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Systemic Review on the association between Periodontitis and Head and Neck cancer; Meta-Analysis

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Abstract

Systemic Review on the association between Periodontitis and Head and Neck cancer; Meta-Analysis

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Background

The purpose of study is to estimate the association between periodontitis and risk of head and neck cancer by meta-Analysis.

Method

Literature was selected according to RPISMA guideline in PubMed, and Cochrane Library database. The association between periodontitis and the risk of having head and neck cancer was evaluated by meta-analysis using RevMan program. Random effect model was used and fixed effect model was analyzed as reference. Also,

Subgroup analyses were done including covariates adjustment, study design, tumor site, ethnicity and type of assessment of periodontal disease. Publication bias were evaluated by Funnel plot using RevMan program. Egger's regression test was also performed by using comprehensive meta-analysis program to evaluate publication bias.

Result

Out of 13 studies selected, 14 results included in this meta-analysis. The association between periodontitis and head and neck cancer was odds ratio (OR) was 2.35 with 95% confidence interval (95% CI) was between 1.69 and 3.26 for random effect model (p value < 0.00001) and OR was 1.27 with 95% CI was between 1.20 and 1.35 for fixed effect model (p value <0.00001). In Subgroup analysis, adjusted covariates was OR of 2.13 with 95% CI of 1.55 to 2.92. (p value < 0.0001) in random effect model. As for the result of study design, OR of case control studies was 2.51 with 95% CI of 1.77 to 3.57 in random effect model. Result of assessment method of periodontal disease, alveolar bone loss (ABL) was shown to be OR of 2.61 (95% CI [1.43, 4.79], random effect model) and clinical attachment loss (CAL) was OR of 3.66 (95% CI [0.67, 20.15], random effect model) and combining ABL and CAL shown to be OR of 2.68 (95% CI [1.62, 4.44], random effect model). In tumor site, the result of oral cavity was OR of 1.70 in random effect model (95% CI [1.24, 2.32]), head and neck was OR of 2.57 in random effect model (95% CI

[1.60, 4.15]) and in ethnicity, the result of Europe was OR of 2.53 in fixed model (95% CI [1.82, 3.51]). As for the Egger's regression test, intercept value was 3.44059 with p value of 0.00087 which shown that there is no publication bias.

Conclusion

The result of meta-analysis indicated that periodontitis could be associated with the risk of head and neck cancer. This kind of association could be different from co-variates adjustment, study design, tumor site, ethnicity, and type of assessment of periodontal disease. To clarify this kind of link between periodontitis and risk of head and neck cancer, further studies is needed such as well-designed cross sectional studies or case control study with well-controlled sample size and type of assessment of periodontal disease, covariates adjustment, ethnicity, tumor site, etc.

Keywords : Head and neck cancer, Periodontitis, Meta-analysis

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I. Introduction

Head and neck cancer including oral cavity, oropharynx, pharynx, and larynx occur frequently with each year over 500,000 new head and neck cancer cases diagnosed (Mehanna et al., 2010). Head and neck cancer has high mortality with 5 - year survival rates little above 50% (Warnakulasuriya, 2009). The cause of head and neck cancer is unknown but well- known risk factor is excessive smoking (Blot et al., 1988, Goldstein et al., 2010) and other risk factors associated with head and neck cancer are genetic (Rusin et al., 2008), malnutrition (Chasen and Bhargava, 2009, Ritchie et al., 2002), radiation (Hashibe et al., 2005), systemic disease such as diabetes (Goutzanis et al., 2007) cardiovascular diseases, and virus infection such as human papilloma virus (Conway et al., 2009). Early diagnosis of head and neck cancer might improve the prognosis of head and neck cancer but there is no discrete diagnosis tool for head and neck cancer (Martin et al., 2016).

Periodontitis is a chronic inflammation that caused by the breakdown between systematic immune system and local inflammation through head and neck cavity. This leads to the gradual destruction of the tissues and structure (such as gingiva, periodontal ligament, and alveolar bone) that supports teeth (Loesche and Gross-

man, 2001, Irfan et al., 2001). If periodontitis left untreated, progress of periodontitis is proceeded and changes the anatomical structure of tooth and supporting tissue of the tooth pathologically and ultimately it leads to tooth loss. As result of periodontitis, excreting of inflammatory cytokine, enzymes and toxic happens. Prevalence of periodontitis differs from race, age, geographical variance (Papapanou, 1996). Major risk factors are systemic diseases, such as diabetes(Guzman et al., 2003), excessive smoking habit(Muller et al., 2001, Bunyaratavej, 2006), excessive drinking (Pitiphat et al., 2003), poor oral hygiene (Bunyaratavej, 2006, Greene, 1963), low socioeconomic status (Gundala and Chava, 2010), genetic (Michalowicz et al., 2000), medication (Ciancio, 2005), and virus such as Human papilloma virus (HPV) (Horewicz et al., 2010, Tezal et al., 2009) are well- known risk factors.

The association between cancer and inflammation was first suggested by Rudolf Virshow in 1863. Virchow suggested that chronic inflammation at the site of cancer origin was due to infiltration of lymphoreticular which made inflammation is critical in prevention, treatment and progression of cancer (Balkwill and Mantovani, 2001). Periodontitis is predominant infection in oral cavity and it is plausible that this inflammation might increase the exposure of having oral cancer according

to hypothesis of Virshow (Michaud et al., 2008). In 2007, Tezal et al., proposed that progression of cancer is related to the loss of the alveolar bone which is the critical sign in periodontitis and many studies showed similar results of association between periodontitis and oral cancer (Tezal et al., 2007). Several researches were done to see the association between two diseases but the results are contradictory.

In this study, we reviewed literatures to see the correlation between the two diseases. We also performed meta-analysis of studies that were aimed to seek the correlation between head and neck cancer and periodontitis.

II. Materials and Methods

1. Literature Search and Eligibility criteria

We searched 2 major databases (PubMed, Cochrane Database) for studies that have conducted to seek the association between periodontitis and head and neck cancer from 1990 to 2017 including keywords of 1) oral cancer or head and neck cancer or carcinoma or 2) periodontal disease or periodontitis.

Based on the search using keywords, we have sorted literature by inclusion and exclusion criteria. Eligible study designed were included such as cohort studies, case control studies, and cross-sectional studies performed to seek the association between head and neck cancer and periodontitis.

Studies should be available in full-texts in English, available odds ratio, relative risks, associated 95% confidence interval (Cis) or hazard ratio, and having distinctive criteria of periodontitis or head and neck cancer.

2. Data extraction

We have collected data form each included journal. Characteristics of study such as reference (Surname of first author, year of publication), design of study (cohort study, case control study, cross sectional study), name of country where the study was conducted, sample size, age, periodontal assessment, tumor site, ratio of the event occurred (odds ratio, hazard ratio, relative risk) and associated 95% confidence intervals, and adjustments in each study were collected were summarized from each studies.

3. Data Analysis

To see the association between studies, odds ratios were used as a crude measurement. Each value of odds ratio was used to see the relationship between head and neck cancer and periodontitis. Each odds ratio was used to determine the standard error for each study. Hazard ratio was transformed into odds ratio (Greenland, 2004, Zhang and Yu, 1998). The limitation of this transformation is that odds ratio that was converted from the hazard ratio might lead to overestimation of variance.

The random effect and fixed effect meta-analysis was used to see the heterogeneity of studies. These analyses were carried out by the Revman manager software (Revman, version 5.3 Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). There was one study with hazard ratio so we transformed hazard ratio to odds ratio by using formula presented on Zang et al. (Zhang and Yu, 1998). During the transformation process, transformed odds ratio might be overestimated. First, we transformed odds ratio of each study into natural logarithms and calculate standard error by converting odds ratio using formula (Zhang and Yu, 1998). Using installed formula presented by Revman manager using inverse variance method, heterogeneity was assessed (Higgins and Thompson, 2002). Heterogeneity is the value that refers to the variation between studies that was included in meta-analysis. I^2 refers to the variation among studies due to the heterogeneity. The I^2 value of 25%, 50%, 100% indicates low, moderate and high (Higgins et al., 2003). For fixed model, we used I^2 value less than 25% and for random model, we used value that was more than 25%. We have used both random effect and fixed effect model and also generated forest plot.

We also performed subgroup analyses based on each categorization that we se-

lected such as geographical region, design of study, assessment type of periodontitis, site of tumor. Lastly, through funnel plot publication bias was inspected. Meta regression test was performed by using Comprehensive Meta - Analysis program. Egger's regression test was performed by using Comprehensive Meta - Analysis program. Egger's regression is the method to determine asymmetry of funnel plot. In Egger's regression test, p value above 0.05 considered there is an evidence of publication bias. (Egger et al., 1997).

III. Results

1. Study selection and characteristics

From initial search of 403 journals, 13 studies were fitted into eligible criteria which were further analyzed by meta-analysis. Figure 1 showed eligibility test using flow chart by PRISMA guideline.

Table 1 showed characteristics and adjusted covariates of each 14 studies; country, design of study, sample size, type of periodontitis assessment, type of head and neck cancer Among the included studies, Guha, 2008 study was the only study that was performed on multicentric study which counted as separate studies and Michaud, 2008 study was the only study that was done by cohort study.

2. Overall estimates

We evaluated the heterogeneity statistically of 14 studies. The overall estimates of risk of odds ratio for each study were pooled using both random and fixed effect.

Heterogeneity was measured automatically using Revman software. The correlation between the risk of periodontitis and head and neck cancer was OR = 2.35 (Heterogeneity of I^2 = 92%, 95% CI = [1.69, 3.26], $p < 0.00001$) (Fig.2) in random effect model. This The result indicated that risk of having head and neck cancer will increase the risk of having head and neck cancer by 1.27 fold in fixed - effect model (Heterogeneity of I^2 = 92%, 95% CI = [1.20, 1.35], $p < 0.00001$), 2.35 fold on random-effect model.

3. Subgroup analysis

Table 2 shows the result of subgroup analysis based on the covariates adjustments, assessment of periodontitis, site of tumor and ethnicity. For covariates adjustment, total 13 studies were included with the odds ratio of 2.13 (Heterogeneity of I^2 = 91%, 95%CI = [1.55, 2.92], $p < 0.00001$) on random effect model. As for the assessment of periodontal disease, ABL, CAL, tooth mobility, CPITN, oral condition, loss of tooth, ABL+ CAL and self-reported periodontitis was analyzed with the odds ratio of 2.61 (I^2 = 85%, 95%CI = [1.43, 4.79], p = 0.002), 3.66 (I^2 = 74%, 95%CI = [0.67, 20.15], p = 0.14), 1.33 (95%CI = [1.07, 1.65], p = 0.01), 12.67 (95%CI = [4.90, 32.76], $p < 0.00001$), 2.07 (I^2 = 52%, 95%CI = [1.66, 2.59],

p < 0.00001), 2.02 (95%CI = [1.29, 3.17], p = 0.002), 2.68 (I^2 = 81%, 95%CI = [1.62, 4.44], p = 0.0001), 1.09 (95%CI = [1.02, 1.16], p = 0.01) respectively. The result of tumor site, oral cavity showed odds ratio of 1.70 (I^2 = 80%, 95%CI = [1.24, 2.32], p = 0.0009), head and neck region showed odds ratio of 2.57 (I^2 = 83%, 95%CI = [1.60, 4.15], p = 0.0001), tongue showed odds ratio of 5.23 (95%CI = [2.64, 10.36], p < 0.00001) and oropharyngeal showed odds ratio of 3.68 (I^2 = 95%, 95%CI = [0.35, 38.55], p = 0.28). As for the ethnicity it was divided into 4 subgroups; USA, Europe, Latin America, and Asia and each odds ratio was 1.98 (I^2 = 95%, 95%CI = [1.17, 3.34], p = 0.01), 2.53 (95%CI = [1.82, 3.51], p < 0.0001), 5.79 (I^2 = 89%, 95%CI = [1.27, 26.37], p = 0.02), 1.93 (95%CI = [1.38, 2.71], p = 0.0001), respectively.

4. Publication bias

Figure 3 show the funnel plot. Each dot is represented as a single study that was included in the study. The result of funnel plot was obvious asymmetrical which refers that there was publication bias. Egger's regression of meta-analysis showed p value and intercept value of 0.00087 and 3.44059 respectively.

IV. Discussion

1. Main findings

Head and neck cancer, despite modern treatment and technology including surgery, chemotherapy, radiation (Buglione et al., 2016), drug therapy (Sultana et al., 2014), etc has high mortality and survival rate. However, early detection of the disease increases the survival rate dramatically. Early diagnosis of the head and neck cancer, unfortunately has been small improvement compared with other cancer diseases. It is important to acknowledge the risk factors for prevention of head and neck cancer.

Periodontitis is a chronic inflammation disease which is caused by gram-negative anaerobic bacteria that leads to destruction of supporting tissue and structure of tooth. During periodontitis, cytokines, inflammation pathogens, toxins are

released and affect the patient's health systematically (Pendyala et al., 2013).

In the study, we aimed to see periodontitis is the important risk factor for head and neck cancer by meta-analysis. Total 14 included studies were included in the database. Patients with periodontitis tend to have 2.35-fold higher risk for having head and neck cancer. Subgroup analyses were also done to see the relationship between two diseases.

2. Source of heterogeneity

Heterogeneity was observed in meta-analysis extensively due to the differences in method that was used in each study such as population, country, design of study, assessment of periodontal disease, site of oral cancer, adjustment for covariates. In subgroup analysis, ethnicity and design of study showed increase in heterogeneity whereas assessment of periodontal disease, site of oral cancer, adjustment of confounding factors showed decrease in heterogeneity. Decrease in heterogeneity indicate that these characteristics were the factors for heterogeneity. Egger's regression test was p value of 0.00087 and intercept value of 3.44059. Egger's regression test showed to be there is an evidence of no publication bias in the meta-analysis by

interpreting p value less than 0.05.

3. Implication

Head and neck cancer patients often have poor oral health status (Greene, 1963). After Virchow's hypothesis that the association between chronic inflammation and cancer (Balkwill and Mantovani, 2001), substantial studies were done to support the hypothesis. However, still whether periodontitis alone is the risk factor of head and neck cancer is still unknown due to the associated risk factors between two diseases are variant. The meta-analysis that we have conducted showed that with the adjustment of covariates, OR ratio has shown to be 2.13. This result indicates that statistically there is a significant association between two diseases.

In process of carcinogenesis, it has been suggested that oral bacteria are involved in the process (Meurman and Uittamo, 2008). Periodontitis is due to the accumulation of bacterial infection (Loesche and Grossman, 2001) but still the mechanism of how the periodontal disease affect the head and neck cancer is unknown. Periodontitis can be treated with care. Head and neck cancer on the other hand has a high mortality rate. If we know the mechanism or pathogenesis between

head and neck cancer and periodontitis, head and neck cancer might be prevented with a decreasing mortality rate.

4. Limitation of study

Several limitations exist in our study. First, our study was based on observational studies with different confounding factors for adjustment. Second, the result of funnel plot indicated that there was a publication bias, but the plot was not symmetrical enough and number of studies that was included in our study is not large enough. Third is the heterogeneity which showed significant statistical heterogeneity in the main finding and in subgroup analysis, also. Fourth, sample size varies extremely which made studies with relatively large sample size reflect more significantly in analysis and had more statistical power. Lastly, periodontal disease assessment methods were varied between studies.

5. Future Study

For future study, there are just one study conducted a cohort study, so it might be better to conduct more cohort studies as study design in relation to periodontitis and head and neck cancer. Advantages of cohort study are large number of sample

size for long period of time and various variables can be measured (Mann, 2003). Especially for experimental group from hospital case and control group from community case would be possible study design. Main advantages of having community case for control group would show higher statistical significance and higher representative. Also, since the pathological pathway in relation to head and neck cancer and periodontitis, it would be better to see the association from molecular level to clinical level.

V. Conclusion

The meta-analysis of the association between head and neck cancer and periodontitis showed that there is positive relation between two disease which might be strongly due to the risk factors of head and neck cancer such as excessive smoking habit, drinking alcohol and etc.

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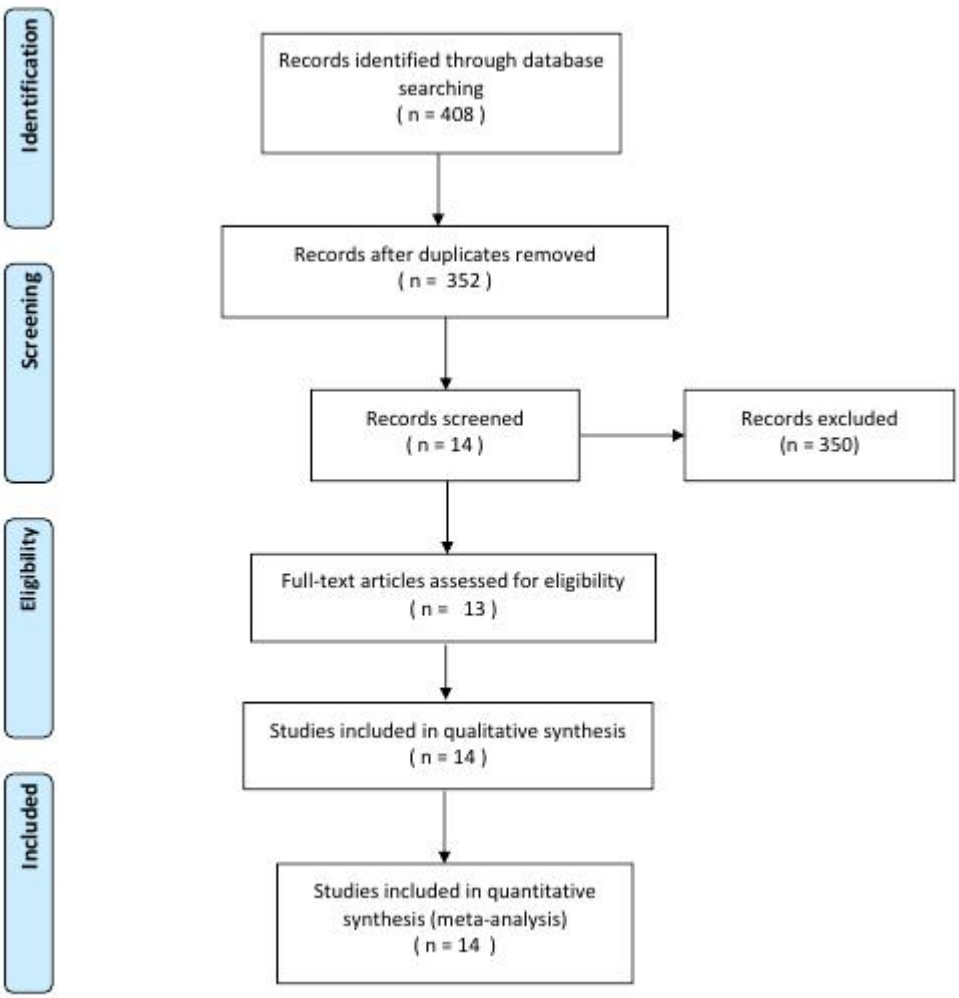


Figure 1. Flow chart of literature selection

* Flow chart of study selection for studies included in meta-analysis following PRISMA guideline

Table 1.Characteristics of studies included in meta-analysis.

Study	Year	Country	Study Design	Sample size		Assessment method of Perio-dontal disease	Adjusted factors	Tumor site
				Control	Patient			
Zheng	1990	China	case control study	404	404	loss of tooth	age, gender, dentition, smok-ing, drinking	1
Rosenquist	2005	Sweden	case control study	320	132	ABL	age, gender, smoking and drinking	1
Tezal	2007	USA	case control study	54	51	ABL	smoking and drinking, num-ber of teeth	3
Guha_C	2007	Central Europe	case control study	566	511	oral condition	age, gender, smoking and drinking	2
Guha_L	2007	Latin America	case control study	1361	1457	oral condition	age, gender, smoking and drinking	2
Hiraki	2008	Japan	case control study	858	429	loss of tooth	age, gender, smoking and drinking	2
Michaud	2008	USA	cohort study	48375	118	ABL	age, smoking and drinking	4
de Rezende	2008	Brazil	case control study	50	50	CPITN	-	4

Tezal	2009	USA	case control study	266	207	ABL	age, gender, smoking and drinking	2
Divaris	2010	USA	case control study	1289	1361	Tooth mobility	age, gender, smoking, drinking	1
Moergel	2013	Germany	case control study	123	178	ABL	age, gender, teeth with caries, missing teeth, mean bone loss, periodontal treatment, smoking and drinking	1
Eliot	2013	USA	case control study	567	513	Self-reported periodontitis	age, sex, race, smoking, alcohol consumption, education, annual household income	1
Moraes	2016	Brazil	case control study	40	35	CAL	age, smoking and drinking	1
Laprise	2016	Southern India	case control study	328	306	CAL	age, gender, year of education, alcohol drinking and smoking	1

Guha, 2007 conducted multicentric analysis of Central Europe(C) and Latin America(L). Both studies are counted as separated dataset. Countries of Russia, Romania, and Poland are included in Central Europe (C) and countries of Argentina, Cuba and Brazil are included in Latin America (L). Subgroup of Tumor site: 1 - oral cavity 2 - head and neck 3 - tongue 4 – oropharyngeal

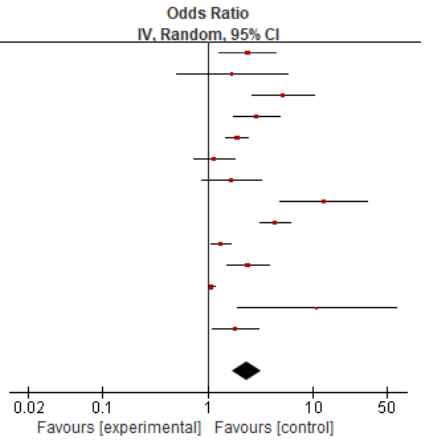
ABL: Alveolar bone loss, CAL: clinical attachment loss, CPITN: community periodontal index of treatment needs

A.

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI	Year
Zheng, 1990	0.8755	0.3207	7.0%	2.40 [1.28, 4.50]	1990
Rosenquist,2005	0.5306	0.6244	4.1%	1.70 [0.50, 5.78]	2005
Tezal,2007	1.6544	0.3487	6.7%	5.23 [2.64, 10.36]	2007
Guha,2007_C	1.0613	0.2589	7.7%	2.89 [1.74, 4.80]	2007
Guha,2007_L	0.6471	0.1267	9.0%	1.91 [1.49, 2.45]	2007
Michaud,2008	0.1398	0.2314	8.0%	1.15 [0.73, 1.81]	2008
Hiraki,2008	0.5188	0.3299	6.9%	1.68 [0.88, 3.21]	2008
de Rezende, 2008	2.5392	0.4847	5.3%	12.67 [4.90, 32.76]	2008
Tezal,2009	1.4725	0.1646	8.7%	4.36 [3.16, 6.02]	2009
Divaris,2010	0.2852	0.111	9.1%	1.33 [1.07, 1.65]	2010
Moergel,2013	0.8755	0.2345	8.0%	2.40 [1.52, 3.80]	2013
Eliot, 2013	0.0862	0.0339	9.4%	1.09 [1.02, 1.16]	2013
Moraes,2016	2.3888	0.8803	2.6%	10.90 [1.94, 61.20]	2016
Laprise,2016	0.6043	0.2589	7.7%	1.83 [1.10, 3.04]	2016
Total (95% CI)			**100.0%**	**2.35 [1.69, 3.26]**	

Heterogeneity: $Tau^2 = 0.30$; $Chi^2 = 156.48$, df = 13 ($P < 0.00001$); $I^2 = 92\%$

Test for overall effect: $Z = 5.11$ ($P < 0.00001$)



B.

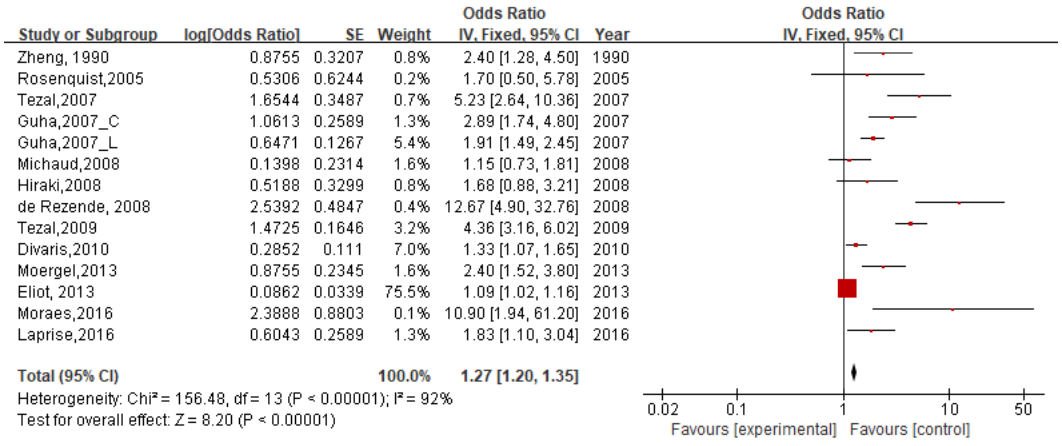


Figure 2. Forest plot of risk of periodontitis and oral cancer. A. Studies pooled with random effect, B. Studies pooled with fixed effect

* Data and p value are obtained from RevMan program using inverse generic method. Heterogeneity, odds ratio (OR), 95% confidence interval (CI), and p value are obtained.

Table 2. Subgroup association of Meta-Analysis

Overall and Subgroup Characteristics		Number of Studies	Heterogeneity		Model	Meta-Analysis		
			I^2(%)	p - value		OR	95% CI	p - value
Total		14	92	p < 0.001	Random	2.35	[1.69, 3.26]	p < 0.001
Adjustment	Yes	13	91	p < 0.001	Random	2.13	[1.55, 2.92]	p < 0.001
	No	1	-		Fixed	12.67	[4.90, 32.76]	p < 0.001
Study Design	Case control	13	92	p < 0.001	Radom	2.51	[1.77, 3.57]	p < 0.001
	Cohort	1	-		Fixed	1.15	[0.73, 1.81]	p = 0.55
Assessment method of periodontal disease	ABL	5	85	p < 0.001	Random	2.61	[1.43, 4.79]	p = 0.002
	CAL	2	74	p = 0.05	Random	3.66	[0.67, 20.15]	p = 0.14
	Tooth Mobility	1	-		Fixed	1.33	[1.07, 1.65]	p = 0.01
	CPITN	1	-		Fixed	12.67	[4.90, 32.76]	p < 0.001
	Oral Condition	2	52	p = 0.15	Fixed	2.07	[1.66, 2.59]	p < 0.001
	Loss of Tooth	2	0	p = 0.44	Fixed	2.02	[1.29, 3.17]	p = 0.002
	ABL + CAL	7	81	p < 0.001	Random	2.68	[1.62, 4.44]	p < 0.001
	Self-reported periodontitis	1			Fixed	1.09	[1.02, 1.16]	p = 0.01
Tumor Site	Oral cavity	7	80	p < 0.001	Random	1.70	[1.24, 2.32]	p < 0.001
	Head and neck	4	83	p < 0.001	Random	2.57	[1.60, 4.15]	p < 0.001
	Tongue	1	-		Fixed	5.23	[2.64, 10.36]	p < 0.001
	Oropharyngeal	2	95	p < 0.001	Random	3.68	[0.35, 38.55]	p = 0.28
Ethnicity	USA	5	95	p < 0.001	Random	1.98	[1.17, 3.34]	p = 0.01
	Europe	3	0	p = 0.70	Fixed	2.53	[1.82, 3.51]	p < 0.001
	Latin America	3	89	p < 0.001	Random	5.79	[1.27, 26.37]	p = 0.02
	Asia	3	0	p = 0.71	Fixed	1.93	[1.38, 2.71]	p < 0.0001

* Data and p value are obtained from RevMan program using inverse generic method. Heterogeneity , odds ratio (OR), 95% confidence interval (CI), p value are obtained.

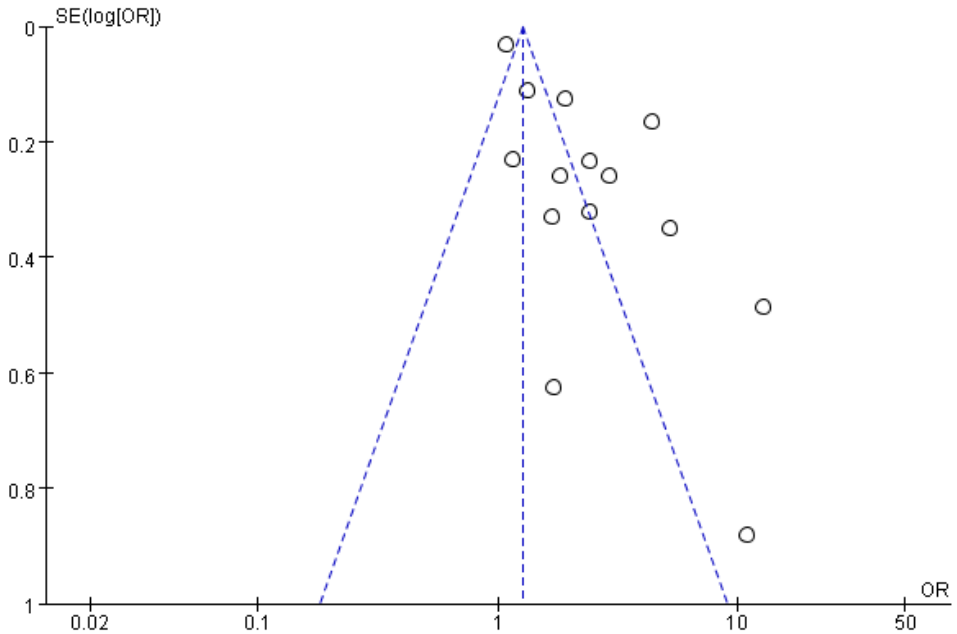


Figure 3. Funnel plot of overall result of studies included in meta-analysis

* Each study is indicated as a single dot for indicated association. Mean effect size is represented as vertical line.

Appendix

Figure 2 Output

Study, Year	Odds ratio	95% confidence interval		Log Odds ratio	Variance	Standard Error
		Lower Limit	Upper Limit			
Zheng, 1990	2.4	1.3	4.5	0.8755	41.44464	0.3207
Rosenquist, 2005	1.7	0.5	5.78	0.5306	176.2097	0.6244
Tezal, 2007	5.23	2.64	10.36	1.6544	12.77045	0.3487
Guha, 2007_C	2.89	1.74	4.8	1.0613	11.65919	0.2589
Guha, 2007_L	1.91	1.49	2.53	0.6471	22.27859	0.1434
HIraki, 2008	1.68	0.88	3.21	0.5188	0.40077	0.3299
Michaud, 2008	1.15	0.73	1.81	0.1398	6.319	0.2314
De Rezende, 2009	12.669	4.9	32.76	2.5392	23.4953	0.4847
Tezal, 2009	4.36	3.16	6.02	1.4725	12.815	0.1646
Divaris, 2010	1.33	0.9	1.65	0.2852	32.06391	0.1100
Eliot, 2013	1.09	1.02	1.16	0.0862	1.089138	0.0339
Moergel, 2013	2.4	1.5	3.8	0.8755	16.54575	0.2345
Moraes, 2016	10.9	1.98	61.2	2.3888	58.11936	0.8803
Laprise, 2016	1.83	1.11	3.04	0.6043	48.34664	0.2589

Table 1. Figure 2 output of Odds ratio, 95% confidence interval, Log odds ratio, variance and starndard error.

Table 2 Output – Subgroup analysis

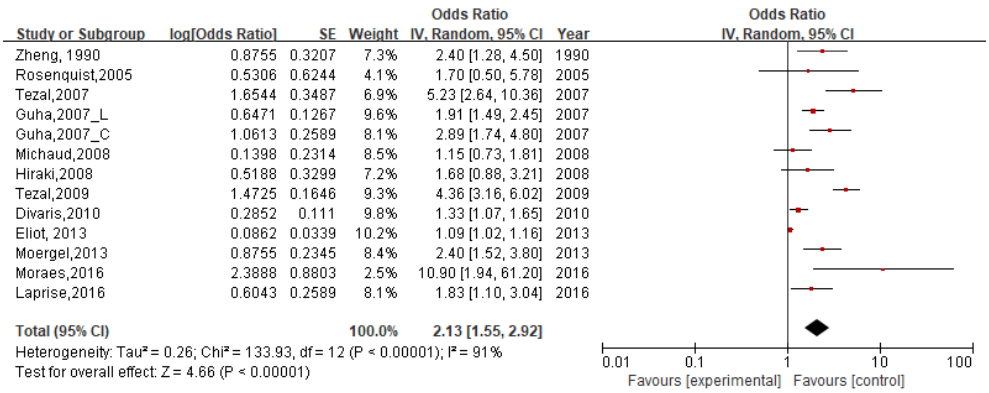


Figure 1. Forest plot for subgroup analysis - Covariates adjustment

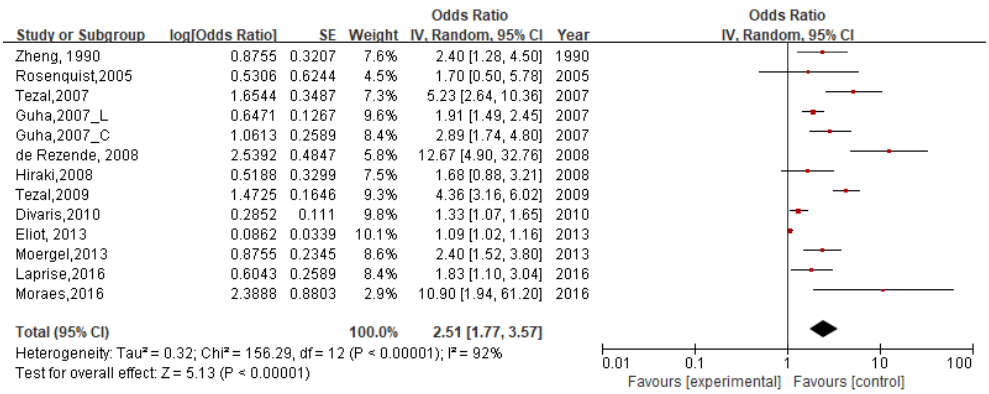


Figure 2. Forest plot for subgroup analysis – Case control study

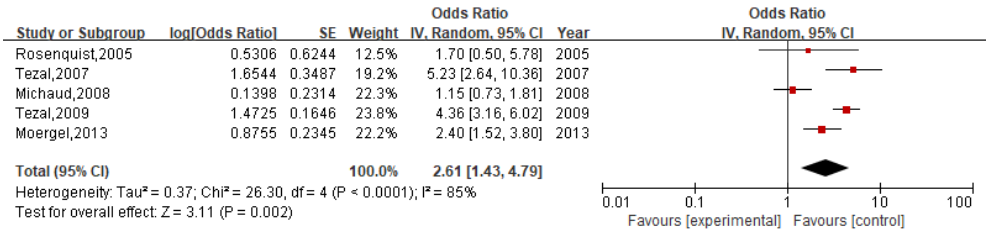


Figure 3. Forest plot for subgroup analysis –Alveolar bone loss (ABL) (Periodontal disease assessment)

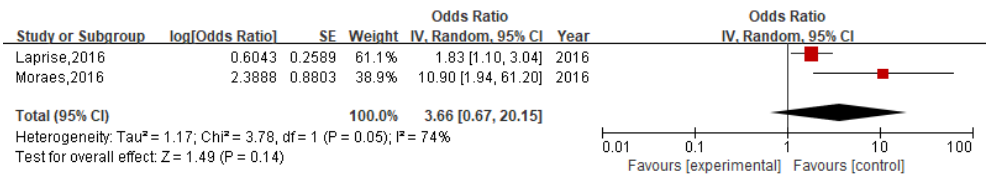


Figure 4. Forest plot for subgroup analysis - Clinical attachment level (CAL) (Periodontal disease assessment)

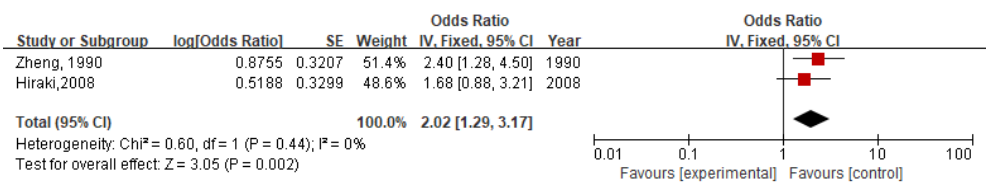


Figure 5. Forest plot for subgroup analysis - C. Loss of tooth (Periodontal disease assessment)

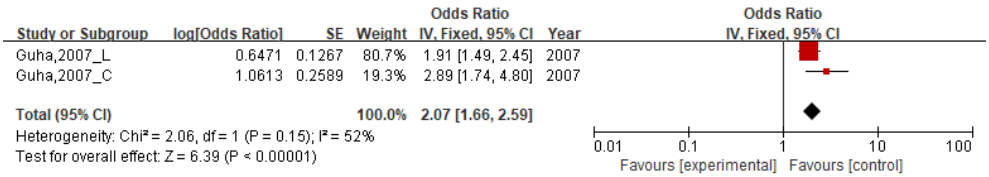


Figure 6. Forest plot for subgroup analysis - D. Oral condition (Periodontal disease assessment)

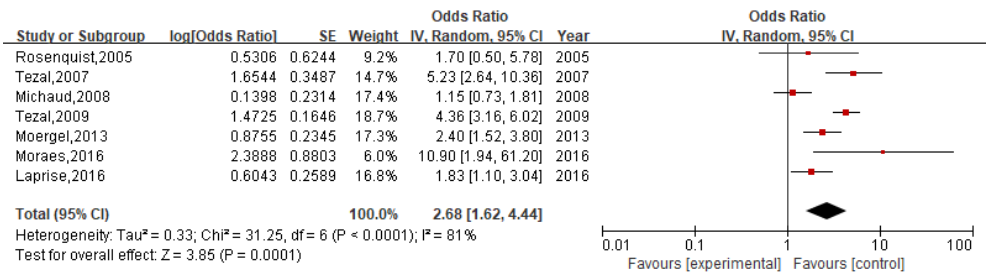


Figure 7. Forest plot for subgroup analysis – ABL + CAL (Periodontal disease assessment)

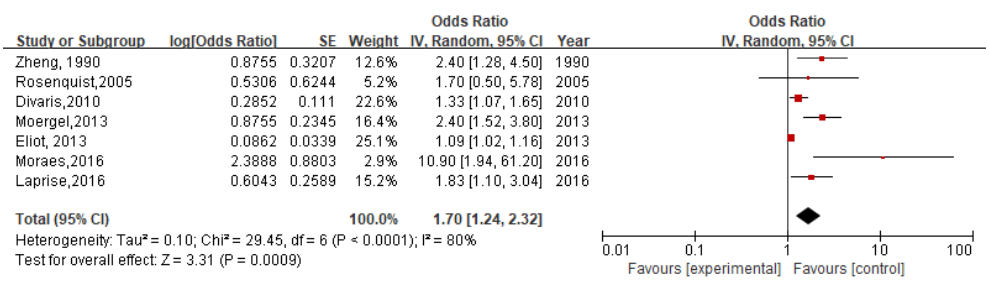


Figure 8. Forest plot for subgroup analysis – Oral cavity (Tumor site)

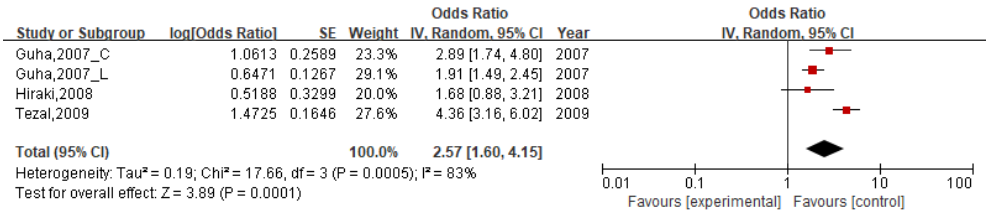


Figure 9. Forest plot for subgroup analysis – Head and neck (Tumor site)

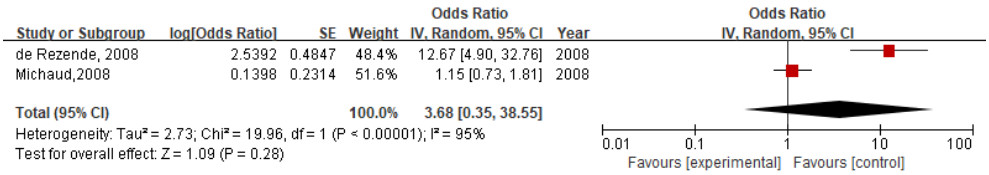


Figure 10. Forest plot for subgroup analysis – Oropharyngeal (Tumor site)

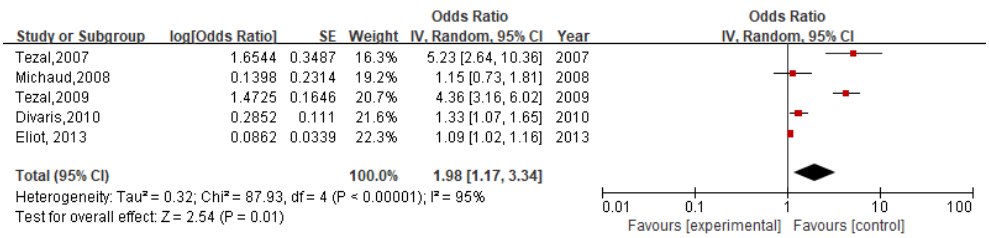


Figure 11. Forest plot for subgroup analysis – USA (Ethnicity)

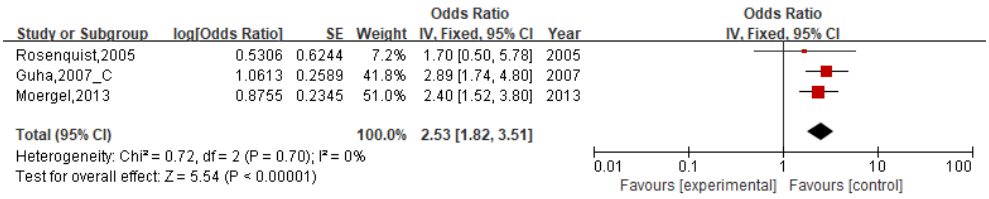


Figure 12. Forest plot for subgroup analysis – Europe (Ethnicity)

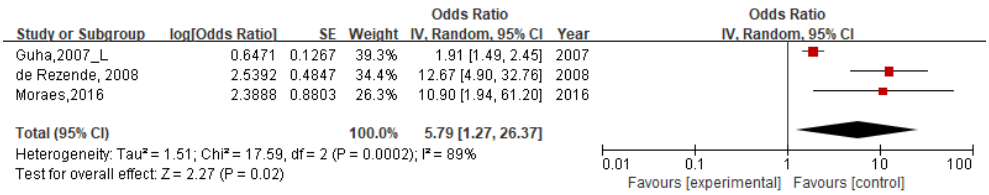


Figure 13. Forest plot for subgroup analysis – Latin America (Ethnicity)

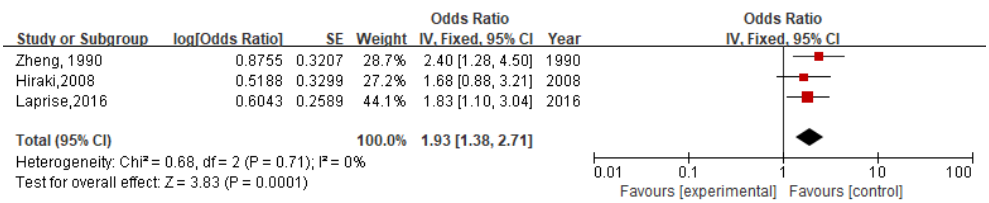


Figure 14. Forest plot for subgroup analysis – Asia (Ethnicity)

Figure 3 Output

Intercept	Standard error	95% lower limit	95% upper limit	t-value	df	p value (1 tailed)	p value (2 tailed)
3.44059	0.78294	1.73470	5.14647	4.39442	12	0.00044	0.00087

Table 2. Egger's regression test

* Regression analysis of 13 studies included in meta-analysis. Data and p value are obtained from comprehensive meta-analysis program.

국문초록

1. 연구목적

구강암은 구강 내에 발병하는 악성 종양으로서 조기진단이 불가능하고 사망률이 높은 유일한 구강 내 질환이다. 다른 암에 비해 발현 빈도는 낮으나 악성도가 높고 생존율은 낮다. 구강암을 일으키는 관련 유발인자로는 담배, 알코올 과다섭취, 방사선치료, 유전적 요인, 인간 유두종 바이러스로 인한 감염 등이 있다. 만성적 염증이 발암단계에서 다양한 역할을 할 수 있음이 부각되고 있다. 통계에 따르면 만성 염증은 15-20%의 암을 발병시킨다고 보고하고 있다. 치주 질환은 구강 내에 존재하는 다양한 치주세균에서 분비되는 내독소 및 염증 유발인자들과 인체 내 면역간의 만성적 불균형에 의한 만성염증이다. 최근 구강 내 만성염증이 구강암의 원인 위험인자로 인식되면서, 치주염과 구강암의 연관성이 많이 보고되고 있다. 그러나 아직까지 구강암과 치주염의 연관성에 대한 학계의 합의는 존재하지 않는다. 치주염과 구강암의 연관성에 대한 합의

를 이끌어 낸다면, 치주염 관리를 통한 구강암의 조기진단 및 예방의 가능성이 있다. 따라서 본 논문의 목적은 치주염과 구강암의 연관성을 기존에 발표된 자료를 활용한 메타분석으로 평가하는 것이다.

2. 연구방법

문헌 선택을 PRISMA guideline에 따라서 PubMed, Cochrane Data-base를 이용하였다. 두 질병의 연선성은 RevMan 5.3 프로그램을 사용하여 분석하였다. 이질성에 따라서 무작위 효과 모형 (random effect model)을 분석에 적용하였다. 하위그룹의 분석 공변수 보정, 연구 디자인, 암의 위치, 인종 그리고 치주염 진단 방법 등을 범주화하였다. 출판 편의는 funnel plot과 Egger's regression test를 사용하여 분석하였다.

3. 결과

2017년까지 보고된 논문들 중 치주염과 구강암의 연관성 검토에 선택

된 논문은 총 14편이었다. 논문들 간의 이질성은 92%이어서 변량 효과 모형이 적용되었다. 치주염과 구강암 발병의 연관성은 변량 효과 모형에서 교차비 (Odds ratio, OR) 가 2.35이었고, 95% 신뢰구간은 1.69 – 3.26 이었다 (p value < 0.00001). Funnel plot과 Egger's regression test를 본 결과 Egger's regression의 p value가 0.00087이였기 때문에 본 메타분석에서는 출판 편의를 포함하지 않았다 (Egger's regression, p value > 0.05). 하위그룹 분석에서 두 질환의 연관성은, 공변수 보정을 한 13개 논문에서 교차비는 2.13로 95%신뢰구간은 1.55 – 2.92 이었고 (p value < 0.00001), 치조골 소실 (Alveolar bone loss, ABL) 을 치주염 진단 방법으로 사용한 5개의 논문에서 교차비는 2.61로 95% 신뢰구간 1.43 – 4.79이였으며, 임상적 결합수준 (Clinical attachment level, CAL)을 치주염 진단 방법으로 사용한 2개의 논문에서 교차비는 3.66이었고, 95% 신뢰구간 0.67 – 20.15 이었다.

4. 결론

총 14개의 논문을 사용하여 분석한 메타분석 결과 치주염과 구강암은 연관성이 있었다. 하위그룹분석 치주염 진단 방법으로 치조골 소실과 임상적 결합수준을 사용한 논문들에서 상대적으로 강한 연관성이 있었다. 따라서 치과 의사들은 치주 건강이 구강암에 영향을 미친다는 중요성을 인식해야 한다.

주요어: 치주염, 구강암, 메타분석

학번: 2014-23058