The Saudi Dental Journal (2023) 35, 714–719

King Saud University

The Saudi Dental Journal

www.ksu.edu.sa
www.sciencedirect.com

ORIGINAL ARTICLE

The analysis of periodontal diseases and squamous cell esophageal cancer: A retrospective study

Tahsinul Haque [a,*], **Abdullah Bin Nabhan** [b,*], **Fatema Akhter** [c], **Hamad Nasser Albagieh** [d]

[a] *Department of Preventive Sciences, College of Dentistry, Dar Al Uloom University, Riyadh, Saudi Arabia*
[b] *Department of Surgical and Diagnostic Sciences, College of Dentistry, Prince Sattam Bin Abdulaziz University, Riyadh 12985, Saudi Arabia*
[c] *Department of Surgical and Diagnostic Sciences, College of Dentistry, Dar Al Uloom University, 13314, Riyadh, Saudi Arabia*
[d] *Department of Oral medicine and Diagnostic Sciences, College of Dentistry, King Saud University, 12372- 7185, Riyadh, Saudi Arabia*

Received 24 February 2023; revised 28 May 2023; accepted 31 May 2023
Available online 7 June 2023

KEYWORDS

Periodontal disease;
Squamous Cell Esophageal Cancer;
Risk factors;
Adults

Abstract *Aim:* The potential links between periodontal disease and various cancers have drawn more and more attention in recent years. The objective of the current study was to investigate any potential associations between parameters of periodontal disease, the number of teeth lost, and the risk of developing squamous cell esophageal cancer in a representative adult sample.

Materials and Methods: The study sample included 178 healthy individuals with matched age and socioeconomic status as controls and 60 patients with the primary histological type of esophageal cancer, Squamous Cell Esophageal Cancer. Data were collected from cases and controls on epidemiological factors like age, gender, smoking status, alcohol intake, socio-economic status, level of education, and prior medical/dental history. The clinical data on periodontal health status was obtained through a clinical examination. This data concerned Probing Pocket Depth (PPD), Clinical Attachment Loss (CAL), the number of teeth lost, and the common risk factors for Squamous Cell Esophageal Carcinoma. Additionally, univariate, and logistic regression models that were modified for potential confounders were used to estimate unadjacent and adjacent odds ratios (ORs) and 95% confidence intervals (CIs).

Results: Lower socioeconomic status ($p = 0.048$) (OR = 1.882, 95% CI = 0.987–3.591), smoking ($p = 0.052$) (OR = 1.768, 95% CI = 0.931–3.359), moderate and heavy alcohol abuse

* Corresponding authors at: Department of Preventive Sciences, College of Dentistry, Dar Al Uloom University, 13314 Riyadh, Saudi Arabia(T. Haque), Department of Surgical and Diagnostic Sciences, College of Dentistry, Prince Sattam Bin Abdulaziz University, 12985 Riyadh, Saudi Arabia(A. Nabhan).
E-mail addresses: mdhaque@dau.edu.sa (T. Haque), a.binnabhan@psau.edu.sa (A. Bin Nabhan).
Peer review under responsibility of King Saud University. Production and hosting by Elsevier.

Production and hosting by Elsevier

https://doi.org/10.1016/j.sdentj.2023.05.030

(p = 0.035) (OR = 1.880, 95% CI = 0.987 3.579), and irregular tooth brushing frequency (p = 0.001) (OR = 0.326, 95% CI = 0.171–0.619) were indeed discovered to be significantly linked.

Conclusion: Individuals with lower socio-economic status, smoking, moderate and heavy alcohol consumption, and irregular tooth brushing frequency were significantly associated with Periodontal diseases and Squamous Cell Esophageal Cancer.

1. Introduction

Periodontal disease (PD), also known as gingivitis and primarily chronic periodontitis, is a chronic, multifactorial inflammatory condition that is partly responsible for tooth loss. It is characterized by the gradual degeneration of the supportive oral tissues and is caused by oral microorganisms (Tonetti and Dyke, 2013). Recently, potential relationships between PD and numerous systemic diseases and disorders have garnered growing attention (Lockhart et al., 2012), all of which may be related to systemic inflammation and infections (Mawardi et al., 2015), including cancers (Fitzpatrick and Katz, 2010). Growing evidence suggests that inflammation plays a role in both periodontitis and cancer (Michaud et al., 2008), and immune-inflammatory processes may play a role in both conditions (Chung et al., 2016). In addition to oral tissues, periodontal bacteria and their by-products associated with chronic periodontitis can cause persistent systemic inflammation (Amabile et al., 2008). Porphyromonas gingivalis and Fusobacterium species have also been identified in esophageal and colorectal carcinomas (Gao et al., 2016; Kostic et al., 2012). These findings suggest that periodontal bacteria are involved in carcinogenesis. The two predominant types of esophageal malignancies are squamous cell esophageal cancer (SCEC) and esophageal adenocarcinoma (EAC), accounting for 90% and 10% of cases, respectively. The risk factors include male sex; age above 50 years; tobacco use; alcohol consumption; lower levels of education and socio-economic status (SES); thermal irritation from intake of hot beverages and food; physical irritation due to tooth loss (poor oral hygiene); carcinogens such as nitrosamines and poly-aromatic hydrocarbons; HPV 16 and 18 infections (Brown et al., 2001; Freedman et al., 2007; Kamangar et al., 2009); and genetic susceptibilities such as loci at PLCE1, C20orf54, ADH1B, and ALDH2 (Cui et al., 2009; Wang et al., 2010). Although studies have revealed an elevated risk of SCEC in PD patients, they have significant limitations, including insufficient sample sizes and correction for potential confounders. Poor oral health, as demonstrated by PD and tooth loss/decay, is a potentially significant and controllable risk factor for changes in the oral microbiome, which may support the development of esophageal cancer (Marques et al., 2019). Numerous epidemiological studies have examined oral health as measured by tooth loss, DMFT score, periodontal health, and oral hygiene practices, including brushing, as risk factors for SCEC (Abnet et al., 2001; Brandilyn et al., 2017; Fitzpatrick and Katz, 2010; Lee et al., 2014). However, prospective studies conducted in different countries found no association. Our study aimed to evaluate the potential contribution of PD indices and tooth loss rates to the incidence of SCEC in an adult population.

2. Materials and Methods

2.1. Study population sample and design

After receiving approval from our institute's ethics committee, Lugansk State Medical University Committee, Ukraine, with study trial no LSMU-CT 6523–893021, this control research was carried out between April 2021 and September 2022 as part of a retrospective study. The study sample was analyzed using SCEC incidence, which was calculated with a 90% confidence interval (CI) and relative precision of 50%, in accordance with the criteria by (Hyman and Reid, 2003). The age group was based on the recommendations of the World Health Organization (Lwanga and Lemeshow, 1991) for calculating PD incidence. The study sample comprised 147 men and 91 women with 178 healthy controls and 60 women with SCEC aged 45–75 years.

2.2. Data collection

Data were collected from cases and controls were based on epidemiological factors such as age, sex, smoking status, alcohol intake, SES, level of education, and prior medical/dental history. The age categories included 45–50, 51–60, 61–70, and 71 + years; educational categories included elementary school and university/college graduates; SES categories included $\leq$ 1,000 and > 1,000 €/month; smoking categories included nonsmokers and former/current smokers; and alcohol consumption categories included light drinking $\leq$ 12.5 g of alcohol/day and moderate-to-heavy drinking > 50 g/day.

To establish the intra-examiner variance, an arbitrarily selected sample of 48 (20%) participants was re-assessed clinically by the same dentist after 3 weeks, and no differences were found between the first and second clinical evaluations (Cohen's kappa = 0.95). During this period, oral hygiene instructions were not provided to the participants.

2.3. Periodontal status examination

The number of teeth present was determined using a standard reference value of 28. This obtained number was then subtracted from 28, in which revealed some lost or missing teeth. A manual periodontal probe (UNC-15; Hu Friedy Mfg Co. Inc., Chicago, IL, USA) was used to assess periodontal health status at six sites (distobuccal, mid-buccal, mesiobuccal, mesiolingual, mid-lingual, and distolingual) on all teeth, excluding the third molars. For each participant, the greatest probing pocket depth (PPD) and clinical attachment loss (CAL) values at six sites per tooth were recorded and coded as dichotomous

variables. The PPD index was classified as 0–3 mm (absence of disease/mild disease) and ≥ 4 mm (moderate to severe disease) (Cutress et al., 1987), while CAL severity was classified as mild, 1–2 mm of attachment loss and moderate/severe, ≥3 mm of attachment loss (Wiebe and Putnins, 2000). Moreover, tooth loss was categorized as none, 1–4, 5–10, and > 10 missing teeth (Yoon et al., 2019).

2.4. Statistical analysis

The greatest PPD and CAL values at the selected sites per tooth for each participant and presence or absence of bleeding on probing were noted and classified as dichotomous variables. The distribution of missing teeth was labeled as 0, 1, 2, and 3 for 0, 1–4, 5–10, and > 10 missing teeth, respectively. Former or current smokers, individuals with a high SES (monthly income ≥ 1,000 €), those with advanced degrees (graduated from university or college), those who reported moderate-to-heavy drinking (> 50 g/day), and those with good oral hygiene (brushing their teeth ≥ 2 times/day) were all labeled as 1. The age groups for those aged 45–50, 51–60, 61–70, and 71 + years were identified as 0, 1, 2, and 3, respectively.

The correlation between independent variables and SCEC risk was evaluated using univariate analysis and chi-square tests. The relationships between the dependent variable, SCEC, and the independent variables discovered using the enter technique were investigated using a multivariate regression model. The 95% CI and unadjusted and adjusted odds ratios (ORs) were also evaluated. To gradually estimate the indices that exhibited significant relationships with the dependent variable, independent variables were added to the stepwise procedure. SPSS version 19.0 was used for statistical analysis and $p < 0.05$ was considered statistically significant.

3. Results

The average age of the participants was 55.6 ± 4.2 years. The primary histological type was SCEC. Adenocarcinoma cases were excluded from the study owing to their distinct etiologies. Following the univariate analysis, Table 1 lists the epidemiological factors of SCEC patients and controls. The odds for developing SCEC were significantly correlated with a higher SES ($p = 0.03$) and irregular tooth brushing frequency ($p = 0.000$).

Table 1 also includes the unadjusted ORs and 95% CI for each variable under consideration. Following the application

Table 1 Univariate analysis of cases and controls regarding each independent variable.

Variables	Cases	Controls	p-value	Odds ratio and 95% confidence interval
Sex				
Male	38 (63.3)	109 (61.2)	0.772	1.093 (0.597–2.003)
Female	22 (36.7)	69 (38.8)		
Age (years)				
45–50	7 (11.7)	22 (12.4)		
51–60	16 (26.7)	47 (26.4)	0.986	
61–70	25 (41.7)	77 (43.3)		
71 +	12 (20.0)	32 (18.0)		
Educational level				
Low	24 (40.0)	91 (51.1)	0.136	0.637 (0.352–1.155)
High	36 (60.0)	87 (48.9)		
Socioeconomic status				
Low	19 (31.7)	85 (47.8)	**0.030***	0.507 (0.273–0.941)
High	41 (68.3)	93 (52.2)		
Smoking status				
No	21 (35.0)	84 (47.2)	0.100	0.603 (0.329–1.105)
Yes	39 (65.0)	94 (52.8)		
Tooth brushing frequency				
< 1 time/day	42 (70.0)	78 (43.8)	**0.000***	2.991 (1.599–5.597)
≥ 2 times/day	18 (30.0)	100 (56.2)		
Alcohol consumption				
< 12.5 g/day	20 (33.3)	82 (46.1)	0.085	0.585 (0.317–1.080)
> 50 g/day	40 (66.7)	96 (53.9)		
Probing pocket depth				
0–3.00 mm	28 (46.7)	86 (48.3)	0.825	0.936 (0.521–1.682)
≥ 4.0 mm	32 (53.3)	92 (51.7)		
Clinical attachment loss				
1.00–2.00 mm	24 (40.0)	93 (52.2)	0.101	0.609 (0.336–1.104)
≥ 3.0 mm	36 (60.0)	85 (47.8)		
Tooth loss				
None	6 (10.0)	16 (9.0)		
1–4 teeth	8 (13.3)	37 (20.8)	0.645	
5–10 teeth	28 (46.7)	78 (43.8)		
> 10 teeth	18 (30.0)	47 (26.4)		

* p-value statistically significant.

of the first method (step 1a) of the logistic regression model, we discovered that SCEC risk was significantly correlated with SES (p = 0.053), smoking (p = 0.067), moderate-to-heavy alcohol consumption (p = 0.051), and irregular tooth brushing frequency (p = 0.001) (Table 2).

Table 2 also includes the unadjusted ORs and 95% CIs for each variable. As shown in Table 2, in the final step of the multivariate regression analysis model (Wald method), there was a significant relationship between the risk of SCEC and SES (p = 0.048), smoking (p = 0.052), moderate-to-heavy alcohol consumption (p = 0.035), and irregular tooth brushing frequency (p = 0.001).

4. Discussion

Although the relationship between PD indices and cancer risk has been studied for over 50 years, the results have not been useful as indicators for cancer prevention strategies. Since evidence suggests that people with PD are likely to develop malignancies of the head and neck, upper gastrointestinal tract, pancreas, and lungs, there has been an increased research interest for this association (Yin et al., 2016; Zeng et al., 2013, 2016). The results of this study demonstrate a strong relationship between the risk of developing SCEC and poor SES, smoking, moderate-to-heavy alcohol intake, and irregular tooth brushing frequency. SCEC risk is increased by epidemiological factors including male sex and poor education (Kamangar et al., 2009; Nagel et al., 2007). The correlation between lower education level and SCEC risk was not confirmed by our study or a large-scale Swedish case-control investigation (Jansson et al., 2005) since non-significant relationships were noted. Furthermore, no correlation between male sex and the risk of developing SCEC was found in our study.

Higher SES has been associated with a decreased likelihood of developing SCEC (Jansson et al., 2005; Nagel et al., 2007), which is consistent with the findings of our study. Smoking is a significant risk factor for PD, and the bacterial microbiome of PD patients varies between smokers and nonsmokers. The microbiomes of smokers are less diverse and more likely to contain organisms associated with PD (Bizzarro et al., 2013). Tooth loss and poor periodontal health are associated with an increased risk of SCEC (Abnet et al., 2001, 2008). Poor oral health, as observed in PD and tooth loss/decay, is a potentially significant and avoidable risk factor suggesting that changes in the oral microbiome may aid in the development of esophageal cancer. Numerous epidemiological studies have examined oral health as a risk factor for SCEC characterized by tooth loss, low DMFT score, poor periodontal health, and poor oral hygiene behaviors. Previous case-control and large-scale prospective cohort studies have frequently revealed a strong correlation between tooth loss and the risk of developing SCEC (Abnet et al., 2001, 2008). Our study found that regular tooth brushing had a preventive effect against SCEC, as demonstrated in other studies (Abnet et al., 2008; Chen et al., 2017). Recent *meta*-analyses indicate an OR of 0.60 when comparing high versus low tooth brushing frequencies (Chen et al., 2015) and an OR of 1.3–1.5 when comparing the highest versus the lowest number of teeth lost (Chen et al., 2015, 2016) for overall EC risk. When the study was limited to SCEC, the ratios were marginally lower for tooth loss and higher for tooth brushing (Chen et al., 2015, 2016).

When studies were limited to EAC, the ratios for tooth loss were slightly lower (Chen et al., 2015, 2016) and marginally higher (Chen et al., 2015) than that of previous studies. Only one study (Abnet et al., 2005) distinguished between the histological types of SCEC and EAC, because poor oral health may have an impact on the histological subtypes. Therefore, the detection of risk associations may have been limited. However, the relative importance of poor oral health as a potential risk factor for EC, especially SCEC, may differ between the high- and low-incidence regions.

Table 2 Association between potential risk factors and BC according to the enter (first step 1a) and Wald (last step 12a) method of the multivariate logistic regression analysis model.

Variables in the equation									
95% CI for Exp (B)									
	Sex	B	S.E	Wald	df	Sig	Exp (B)	Lower	Upper
	Age group	,005	,333	,000	1	,988	1,005	,523	1,931
	Socioeconomic status	,243	,160	2,287	1	,131	,785	,573	1,074
	Educational level	-,587	,339	3,000	1	,063	1,798	,926	3,494
Step 1a	Smoking status	-,467	,330	2,009	1	,156	1,595	,836	3,043
	Alcohol consumption	,543	,340	2,558	1	,067	1,722	,885	3,351
	Tooth brushing frequency	,699	,342	4,182	1	,051	2,011	1,029	3,929
	Probing pocket depth	−1,188	,345	11,874	1	,001	,305	,155	,599
	Clinical attachment loss	,547	,381	2,058	1	,151	,579	,274	1,222
	Tooth loss	,804	,385	2,370	1	,037	1,134	1,051	2,747
	Constant	,343	,196	3,059	1	,080	1,409	,959	2,069
	Socioeconomic status	2,347	,700	11,247	1	,001	,096	———	———
	Smoking status	-,633	,330	3,685	1	**,048***	1,882	,987	3,591
Step 7	Alcohol consumption	,570	,327	3,028	1	**,052***	1,768	,931	3,359
	Tooth brushing frequency	,631	,328	3,692	1	**,035***	1,880	,987	3,579
	Constant	−1,122	,328	11,713	1	**,001***	,326	,171	,619
		1,708	,407	17,581	1	,000	,181	———	———

* p-value statistically significant.

This is the first study to directly analyze the relationship between these indices and SCEC risk. Periopathogens may play a direct role in carcinogenesis. Among PD patients, periodontal bacteria from the mouth cavity enter the bloodstream during activities such as brushing, flossing, and biting (Van and Winkelhoff, 2013). Although oral bacteria in the bloodstream are quickly removed, there is still a significant cumulative exposure to tissues (Tomas et al., 2013). Inflammation is another potential mechanism through which PD may affect systemic processes, such as esophageal carcinogenesis (Chan et al., 2015). PD is the cause of chronic systemic inflammation, which is characterized by elevated levels of C-reactive protein (Noack et al., 2001), interleukin (IL)-1, IL-6, tumor necrosis factor-α, and other biomarkers in the blood circulation, all of which can influence carcinogenesis (Elinav et al., 2013).

Therefore, the human oral microbiome may play a role in the development of SCEC (Ahn et al., 2012). The follow-up of our study was thorough and the cohort was well described, making it possible to investigate confounding factors and the interplay of established risk variables to prevent secondary biased relationships. Another essential finding is that PD was diagnosed by oral clinical examination rather than by self-reporting, eliminating any chance of exposure to misclassified PD. Such incorrect classifications based on self-reported data may result in an underestimation of the association under investigation. The potential for confounding the risk estimates due to new unidentified variables is a possible restriction.

5. Conclusion

Lower SES, smoking, moderate-to-heavy alcohol consumption, and irregular tooth brushing frequency were significantly associated with PD and SCEC. Regular tooth brushing has a protective effect against SCEC, as confirmed by our study.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgment

The author was thankful to the Deanship of Graduate Studies and Scientific Research at Dar Al Uloom University for the financial Support for this project and to Dr. Tshetiz Dahal, Clinical Researcher, Lugansk State Medical University, Luhansk Oblast, 93000 Luhansk, Ukraine, for assisting data collections.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.sdentj.2023.05.030.

References

Abnet, C.C., Qiao, Y.L., Mark, S.D., Dong, Z.W., Taylor, P.R., Dawsey, S.M., 2001. Prospective study of tooth loss and incident esophageal and gastric cancers in China. Cancer Causes Control. 12 (9), 847–854.

Abnet, C.C., Kamangar, F., Dawsey, S.M., Stolzenberg-Solomon, R. Z., Albanes, D., et al, 2005. Tooth loss is associated with increased risk of gastric non-cardia adenocarcinoma in a cohort of Finnish smokers. Scand. J. Gastroenterol. 40, 681–687.

Abnet, C.C., Kamangar, F., Islami, F., Nasrollahzadeh, D., BrennanP, A.K., et al, 2008. Tooth loss and lack of regular oral hygiene are associated with higher risk of esophageal squamous cell carcinoma. Cancer Epidemiol. Biomark. Prev. 17, 3062–3308.

Ahn, J., Chen, C.Y., Hayes, R.B., 2012. Oral microbiome and oral and gastrointestinal cancer risk. Cancer Causes Control. 23, 399–404.

Amabile, N., Susini, G., Pettenati-Soubayroux, I., Bonello, L., Gil, J.-M., Arques, S., et al, 2008. Severity of periodontal disease correlates to inflammatory systemic status and independently predicts the presence and angiographic extent of stable coronary artery disease. J. Intern. Med. 263, 644–652.

Bizzarro, S., Loos, B.G., Laine, M.L., Crielaard, W., 2013. Zaura E Subgingival microbiome in smokers and non-smokers in periodontitis: an exploratory study using traditional targeted techniques and a next-generation sequencing. J. Clin. Periodontol. 40, 483–492.

Brandilyn, A.P., Jing, W., Zhiheng, P., Liying, Y., Mark, P.P., Neal, D.F., et al, 2017. Oral microbiome composition reflects prospective risk for esophageal cancers. Cancer Res. 77 (23), 6777–6787.

Brown, L.M., Hoover, R., Silverman, D., Baris, D., Hayes, R., Swanson, G.M., et al, 2001. Excess incidence of squamous cell esophageal cancer among US Black men: role of social class and other risk factors. Am. J. Epidemiol. 153, 114–122.

Chan, D.S., Bandera, E.V., Greenwood, D.C., Norat, T., 2015. Circulating c-reactive protein and breast cancer risk-systematic literature review and meta-analysis of prospective cohort studies. Ca Epidemiol. Biomarkers Prev. 10, 1439–1449.

Chen, H., Nie, S., Zhu, Y., Lu, M., 2015. Teeth loss, teeth brushing and esophageal carcinoma: A systematic review and meta-analysis. Sci. Rep. 5, 15203.

Chen, X., Yuan, Z., Lu, M., Zhang, Y., Jin, L., Ye, W., 2017. Poor oral health is associated with an increased risk of esophageal squamous cell carcinoma-A population-based case-control study in China. Int. J. Cancer 140, 626–635.

Chen, Q.L., Zeng, X.T., Luo, Z.X., Duan, X.L., Qin, J., Leng, W.D., 2016. Tooth loss is associated with increased risk of esophageal cancer: Evidence from a meta-analysis with dose-response analysis. Sci. Rep. 6, 18900.

Chung, S.D., Tsai, M.C., Huang, C.C., Kao, L.T., Chen, C.H., 2016. A population-based study on the associations between chronic periodontitis and the risk of cancer. Int. J. Clin. Oncol. 21 (2), 219–223.

Cui, R., Kamatani, Y., Takahashi, A., Usami, M., Hosono, N., Kawaguchi, T., et al, 2009. Functional variants in ADH1B and ALDH2 coupled with alcohol and smoking synergistically enhance esophageal cancer risk. Gastroenterology 137, 1768–1775.

Cutress, T.W., Ainamo, J., Sardo-Infrri, J., 1987. The community periodontal index of treatment needs (CPITN) procedure for population groups and individuals. Int. Dent. J. 37 (4), 222–233.

Elinav, E., Nowarski, R., Thaiss, C.A., Hu, B., Jin, C., Flavell, R.A., 2013. Inflammation-induced cancer: crosstalk between tumours, immune cells and microorganisms. Nat. Rev. Cancer 13, 759–771.

Fitzpatrick, S.G., Katz, J., 2010. The association between periodontal disease and cancer: a review of the literature. J. Dent. 38, 83–95.

Freedman, N.D., Abnet, C.C., Leitzmann, M.F., Mouw, T., Subar, A. F., Hollenbeck, A.R., et al, 2007. A prospective study of tobacco, alcohol, and the risk of esophageal and gastric cancer subtypes. Am. J. Epidemiol. 165, 1424–1433.

Gao, S., Li, S., Ma, Z., Liang, S., Shan, T., Zhang, M., et al, 2016. Presence of Porphyromonas gingivalis in esophagus and its association with the clinicopathological characteristics and survival in patients with esophageal cancer. Infect. Agent Cancer 11, 3.

Hyman, J.J., Reid, B.C., 2003. Epidemiologic risk factors for periodontal attachment loss among adults in the United States. J. Clin. Periodontol. 30 (3), 230–237.

Jansson, C., Johansson, A.L., Nyren, O., Lagergren, J., 2005. Socioeconomic factors and risk of esophageal adenocarcinoma: a nationwide Swedish case-control study. Cancer Epidemiol. Biomarkers Prev. 14, 1754–1761.

Kamangar, F., Chow, W.H., Abnet, C.C., Dawsey, S.M., 2009. Environmental causes of esophageal cancer. Gastroenterol. Clin. North Am. 38 (27–57), vii.

Kostic, A.D., Gevers, D., Pedamallu, C.S., Michaud, M., Duke, F., Earl, A.M., et al, 2012. Genomic analysis identifies association of Fusobacterium with colorectal carcinoma. Genome Res. 22, 292–298.

Lee, Y.-L., Hu, H.-Y., Yang, N.-P., Chou, P., Chu, D., 2014. Dental prophylaxis decreases the risk of esophageal cancer in males; A nationwide population-based study in Taiwan. PLoS ONE 9 (10), e109444.

Lockhart, P.B., Bolger, A.F., Papapanou, P.N., Osinbowale, O., Trevisan, M., Levison, M.E., et al, 2012. Periodontal disease and atherosclerotic vascular disease: does the evidence support an independent association?: A scientific statement from the American Heart Association. Circulation 125, 2520–2544.

Lwanga, S.K., Lemeshow, S., 1991. World Health Organization. Sample size determination in health studies: a practical manual. World Health Organization.

Marques, M.M., Berrington de Gonzalez, A., Beland, F.A., Browne, P., Demers, P.A., Lachenmeier, D.W., et al, 2019. Advisory Group recommendations on priorities for the IARC Monographs. Lancet Oncol. 20, 763–764.

Mawardi, H.H., Elbadawi, L.S., Sonis, S.T., 2015. Current understanding of the relationship between periodontal and systemic diseases. Saudi Med. J. 36, 150–158.

Michaud, D.S., Liu, Y., Meyer, M., Giovannucci, E., Joshipura, K., 2008. Periodontal disease, tooth loss, and cancer risk in male health professionals: a prospective cohort study. Lancet Oncol. 9, 550–558.

Nagel, G., Linseisen, J., Boshuizen, H.C., Pera, G., Del Giudice, G., et al, 2007. Socioeconomic position and the risk of gastric and oesophageal cancer in the European Prospective Investigation into Cancer and Nutrition (EPIC-EURGAST). Int. J. Epidemiol. 36, 66–76.

Noack, B., Genco, R.J., Trevisan, M., Gross, S., Zambon, J.J., De Nardin, E., 2001. Periodontal infections contribute to elevated systemic C-reactive protein level. J. Periodontol. 72, 1221–1227.

Tomas, I., Diz, P., Tobias, A., Scully, C., Donos, N., 2013. Periodontal health status and bacteraemia from daily oral activities: systematic review/meta-analysis. J. Clin. Periodontol. 39, 213028.

Tonetti, M.S., Van Dyke, T.E., 2013. Working group 1 of the joint EFP/AAP workshop Periodontitis and atherosclerotic cardiovasculardisease: consensus report of the Joint EFP/AAP Workshop on Periodontitis and Systemic Diseases. J. Periodontol. 84 (suppl), S24–S29.

Van Dyke, T.E., van Winkelhoff, A.J., 2013. Infection and inflammatory mechanisms. J. Periodontol. 84, S1–S7.

Wang, L.D., Zhou, F.Y., Li, X.M., Sun, L.D., Song, X., Jin, Y., et al, 2010. Genome-wide association study of esophageal squamous cell carcinoma in Chinese subjects identifies a susceptibility locus at PLCE1. Nat. Genet. 42, 759–763.

Wiebe, C.B., Putnins, E.E., 2000. The periodontal disease classification system of the American academy of periodontology an update. J. Can. Dent. Assoc. 66, 594–597.

Yin, X.H., Wang, Y.D., Luo, H., Zhao, K., Huang, G.L., Luo, S.Y., et al, 2016. Association between tooth loss and gastric cancer: a metaanalysis of observational studies. PLoS ONE 11, e 0149653.

Yoon, H.S., Wen, W., Long, J., Zheng, W., Blot, W.J., Cai, Q., 2019. Association of oral health with lung cancer risk in a low-income population of African Americans and European Americans in the Southeastern United States. Lung Cancer 127, 90–95.

Zeng, X.T., Deng, A.P., Li, C., Xia, L.Y., Niu, Y.M., Leng, W.D., 2013. Periodontal disease and risk of head and neck cancer: a meta-analysis of observational studies. PLoS ONE 8, e79017.

Zeng, X.T., Xia, L.Y., Zhang, Y.G., Li, S., Leng, W.D., Kwong, J.S., 2016. Periodontal disease and incident lung cancer risk: a metaanalysis of cohort studies. J. Periodontol. 87, 1158–1164.