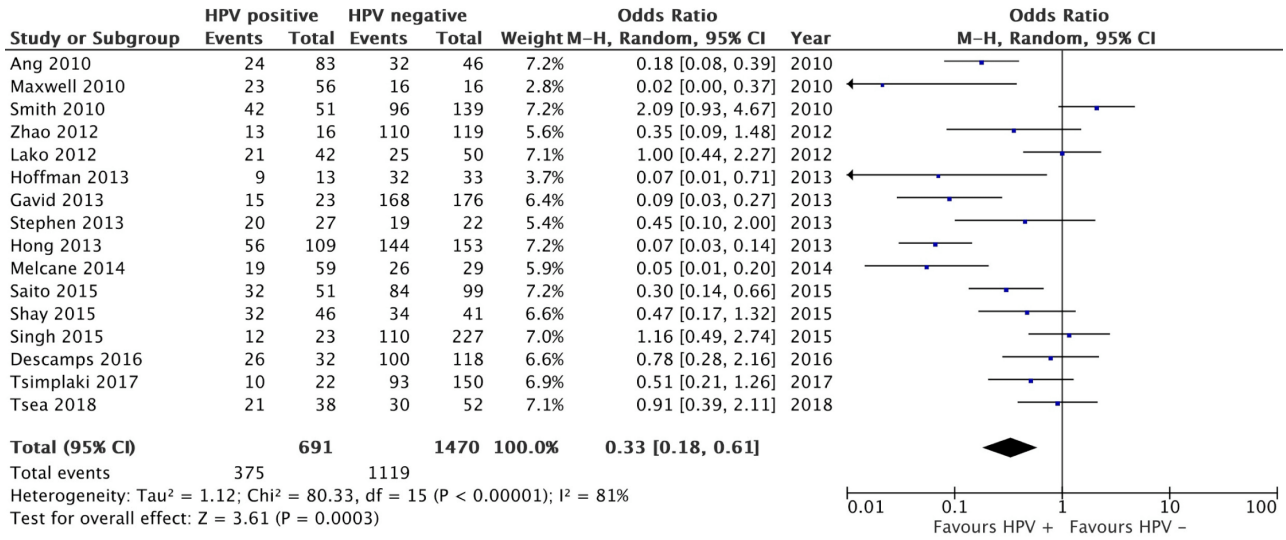

Figure 1. Results of metanalysis, obtained from Review Manager (RevMan).

was detected in 42.2% of samples, with HPV-16 being the most prevalent subtype. HPV-positive patients were more likely to have HNSCC (OR 6.8) compared to HPV-negative patients. Smoking status and alcohol use did not differ significantly between HPV-positive and HPV-negative patients [26].

Results of meta-analysis

Figure 1 presents the results of our meta-analysis. We have compared the number of smokers between HPV positive HNSCC patients (group A) and HPV negative HNSCC patients (group B). The total number of patients included was 2161. We have found that smokers in HPV-positive group were statistically significantly less than smokers in HPV-negative group (OR=0.33 with 95% CI 0.18, 0.61). The test for overall effect was Z=3.61 (p=0.0003). Analyses were performed with the randomized effect model (Heterogeneity x^2=80.33, df=15, I^2=81%).

Discussion

HNSCC is a group of cancers derived from the nasal cavity, paranasal sinuses, oral cavity, salivary glands, pharynx, and larynx. HPV infection is associated with OPC, while the association of HPV infection with the other types of HNSCC remains still unclear [27]. The HPV-induced OPC is a distinctive category of HNSCC; HPV-induced OPC seems to have better prognosis and better response to treatment compared to HPV-negative OPC [28].

The most widely used methods for HPV detection are molecular assays such as HPV DNA PCR and HPV DNA *in situ* hybridization (ISH). Given that this diagnostic approach is expensive and not widely accessible, several studies have evaluated the p16 immunochemistry (p16 ICH) as a surrogate marker for HPV-positivity and as an alternative test to PCR. In addition, the molecular methods cannot distinguish the HNSCC cases that are HPV-driven (HPV is the causative factor of carcinogenesis) from the HNSCC cases with a bystander HPV infection (HPV is not the causative factor but a concurrent infection).

Boscolo et al stated that neither HPV DNA PCR nor ISH nor p16 ICH alone can distinguish the causative HPV infection from the bystander HPV infection; a combination of molecular assays (PCR or ISH) with a p16 ICH in formalin-fixed paraffin-embedded (FFPE) tissues was considered as a reliable algorithm [29]. Also, Alberts et al stated that in a group of HNSCC patients, the patients which were HPV-positive/p16-positive had the best 5-year OS, the patients HPV-positive/p16-negative and HPV-negative/p16-positive had intermediate OS and finally the patients HPV-negative/p16- negative had the worse OS [30]. So, probably the FFPE tissues should be validated both for p16 and HPV status.

The pathogenesis of HPV-induced carcinogenesis is regulated mainly by E6 and E7 oncogenic proteins, which immortalize the keratinocytes. HPV E6 oncoprotein degrades p53, resulting in uncontrolled proliferation of the cells. E7 oncoprotein degrades tumor suppressor Rb protein, which result in p16 upregulation. E6 and E7 dysregulate the cell cycle and lead to the transformation of normal cells into carcinoma. E6 and E7 impair interferon type I (IFN) and IFN-responsive genes, reducing the host immune response [28]. The HPV-negative HNSCC has mutation in the TP53 gene, which also inactivates the p53 and decreases the p16 tumor suppressor and the growth-suppressive pRb [29].

Smoking causes cellular alterations in oral cavity, increasing oral HPV infections [31], while it is associated with persistence of oral HPV infection [29]. Maxwell et al have shown that HPV-positive HNSCC patients who were smoking had poorer disease-specific survival rates and more frequent disease recurrences compared to non-smokers HPV-positive patients [12].

In our study, we tried to investigate a possible synergistic role between smoking and HPV infection in the development of HNSCC. So we have evaluated the number of smokers in HPV-positive group of HNSCC patients compared to the number of smokers patients in HPV-negative group. What we found was that smokers-patients in the HPV-positive group were significantly less than smokers in the HPV-negative group. Even though we have not studied if smoking and HPV infection collaborate synergically in increasing the risk of HNSCC, the findings that in HPV-positive group smokers were less indicates that smoking has not so important role in the pathogenesis of HPV-positive HNSCC as in the pathogenesis of HPV-negative HNSCC.

The major limitation of our study was that in our meta-analysis we only investigated the smoking status as a nominal variable (current smokers vs non-smokers) rather than as a ordinal variable (groups of certain pack-years). Some studies categorized the patients in 2 categories (smokers vs non-smokers), and so, there was no information if the non-smokers group consisted of never smokers and former smokers or only of never smokers. Also, we have included only studies that used PCR or ISH as a method for HPV detection; but among the studies different PCR assays were used, and different types of HPV were assessed. Finally, in our meta-analysis, we have studied the effect of smoking in HPV infection generally in HNSCC. Although HPV status is mainly associated with OPC, we have not investigated the possible association of smoking in HPV infection in this specific site of HNSCC.

Conclusion

In our study we have conducted a meta-analysis in order to compare the number of smokers HPV-positive patients with HNSCC to the number of smokers HPV-negative patients with HNSCC. We have found that smoking is statistically significantly more common in HPV-negative than in HPV-positive group of HNSCC patients. More studies are needed in order to fully understand the pathophysiology of HNSCC, and the possible carcinogenetic pathways induced by HPV and smoking.

Conflict of interests

The authors declare no conflict of interests.

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