META ANALYSIS

High-Risk Human Papillomaviruses in Oral Squamous Cell Carcinoma (OSCC): A Meta-Analysis

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ABSTRACT

Background: The prevalence of high-risk Human Papillomaviruses (HPV) in cases of oral cavity squamous cell carcinoma (OSCC) varies widely. Therefore, the aim of this study was to determine the pooled prevalence of all high-risk HPV by meta-analysis with specific emphasis on HPV type 16/18.

Methods: The studies were retrieved from PubMed and MEDLINE to conduct a comprehensive literature review on HPV detection in OSCC. Search terms included, High-risk HPV, oral cancer, polymerase chain reaction (PCR), in situ hybridization (ISH). We reviewed 47 research studies systematically to report the prevalence of high-risk HPV infection in oral cancer. Included studies published from 1988 to 2018. The meta-analysis was carried out by using MedCalc software version 19.0.3.

Results: A meta-analysis was executed to calculate the pooled prevalence of High-risk HPV types, which revealed overall decreasing order frequency of high-risk HPV and high-risk type displaying the highest number of type16/18 HPV in the reported cases. As 30.71% [24.59 to 37.19 % confidence interval (CI) at 95%] and 28.88 % [22.62 to 35.57% confidence interval (CI) at 95%] followed by other high-risk HPV 3.59% [2.22 to 5.46%] respectively.

Conclusions: According to present meta-analysis, we conclude that 16/18 HPV displaying maximum infection rate as compared to other high-risk HPV type in OSCC cases.

Keywords: High-Risk HPV Detection; PCR; Oral Cancer; Meta-analysis.

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INTRODUCTION

The term "Oral cancer" includes neoplasms affecting pharyngeal regions, salivary glands and oral cavity. However, the term "Oral cancer" has a propensity to be used with Oral squamous cell carcinoma (OSCC), which implies the most common of all oral neoplasms. About 90% of all oral neoplasms are Oral squamous cell carcinoma (OSCC)[1]. This is the sixth most common cancer in the world[2,3]. It accounts for 2-4 % of all cancers globally, with major incidence in western countries[4-6].

With the available therapeutic approaches, there is no improvement in the morbidity and mortality rates of OSCC in the past 30 years[7]. Alcohol, tobacco and smoking are the major independent risk factors in the escalating prevalence of oral cancer; however, their action seems to be combined. The combinations of tobacco and alcohol consumption possess a synergistic effect on the development of oral cancers[8]. However, tobacco alone is one of the most important escapable risk factor that is responsible for one- fourth of cancer deaths worldwide[2,9]. Other risk factors that contribute to the progression of oral cancers include betel quid chewing, areca nut, narcotics and cannabis[10,11]. A part from these risk factors Human Papillomavirus (HPV) has also been implicated to positively associate with oral pre- cancer and cancerous lesions[12,13]. Syrjanen et al. first reported HPV involvement in oral and oropharyngeal carcinogenesis in 1983[1,4]. A sound upsurge of HPV incidence in oral cancer cases has been observed over the last few

decades. It has been positivity associated with OSCC prognosis and young age onset in several developed countries[14].

The human papillomavirus (HPV) belong to the family of DNA Papovaviridae. It consists of double-stranded DNA (approximately 8,000 base pairs long) which is enclosed in a protein capsid[13]. The HPV genome consists of a long non-coding region (LCR), six early and two late open reading frames (ORFs)[15]. Viral replication and transcription of early genes are controlled by the long non-coding region[13]. The two key viral proteins, E6 and E7 play an important role in the transformation and immortalization of the cell by inactivating p53 and Rb genes[16]. More than 200 HPV genotypes have been sequenced out of which 85 are well-characterized[16]. High-risk oncogenic types, HPV 16 and HPV [18] are more closely associated with oropharyngeal cancers[17,18].

In recent years, many researchers have focused on the relationship between HPV and OSCC. However, significant heterogeneity exists in the literature regarding OSCC and HPV frequency. The difference among geographical locations as well as HPV detection method could be the key contributors of the variation. Therefore, it is crucial to implement a meta-analysis to evaluate compressively the relationship between high risk HPV and OSCC. The HPV prevalence rate in oral cancer was found to be varied from 0% to 100% [6, 13, 32]. The main objective of this study was to determine the pooled prevalence of all high-risk HPV including type 16/18 HPV in OSCC patients by meta-analysis.

METHODS

Source of Data

The PubMed and MEDLINE, databases were used to conduct a comprehensive literature review on HPV detection in OSCC. English language studies were considered for literature search, which were published between 1988 and 2018. Search terms included, High-risk HPV, oral cancer, polymerase chain reaction (PCR), in situ hybridization (ISH). Where, 5 studies of ISH and 42 studies of PCR are included.

Results of Search Strategies

Out of 205 publications related to search strategy, those articles, which were in other language (n=18), head and neck cancer (n=36), citation do not relate with this study (n=52), unreliable detection methods (n =15), non-uniformity of data (n=35) were excluded. Based on the initial review, 47 studies that reported HPV prevalence in OSCC were included in this meta-analysis.

Statistical Analysis

The prevalence of high-risk HPV (16, 18, 31, 33, 35, 52 and 56) and 95% confidence intervals (CI) were calculated for each study. Forest plots were constructed to carry out meta-analysis by using MedCalc software version 19.0.3. Overall prevalence was defined as the number of OSCC samples that tested positive for high risk HPV divided by the total number of OSCC samples. We explored the heterogeneity between study-specific results using the chi-square-based Cochran's Q test. Estimates were obtained by random-effects models for overall high-risk HPV and HPV 16/18 type and the fixed-effects model for other high-risk HPV (31, 33, 35, 52 and 56).

RESULTS

Meta-analysis for pooled prevalence based on all high-risk HPV type

The 47 studies evaluated a total of 3775 OSCC cases. The number of cases varied from 13 to 254 (Table 1). The detection rate of high-risk HPV was different based on study and the method of detection. Included studies reported the prevalence rate of high-risk HPV types. On the basis of random effect model the prevalence of high-risk HPV types in OSCC was 30.71% [24.59 to 37.19% confidence interval (CI) at 95%]; the significant heterogeneity ($p<0.0001$) was found in the studies [$I2 = 94.46\%$ with 93.35 to 95.38% confidence interval (CI) at 95%].

Table 1: Prevalence of High-Risk HPV in Oral Cancer based on 47 studies.

Study	Sample size	Proportion (%)	95% CI	Weight (%)
Syrjanen et al.(1988)[40]	51	11.765	4.442 to 23.868	2.12
Chang et al.(1990)[41]	40	2.500	0.0633 to 13.159	2.07
Chang et al.(1990)[41]	40	27.500	14.601 to 43.888	2.07
Holladay and Gerald (1993)[42]	39	17.949	7.535 to 33.535	2.07
Brandwein et al.(1994)[43]	64	25.000	15.016 to 37.399	2.15
Van Rensburg et al.(1995)[45]	66	1.515	0.0384 to 8.155	2.16

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Shindoh et al.(1995) [44]	77	31.169	21.095 to 42.743	2.18
Balaram et al.(1995) [31]	91	41.758	31.501 to 52.567	2.20
Chiba et al(1996) [74]	38	21.053	9.554 to 37.319	2.06
Cruz et al.(1996) [46]	35	54.286	36.646 to 71.173	2.04
Wen et al.(1997) [47]	45	31.111	18.166 to 46.649	2.09
Premoli -De-Percoco et al.(1998) [48]	50	70.000	55.392 to 82.138	2.11
Schwartz et al.(1998) [49]	193	21.244	15.697 to 27.696	2.25
Pillai et al.(1999) [50]	61	27.869	17.147 to 40.829	2.15
Cao et al (2000) [52]	40	72.500	56.112 to 85.399	2.07
Patima et al. (2000) [53]	73	73.973	62.376 to 83.546	2.17
Gillison et al.(2000) [69]	84	11.905	5.859 to 20.805	2.19
Bouda et al.(2000) [51]	19	94.737	73.972 to 99.867	1.87
Premoli -De-Perco et al.(2001) [54]	50	60.000	45.179 to 73.592	2.11
Shima et al.(2000) [77]	44	20.455	9.804 to 35.305	2.09
Schwartz et al.(2001) [55]	254	15.748	11.495 to 20.821	2.27
Nagpal et al. (2002) [56]	110	33.636	24.908 to 43.271	2.22
Kumar et al. (2003) [58]	42	30.952	17.622 to 47.086	2.08
Sugiyama et al. (2003) [60]	86	34.884	24.919 to 45.923	2.19
Chang et al. (2003) [57]	103	49.515	39.514 to 59.544	2.21
Ritchie et al. (2003) [59]	141	14.894	9.462 to 21.861	2.24
Zhang et al. (2004) [64]	73	73.973	62.376 to 83.546	2.17
Correnti et al. (2004) [61]	16	50.000	24.651 to 75.349	1.81
Smith et al. (2004) [63]	106	9.434	4.617 to 16.666	2.21
Dahlgren et al. (2004) [62]	110	10.909	5.765 to 18.281	2.22
Ibieta et al.(2005) [35]	21	66.667	43.032 to 85.412	1.90
Boy et al.(2006) [65]	59	11.864	4.906 to 22.929	2.14
El -Mofty et al. (2006) [66]	94	34.043	24.581 to 44.541	2.20
Badaracco et al.(2006) [70]	60	13.333	5.936 to 24.592	2.14
Nemes et al.(2006) [67]	79	41.772	30.767 to 53.413	2.18
Sugiyama et al. (2007) [68]	27	37.037	19.401 to 57.632	1.98
Smith et al. (2008) [71]	108	24.074	16.368 to 33.251	2.21

Kong et al.(2009)[72]	13	7.692	0.195 to 36.030	1.73
Chaudhary et al.(2010)[37]	208	34.615	28.171 to 41.505	2.26
Attner et al.(2010)[73]	87	78.161	68.015 to 86.310	2.19
Gonzaiez-Ramirez I et al.(2013)[34]	80	5.000	1.379 to 12.310	2.18
Gan et al.(2014)[33]	200	19.500	14.249 to 25.679	2.26
Koukertsu A et al.(2016)[39]	24	54.167	32.821 to 74.447	1.94
Chen et al.(2016)[36]	178	3.371	1.247 to 7.192	2.25
Palve et al.(2018)[38]	106	33.019	24.190 to 42.824	2.21
Rubab Z et al. (2018)[75]	100	32.000	23.022 to 42.077	2.21
De Abreu PM (2018)[76]	90	3.333	0.693 to 9.434	2.20
Total (Random Effects)	**3775**	**30.713**	**24.593 to 37.195**	**100.00**

Test for heterogeneity

Q	830.0819
DF	46
Significance level	P < 0.0001
I2 (inconsistency)	94.46%
95% CI for I2	93.35 to 95.38

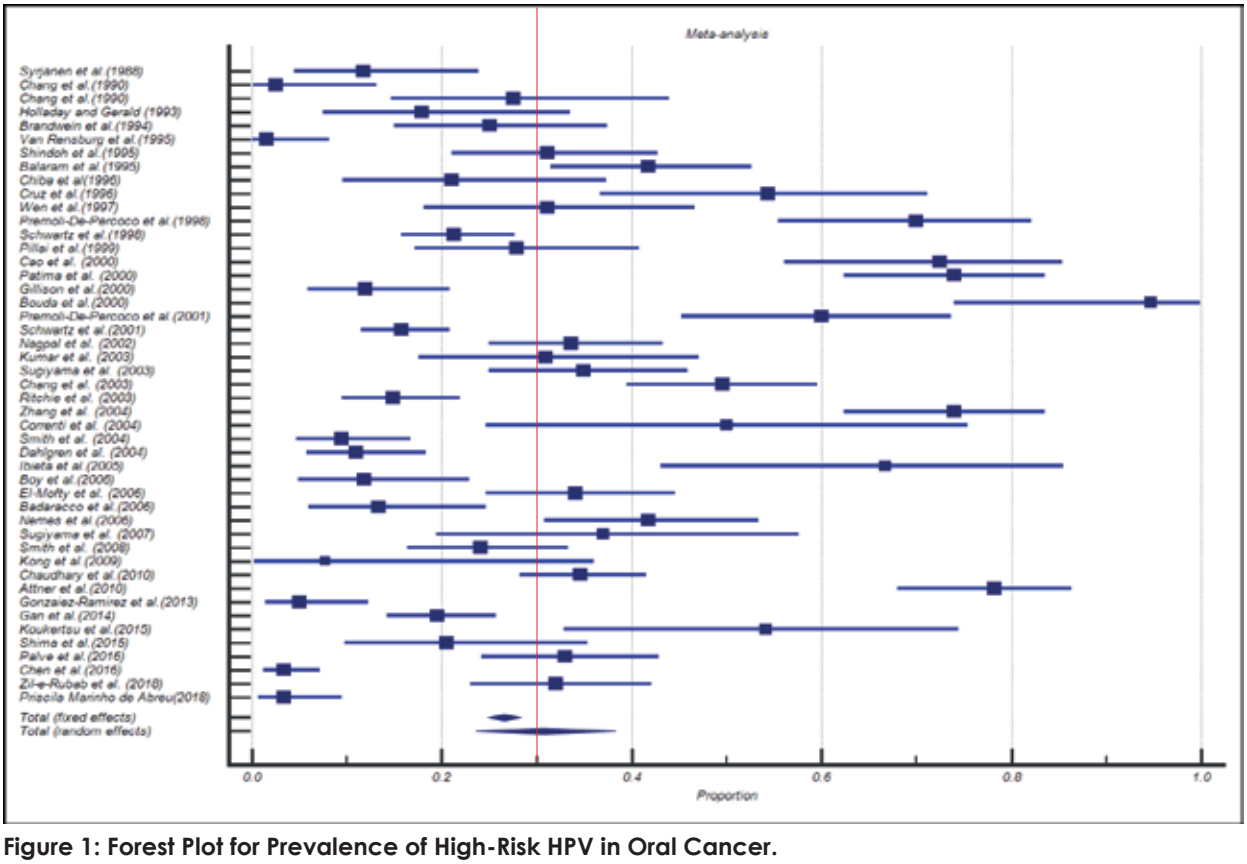

Figure 1: Forest Plot for Prevalence of High-Risk HPV in Oral Cancer.

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Meta-analysis for overall prevalence based on HPV 16/18 type

Of the 47 research studies, 38 studies included to calculate pooled prevalence of HPV- 16/18 in OSCC. The significant heterogeneity ($p<0.0001$) was found among the studies [I^2= 93.96% with 92.57 to 95.10% confidence interval (CI) at 95%]. Out of 3158 patients, 850 patients were positive for HPV-16/18. Proportion of positive cases for HPV 16/18 was also analyzed in the present meta-analysis. Based on random effect model the mean proportion of positive cases was 28.88% [22.62 to 35.57% confidence interval (CI) at 95%].

Table 2: Prevalence of HPV 16/18 in Oral Cancer based on 38 studies.

Study	Sample Size	Proportion (%)	95% CI	Weight (%)
Syrjanen et al.(1988)[40]	51	11.765	4.442 to 23.868	2.59
Chang et al.(1990)[41]	40	2.500	0.0633 to 13.159	2.53
Chang et al.(1990)[41]	40	27.500	14.601 to 43.888	2.53
Holladay and Gerald (1993) [42]	39	17.949	7.535 to 33.535	2.52
Brandwein et al.(1994)[43]	64	25.000	15.016 to 37.399	2.64
Van Rensburg et al.(1995)[45]	66	1.515	0.0384 to 8.155	2.65
Shindoh et al.(1995)[44]	77	31.169	21.095 to 42.743	2.68
Balaram et al.(1995)[31]	91	41.758	31.501 to 52.567	2.70
Cruz et al.(1996)[46]	35	54.286	36.646 to 71.173	2.49
Wen et al.(1997)[47]	45	31.111	18.166 to 46.649	2.56
Premoli -De-Percoco et al.(1998) [48]	50	70.000	55.392 to 82.138	2.59
Schwartz et al.(1998)[49]	193	21.244	15.697 to 27.696	2.78
Pillai et al.(1999) [50]	61	27.869	17.147 to 40.829	2.63
Cao et al. (2000)[52]	40	72.50 0	56.112 to 85.399	2.53
Patima et al. (2000)[53]	73	73.973	62.376 to 83.546	2.67
Gillison et al.(2000) [69]	84	11.905	5.859 to 20.805	2.69
Premoli -De-Percoco et al.(2001) [54]	50	60.000	45.179 to 73.592	2.59
Shima et al.(2000)[77]	44	20.455	9.804 to 35.305	2.56

Schwartz et al.(2001)[55]	254	15.748	11.495 to 20.821	2.80
Nagpal et al. (2002)[56]	110	33.636	24.908 to 43.271	2.73
Kumar et al. (2003)[58]	42	30.952	17.622 to 47.086	2.54
Sugiyama et al. (2003)[60]	86	34.884	24.919 to 45.923	2.69
Zhang et al. (2004)[64]	73	73.973	62.376 to 83.546	2.67
Dahlgren et al. (2004)[62]	110	10.909	5.765 to 18.281	2.73
Ibieta et al.(2005)[35]	21	66.667	43.032 to 85.412	2.30
Boy et al.(2006)[65]	59	11.864	4.906 to 22.929	2.63
Badaracco et al.(2006)[70]	60	13.333	5.936 to 24.592	2.63
Nemes et al.(2006)[67]	79	41.772	30.767 to 53.413	2.68
Sugiyama et al. (2007)[68]	27	37.037	19.401 to 57.632	2.40
Smith et al. (2008)[71]	108	24.074	16.368 to 33.251	2.73
Chaudhary et al.(2010)[37]	208	34.615	28.171 to 41.505	2.79
Gonzaiez-Ramirez I et al.(2013)[34]	80	5.000	1.379 to 12.310	2.68
Gan et al.(2014)[33]	200	19.500	14.249 to 25.679	2.79
Koukertsu A et al.(2016)[39]	24	54.167	32.821 to 74.447	2.36
Chen et al.(2016)[36]	178	3.371	1.247 to 7.192	2.78
Palve et al.(2018)[38]	106	33.019	24.190 to 42.824	2.72
De Abreu PM (2018)[76]	90	3.333	0.693 to 9.434	2.70
Rubab Z et al. (2018)[75]	100	32.000	23.022 to 42.077	2.72
Total (random effects)	**3158**	**28.877**	**22.617 to 35.570**	**100.00**

Test for heterogeneity

Q	612.7992
DF	37
Significance level	P < 0.0001
I2 (inconsistency)	93.96%
95% CI for I2	92.57 to 95.10

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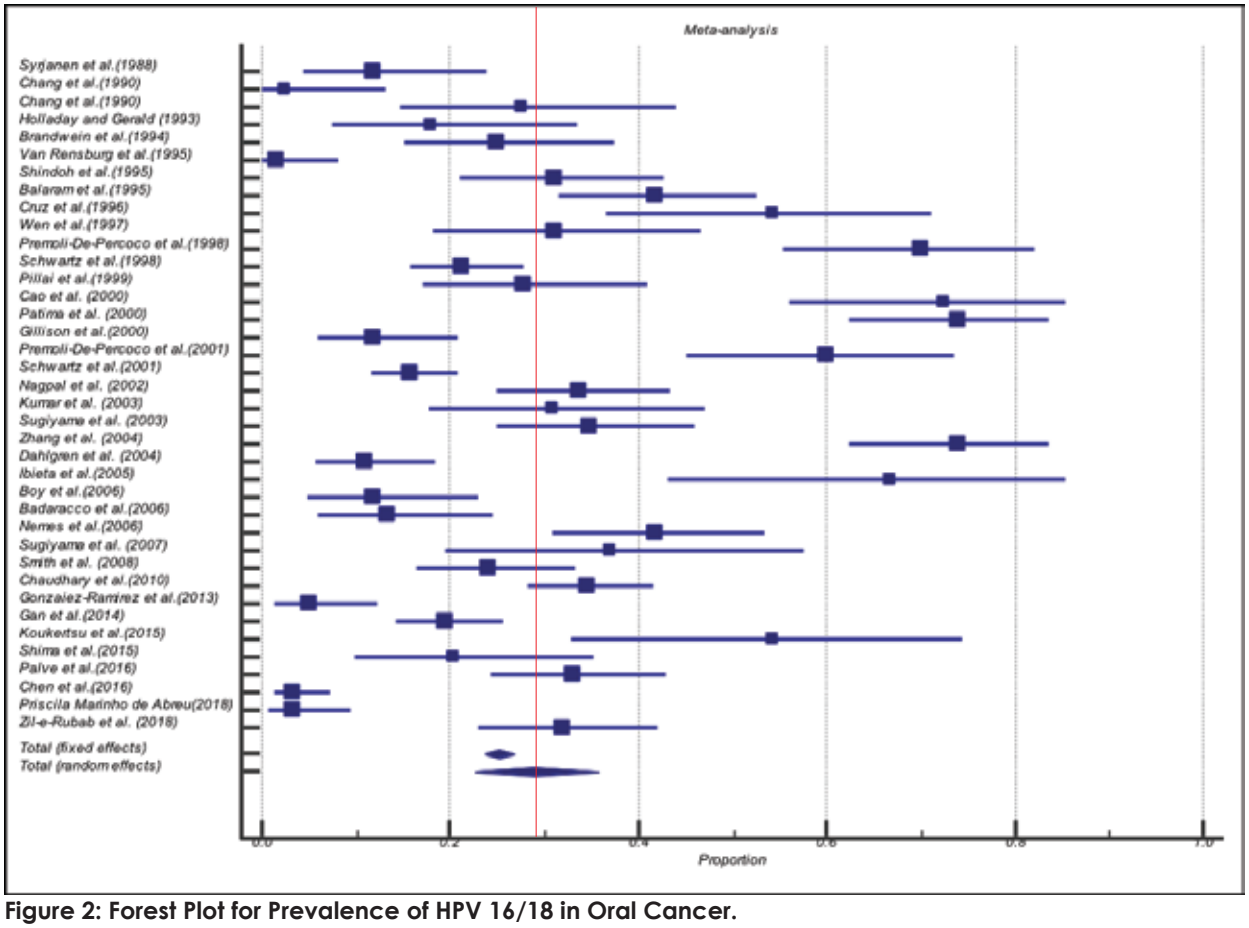

Figure 2: Forest Plot for Prevalence of HPV 16/18 in Oral Cancer.

Meta-analysis for overall prevalence based on 31, 33, 35, 52 and 56 HPV type

Of the 47 research studies, 7 studies included to calculate pooled prevalence of HPV- 31, 33, 35, 52 and 56) in OSCC. The insignificant heterogeneity (p=0.2294) was found among the studies [I^2= 26.11% with 0 to 67.83% confidence interval (CI) at 95%].

Out of 563 patients, 19 patients were positive for HPV-31/33/ 35/ 52/56. Proportion of positive cases for HPV 31/33/ 35/ 52/56 was also analyzed in the present meta-analysis. Based on fixed effect model the mean proportion of positive cases was 3.591% [2.221 to 5.465% confidence interval (CI) at 95%].

Table 3: Prevalence of other high-risk HPV in Oral Cancer based on 7 studies.

Study	Sample size	Proportion (%)	95% CI	Weight (%)
Bouda et al.(2000)[51]	19	5.263	0.133 to 26.028	3.51
Chang et al. (2003)[57]	103	0.971	0.0246 to 5.291	18.25
Ritchie et al. (2003) [59]	141	2.837	0.778 to 7. 104	24.91
Smith et al. (2004) [63]	106	2.830	0.587 to 8.049	18.77
El -Mofty et al. (2006)[66]	94	2.128	0.259 to 7.475	16.67
Kong et al.(2009)[72]	13	7.692	0.195 to 36.030	2.46
Attner et al.(2010)[73]	87	8.046	3.296 to 15.878	15.44
Total (fixed effects)	**563**	**3.591**	**2.221 to 5.465**	**100.00**

Test for heterogeneity

Q	8.1200
DF	6
Significance level	P = 0.2294
I2 (inconsistency)	26.11%
95% CI for I2	0.00 to 67.83

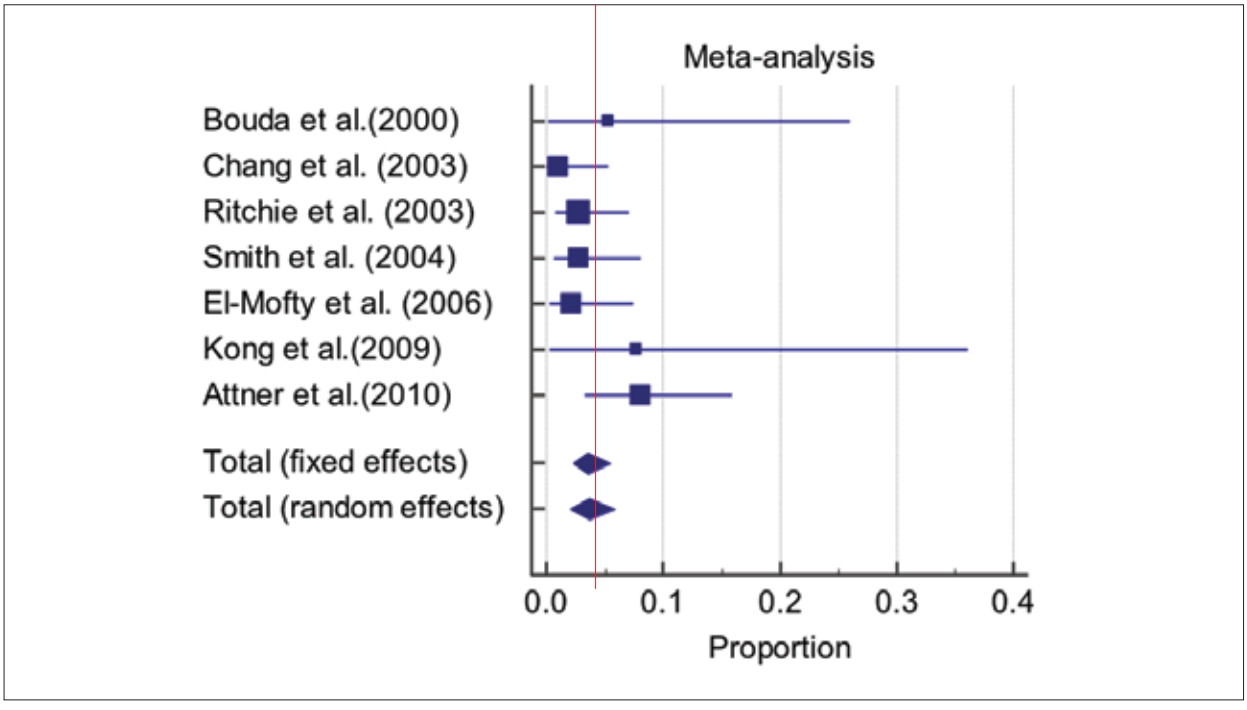

Figure 3: Forest Plot for Prevalence of HPV 31/33/ 35/ 52/56 in Oral Cancer.

DISCUSSION

The present study was designed to analyze the existing highly varied and controversial data on high-risk HPV detected in OSCC in order to calculate the pooled prevalence rate of high-risk HPV and especially HPV 16/18 in oral squamous Cell Carcinoma cases by meta-analysis. The consensus decision supports the moderate prevalence of high-risk HPV type as 30.71% depicting a definite role of high risk HPV in oral oncogenes. Moreover, as highly supported in the literature HPV type 16/18 standout as the predominant risk factors amongst all. Collectively there seems to be an alarming prevalence of HPV in relation to oral cancer signifying an important role in the etiopathogenetic mechanism, which is in conformity with the already established role of HPV 16/18 in cervical oncogenesis. The massive representing from the western world could be related to the promiscuous society and practice of oral sex.

Well, out of all the high-risk viruses HPV 16/18 is most commonly implicated in the oral carcinogenesis model. However, we have also estimated the prevalence of other less common high-risk HPV types to prompt further investigation in this subject area. Since most of the work available in the literature has focused on the type 16/18 only. So we analyzed this data separately also for the conclusive comment. However, we could not determine a significant role of other high-risk viruses.

The association of HPV with oral cancer was first proposed in 1983[1] and then supported by several other studies. The HPV prevalence rate in oral cancer was found to be varied from 0% to 100% [13]. The studies including large sample size (> 90 cases) have shown low prevalence 3.37% to 49.51% as compared to the studies based on small sample size 1.52% to 94.73% of high-risk HPV amongst OSCC. The reason of this huge widespread variability maybe due to differences in detection methodology of HPV, differences in population, social habits, and sampling of oral specimen[19-21]. Moreover, many research studies have stated inconsistent results for the prognostic role of HPV[22, 23]. This is still in debate and needs future investigation.

A study reported that serum analysis, histopatholo-

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gy examination and OralCDx® (oral scrapings) diagnostic methods are significant in identifying the HPV DNA. A diagnostic method is considered essential for estimating the prevalence or association of HPV and oral cancer[24]. According to current study, majority of the research studies used PCR method, which is definitely a standard presently.

Based on our study's statistical results, the overall positive prevalence of high-risk HPV and particularly type 16/18 HPV in OSCC was 30.71% and 28.88% respectively. In addition, 7 out of 47 studies, which determine less than 10% prevalence of all high-risk HPV in OSCC, as, showed in Figure 1. On the contrary, Bouda et al. found high prevalence of 94.74% with 93.69 – 95.71 CI at 95%. While Schwartz et al. studied on the highest number of patients (Table 1). Although, there were only 5 out of 38 studies which determine less than 10% prevalence of HPV16/18 in OSCC, as shown in Figure 2. On the contrary, Patima et al. and Zhang et al. found high prevalence of 73.97% with 62.37 to 83.54% and 62.37 to 83.54% CI at 95% respectively. This large variation in the data requires future rigorous investigation of research derives with good number of cases and uniformity of standardized molecular genetics techniques.

Furthermore, according to earlier published systematic review and meta-analysis our result was almost similar to that stated by Syrjänen et al. 33.7%[25] although our result was greater than Miller and White 26.2% [26], Ndiaye et al. 24.2% [27], Kreimer et al. 23.5% [28], and O'Rorke et al. 22.8% [29]. Whereas our result was, lower than Termine et al. 38.1%[3], Miller and Johnstone 46.5%[30], Chaitanya et al. 58% [24].

CONCLUSION

According to the current meta-analysis, we assumed that high infection rate of type 16/18 HPV as compared to other high-risk HPV, which were found in OSCC cases remains a scientific reality in the risk-factor profile.

LIST OF ABBREVIATIONS

OSCC	Oral Squamous Cell Carcinoma
HPV	Human Papillomaviruses
PCR	Polymerase Chain Reaction
ISH	In-situ Hybridization
CI	Confidence Interval
DNA	Deoxyribonucleic Acid
LCR	Long non-Coding Region
ORF	Open Reading Frame
DF	Degree of Freedom

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CONFLICT OF INTEREST

There was no conflict of interest among the authors.

AUTHORS' CONTRIBUTIONS

TM conceived the idea, guided the manuscript, overall supervised the project, SU wrote introduction of the manuscript and facilitated in online data collection, AW collected online data, did meta-analysis and wrote the manuscript.

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