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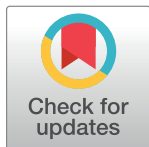
Dental health in patients with and without HPV-positive oropharyngeal and tongue cancer

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Data Availability Statement: The datasets generated and analyzed during the current study are not publicly available because they contain information that could compromise research participant privacy. The national law (Act on Secondary Use of Health and Social Data) in Finland unfortunately prevents the sharing of material containing personal information at the individual level. Restrictions on data sharing were also imposed by the ethics committee of the Hospital District of Helsinki and Uusimaa (eettinen.toimikunta@hus.fi). Data access requests may be

Abstract

Background

Human papilloma virus is associated with oral and oropharyngeal cancer. Our aim was to examine oral health in patients with oropharyngeal (OPSCC) and oral tongue cancer (OTSCC), expecting better oral health among OPSCC patients.

Material and methods

Fifty-five OPSCC patients with known HPV status and 59 OTSCC patients were randomly selected from a list of consecutive patients of the Helsinki University Hospital, Finland. Oral health was assessed from panoramic jaw radiographs. Total Dental Index (TDI) summarizing the dental health status was calculated and Finnish population study data were used for comparison. Descriptive statistics were used for analyses.

Results

Patients with HPV-positive OPSCC had higher periapical lesion index compared with HPV-negative OPSCC patients or with OTSCC patients. Residual roots were more common among OPSCC patients compared with OTSCC patients, because of their higher occurrence among HPV-negative OPSCC patients compared with OTSCC patients. Similarly, modified TDI score was significantly higher among OPSCC patients than among OTSCC patients, because of higher TDI score among HPV-negative OPSCC patients compared with OTSCC patients. OPSCC patients more often used a removable prosthesis than OTSCC patients. Dental health of the cancer patients was poorer when compared with the population data.

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Conclusions

Our study hypothesis was only partly confirmed. Periapical lesions were more prevalent among HPV-positive OPSCC patients, compared with the other groups. The number of residual roots was higher among HPV-negative subgroup. Thus, OPSCC patients had worse oral health parameters than OTSCC patients.

Introduction

Head and neck cancers (HNCs) represent a global public health problem with an estimated 355 000 new cases of oral cancer and 93 000 oral pharyngeal cancer, respectively, occurring in 2018 worldwide [1]. Smoking and alcohol consumption are the most important risk factors for these tumors, and they typically present at older age. However, an increasing subset of especially oropharyngeal cancers (OPSCC) is related to human papillomavirus (HPV) infection [2]. The average age of patients with HPV-related cancer seems to be lower than that of the non-HPV-related group and these populations also differ in their drinking and smoking habits [3]. In a recent study on OPSCC patients, smoking and heavy alcohol consumption were significantly more common among HPV-/p16- OPSCC patients but also rather common among HPV+/p16+ patients [4]. Furthermore, as another recent study showed, there seems to be a shift towards the HPV-related oral and oropharyngeal cancer when compared with HPV-negative cases, in other words, the incidence of HPV+ cases are increasing [5]. Predisposing factors also include nutritional deficits, occupational hazards, anemia, fungal and certain other viral infections, hereditary factors, immunosuppression, and potentially malignant disorders such as leukoplakia and oral lichen planus [6, 7].

There is cumulative evidence that oral infections and poor oral hygiene are associated with HNCs but the exact mechanism remains unclear [8–16]. Most clearly poor oral hygiene manifests itself in the oral cavity as caries and periodontitis. Periodontitis is a chronic infection and causes chronic inflammation locally in the oral cavity and also has adverse effects on systemic health. An association has been suggested between periodontitis and certain subsites of HNC, and it seems to be strongest for oral cavity, followed by oropharynx and larynx [11, 12]. Substantial evidence supports the role of chronic infection and inflammation in initiating and promoting carcinogenesis in general [17]. Furthermore, it has even been proposed that cariogenic bacterial flora might be a protective factor against cancer [8]. Evidence also suggests that carcinogenic effect of alcohol is mediated by its first metabolite—acetaldehyde. Oral bacteria can enzymatically convert ethanol to acetaldehyde, and this has been proposed as a mechanism between poor dental status and increased oral cancer risk [9, 18]. Further, poor oral hygiene-associated bacterial overgrowth and ecological shift towards acetaldehyde producing bacteria may contribute to carcinogenesis. There is also a correlation between poor oral hygiene and the number of extracted teeth with the prevalence of HPV, which finding emphasizes the importance for maintaining good oral health also in this regard [19].

The primary aim of this study was to examine dental health in a subset of HNC patients, namely those with oral tongue cancer (OTSCC) and those with OPSCC whose HPV status had been analyzed. Our secondary aim was to compare these two tumor sites in terms of oral health as our hypothesis was that the OPSCC patients would have better oral health status. Radiologic assessment, *i.e.* panoramic tomography taken at the time of cancer diagnosis, was used to evaluate the accumulated burden of dental diseases. A Finnish population study data on dental health were used for comparison.

Subjects and methods

Patients

All consecutive patients diagnosed with OPSCC (n = 132) or OTSCC (n = 90) between the years 2005 and 2008 at the Helsinki University Hospital, Helsinki, Finland were identified from hospital registries. For further assessment, 138 patients (69 patients with OPSCC and 69 patients with OTSCC) were randomly selected from the consecutive patient groups. Oral health at diagnosis among the study population was assessed by reviewing panoramic radiographs. Patients with no panoramic radiograph at the time of diagnosis or patients who had previously received radiotherapy to the head and neck region (14 OPSCC and 10 OTSCC patients) were considered ineligible for our analysis. Eventually, the study sample consisted of 114 patients (55 OPSCC patients and 59 OTSCC patients).

Panoramic radiographs

All panoramic radiographs were analyzed by two persons (J.S. and an experienced dental radiologist A.S.). The other reader (J.S.) analysed the images first independently, followed by consensus reading. For practical reasons the examiners were not blinded to cancer status. The following variables were determined: number of teeth in the upper and lower jaw, carious lesions extending to dentin, root fragments, periapical lesions (apical periodontitis or widening of the periodontal space), endodontically treated teeth, technically inadequate endodontic treatments (the gap between filling and apex more than 3 mm, pulpotomy, or overfilling), and furcation lesions, as well as horizontal bone loss, vertical bone pockets, pericoronitis (radiolucent follicle around third molars with a diameter of 3 mm or more), and dental calculus. The Total Dental Index introduced by Mattila et al. [20] was modified and used to illustrate the severity of dental disease burden.

Clinicopathological variables

Details on covariates including age, gender, smoking, alcohol consumption, denture wear, record of clinical mucosal lesions in oral cavity apart from the tumor, existing diagnoses and medications was manually collected from medical records. TNM stage and tumor grade were recorded for all patients and tumor HPV status for patients with OPSCC only. Existing diagnoses were categorized according to the 10th revision of the World Health Organization International Classification of Diseases (ICD-10) and information on medications according to a specific national drug classification (www.terveysportti.fi). Ex-smokers with smoking cessation of over five years were considered non-smokers. All patients in both groups had histopathological squamous cell carcinoma either in the oral cavity or oropharynx. The management of all patients was discussed at a multidisciplinary tumor board at the university hospital and was based on a national treatment protocol. It typically consisted of surgery, (chemo)radiotherapy or their combination.

Statistical data analysis

We used SPSS Version 25.0 (SPSS, Inc., Chicago, IL, USA) for statistical data analysis. The cross-tabulation of categorical variables was performed using χ^2 test with asymptotic or exact p-value when best appropriate. Independent samples T-test was used to compare means of normally distributed continuous variables between two independent groups. Mann-Whitney U test was used to compare two independent groups with skewed distribution. A two-sided P value <0.05 was considered statistically significant.

Ethics statement

This study is a retrospective patient chart review and according to the Finnish Law no Research Ethics Board approval was needed. An institutional research permission was granted (§121, 02.07.2014). All procedures performed in this study involving information on patients were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 World Medical Association Declaration of Helsinki and its later amendments or comparable ethical standards.

Informed consent

As this study was a retrospective chart review, no informed consent was needed according to the Finnish legislation.

Results

Clinicopathological characters of the OPSCC and OTSCC patients

[Table 1](#) shows the baseline characteristics of the study population. The mean age of the whole study population was 59.5 years (range 30.4–89.6 years), and the male-to-female ratio was approximately 2:1. Of the patients for whom the information was available 58% were smokers and 37% were heavy alcohol users. Stage IV and grade 3 tumors were most frequently seen. The median number of drugs in daily use was 1 (range 0–9). Of the patients, 11% were edentulous, 23% had a record of removable prosthesis and 10% had mucosal lesions (other than cancer) in the oral cavity. Ten percent of them had a former cancer diagnosis (*i.e.* C00-D48) and 8% had been previously diagnosed with a head and neck area digestive system diagnosis (*i.e.* K00-K14).

The OPSCC and OTSCC groups did not have a statistically significant difference with regard to age, gender, edentulousness, smoking, heavy alcohol consumption, or number of drugs in use. However, TNM stage and tumor grade were significantly higher in the OPSCC group. Removable prostheses were significantly more frequent in the OPSCC group and mucosal lesions in oral cavity were significantly more frequent in the OTSCC group. There were more C00-D48 category diagnoses and K00-K14 category diagnoses in the OTSCC group. Twenty-one OPSCC patients had a HPV-positive tumor while 24 had a HPV-negative tumor ([Table 2](#)).

Dental status among OPSCC and OTSCC patients

On average, patients had 19 teeth, of which 10 were in mandible and nine in maxilla. Half of them *i.e.* 49% had carious lesions, 14% had residual roots, 54% had vertical bone pockets, 29% had furcation lesions, and 40% had periapical lesions. Of all patients 61% had at least one endodontically treated tooth, and 65% out of these had at least one technically inadequate endodontic treatment. Horizontal bone loss was recorded in 69%, and of those 84% had more than one affected tooth. Comparing the dental status parameters of our patients with known results from Finnish population register studies, the prevalence of caries was higher among the cancer patients; in the mean 49% of patients had at least one carious lesion compared with 32% of the general population, while no difference was found in periodontitis parameters in this respect [[21](#), [22](#)].

The HNC subgroups appeared to be fairly similar in terms of their dental variables. Interestingly, patients with HPV-positive OPSCC had higher periapical lesion index compared with HPV-negative OPSCC patients and with OTSCC patients. The number of residual roots was also higher among OPSCC patients than among OTSCC patients. The subgroup analysis

Table 1. Baseline clinic-pathological characteristics of the patients with oropharyngeal (OPSCC) or oral tongue (OTSCC) squamous cell carcinoma.

	Total	OPSCC	OTSCC	P
No of patients (%)	114 (100)	55 (48.2)	59 (51.8)	
Age yrs. (range)	59.5 (30.4–89.6)	59.5 (33.3–89.6)	59.5 (30.4–85.7)	0.980
Gender				0.174
Male	78 (68.4)	41 (74.5)	37 (62.7)	
Female	36 (31.6)	14 (25.5)	23 (37.3)	
Edentulous	12 (10.5)	5 (9.1)	7 (11.9)	0.630
Smoking				0.285
Yes	56 (58.3)	30 (63.8)	26 (53.1)	
No	40 (41.7)	17 (36.2)	23 (46.9)	
Missing	18	8	10	
Heavy alcohol consumption				0.432
Yes	29 (36.7)	13 (32.5)	16 (41.0)	
No	50 (63.3)	27 (67.5)	23 (59.0)	
Missing	35	15	20	
TNM stage				<0.001
I	21 (18.8)	4 (7.4)	17 (29.3)	
II	32 (28.6)	7 (13.0)	25 (43.1)	
III	11 (9.8)	6 (11.1)	5 (8.6)	
IV	48 (42.9)	37 (68.5)	11 (19.0)	
Missing	2	1	1	
Grade				0.002
1	23 (26.7)	8 (14.8)	15 (46.9)	
2	30 (34.9)	19 (35.2)	11 (34.4)	
3	33 (38.4)	27 (50.0)	6 (18.8)	
Missing	28	1	27	
HPV status				
Positive		21 (46.7)		
Negative		24 (53.3)		
Missing		10		
Median number of drugs in use (range)	1 (0–9)	1 (0–9)	2 (0–9)	0.411
Mucosal lesion	11 (9.6)	2 (3.6)	9 (15.3)	0.036
C00-D48	11 (9.6)	2 (3.6)	9 (15.3)	0.036
K00-K14	9 (7.9)	1 (1.8)	8 (13.6)	0.033

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revealed that the number of residual roots was higher among HPV-negative OPSCC patients compared with those with OTSCC. Similarly, modified TDI score was significantly higher among OPSCC patients than among OTSCC, because of higher number of residual roots among HPV-negative OPSCC than among OTSCC. In addition, use of removable prostheses was more frequent among OPSCC patients than among OTSCC patients.

Discussion

We retrospectively reviewed a series of 114 panoramic tomography studies of OPSCC and OTSCC patients to evaluate their oral health status at the time of cancer diagnosis. In most aspects, the two groups were not found to be substantially different from each other. Periodontal disease—whether assessed by clinical attachment loss, alveolar bone loss, or probing pocket depth—seems to associate with elevated risk for HNC [11, 15, 23]. On the other hand, dental

Table 2. Dental indexes of the study population with oropharyngeal (OPSCC) and oral tongue (OTSCC) squamous cell carcinoma.

	Total	OPSCC			OTSCC	P
		Total	HPV+	HPV-		
No of patients (%)	114 (100)	55 (48.2)	21 (46.7)	24 (53.3)	59 (51.8)	
Caries						0.129 ^a
0	36 (31.6)	12 (21.8)	7 (33.3)	4 (16.7)	24 (40.7)	0.079 ^b
1	40 (35.1)	22 (40.0)	9 (42.9)	11 (45.8)	18 (30.5)	0.703 ^c
2	22 (19.3)	13 (23.6)	5 (23.8)	4 (16.7)	9 (15.3)	0.136 ^d
3	16 (14.0)	8 (14.5)	0 (0.0)	5 (20.8)	8 (13.6)	
Periodontitis						0.608 ^a
0	35 (30.7)	16 (29.1)	6 (28.6)	7 (29.2)	19 (32.2)	0.738 ^b
1	37 (32.5)	17(30.9)	8 (38.1)	8 (33.3)	20 (33.9)	1.000 ^c
2	36 (31.6)	19 (34.5)	7 (33.3)	7 (29.2)	17 (28.8)	0.695 ^d
3	6 (5.3)	3 (5.5)	0 (0.0)	2 (8.3)	3 (5.1)	
Periapical lesions						0.123 ^a
0	36 (31.6)	13 (23.6)	2 (9.5)	8 (33.3)	23 (39.0)	0.029 ^b
1	63 (55.3)	33 (60.0)	14 (66.7)	14 (58.3)	30 (50.8)	0.013 ^c
2	8 (7.0)	5 (9.1)	2 (9.5)	2 (8.3)	3 (5.1)	1.000 ^d
3	7 (6.1)	4 (7.3)	3 (14.3)	0 (0.0)	3 (5.1)	
Pericoronitis						0.482 ^a
0	113 (99.1)	54 (98.2)	21 (100.0)	23 (95.8)	59 (100.0)	1.000 ^b
1	1 (0.9)	1 (1.8)	0 (0.0)	1 (4.2)	0 (0.0)	0.289 ^d
Residual roots						0.006 ^a
0	98 (86.0)	42 (76.4)	17 (81.0)	19 (79.2)	56 (94.9)	0.720 ^b
1	7 (6.1)	5 (9.1)	2 (9.5)	2 (8.3)	2 (3.4)	0.107 ^c
2	5 (4.4)	5 (9.1)	2 (9.5)	1 (4.2)	0 (0.0)	0.032 ^d
≥3	4 (3.5)	3 (5.5)	0 (0.0)	2 (8.3)	1 (1.7)	
Furcation lesions						0.412 ^a
0	81 (71.1)	35 (63.6)	12 (57.1)	17 (70.8)	46 (78.0)	0.388 ^b
1	14 (12.3)	10 (18.2)	4 (19.0)	4 (16.7)	4 (6.8)	0.281 ^c
2	6 (5.3)	4 (7.3)	2 (9.5)	1 (4.2)	2 (3.4)	1.000 ^d
≥3	13 (11.4)	6 (10.9)	3 (14.3)	2 (8.3)	7 (11.9)	
Vertical bone pockets						0.916 ^a
						0.506 ^b
0	53 (46.5)	21 (38.2)	7 (33.3)	10 (41.7)	32 (54.2)	0.692 ^c
1	24 (21.1)	17 (30.9)	6 (28.6)	8 (33.3)	7 (11.9)	0.849 ^d
2	10 (8.8)	7 (12.7)	4 (19.0)	2 (8.3)	3 (5.1)	
≥3	27 (23.7)	10 (18.2)	4 (19.0)	4 (16.7)	17 (28.8)	
Endodontic treatments						0.260 ^a
						0.310 ^b
0	45 (39.5)	20 (36.4)	4 (19.0)	9 (37.5)	25 (42.4)	0.054 ^c
1–2	33 (28.9)	15 (27.3)	8 (38.1)	6 (25.0)	18 (30.5)	0.534 ^d
3–4	25 (21.9)	13 (23.6)	5 (23.8)	7 (29.2)	12 (20.3)	
≥5	11 (9.6)	7 (12.7)	4 (19.0)	2 (8.3)	4 (6.8)	
Removable prostheses						0.047 ^a
						0.142 ^b
No	88 (77.2)	38 (69.1)	18 (85.7)	16 (66.7)	50 (84.7)	1.000 ^c
Yes	26 (22.8)	17 (30.9)	3 (14.3)	8 (33.3)	9 (15.3)	0.078 ^d
TDI score						0.018 ^a

(Continued)

Table 2. (Continued)

	Total	OPSCC			OTSCC	P
		Total	HPV+	HPV-		
0–2	40 (35.1)	12 (21.8)	8 (38.1)	4 (16.7)	28 (47.5)	0.173 ^b
3–5	65 (57.0)	38 (69.1)	12 (57.1)	18 (75.0)	27 (45.8)	0.678 ^c
6–8	9 (7.9)	5 (9.1)	1 (4.8)	2 (8.3)	4 (6.8)	0.029^d

^a OPSCC vs. OTSCC

^b HPV+ OPSCC vs. HPV- OPSCC

^c HPV+ OPSCC vs. OTSCC

^d HPV- OPSCC vs. OTSCC

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caries may act inversely, protecting from cancer [24]. Periodontal diseases and dental caries are common bacterial diseases in general population associated with dental plaque and poor oral hygiene [21, 22, 25–28]. But they are counterparts to each other in the sense that cariogenic bacterial flora is associated with periodontal health [29, 30]. Missing teeth are often used as a substitute for periodontitis, but in a retrospective study design it is impossible to know the reason for tooth loss. In the absence of control patients, we were not able to establish whether or not our findings regarding caries and periodontal disease support findings from previous studies. Nevertheless, caries and periodontal disease indicate poor oral hygiene.

Our hypothesis was that the OPSCC patients would have better oral health status. Contrary to that, considerable similarity of dental variables between OPSCC and OTSCC groups was found. However, this finding might be explained by the close anatomical relation of OTSCC and OPSCC and their common risk factors. If elevated acetaldehyde levels in saliva mediate the carcinogenic effect of poor dental health, as predicted by Homann et al. [8, 18], it would be rather straightforward to assume that while saliva is swallowed the effect will be spread from oral cavity also to oropharynx. Periodontal disease, on the other hand, is known to influence systemic health and to cause disease beyond the oral cavity [31]. According to our analysis, the differences between OPSCC and OTSCC in dental variables were scarce. However, findings of higher number of periapical lesions and residual roots among OPSCC patients may indicate slightly better dental health among OTSCC patients, but the reason for this remains unclear.

The main difference in risk factors between OPSCC and OTSCC seems to be the proportion of HPV induced carcinomas. Findings by Bui et al. [32] suggest that poor oral health may increase the odds of oral HPV infection. Thus, poor oral health would indirectly increase the risk of oropharyngeal cancers [33]. A review article by Combes and Franceschi [34] suggested that the probability of a HPV-attributable fraction of cancer in the oral cavity was estimated to be at least 5-fold lower compared to that in the oropharynx, and HPV prevalence among oral cavity cancer to be about 3%. Worldwide the trend seems to be that even though the use of tobacco declines the incidence of OPSCC rises. This is suggested to be attributable to increased oral HPV infections [35, 36]. Patients with HPV-positive tumors are usually younger and less likely to have a history of smoking or alcohol use than patients with HPV-negative tumors [4]. HPV-positive tumors are diagnosed at more advanced stages, but prognosis among HPV-positive subgroup tends to be better than that of HPV-negative subgroup [36, 37].

We screened the medical records for former head and neck area (K00-K14) and oral cavity mucosal lesions occurring concurrently with the actual tumor, as they are mucosal conditions with a risk of malignant transformation [7, 38]. The fact that OPSCC group had less former K00-K14 category diagnoses and also less oral mucosal lesions recorded at the time of cancer diagnosis may be related to absence of field cancerization effect in HPV-related OPSCC [39].

In the literature the association between mucosal lesions and cancer is mainly studied in oral cavity [7, 38], although it is known that some of these potentially malignant disorders can occur even in oesophagus [40]. However, there is also an assumed causality between these disorders and oropharyngeal cancers [41]. In addition, former cancer and tumor diagnoses (C00-D48) were more common among OTSCC patients. The finding that OTSCC patients had more oral cavity mucosal lesions, K00-K14 and C00-D48 diagnoses, may be related to higher exposure to tobacco carcinogens, heavy drinking lifestyle, and higher occurrence of comorbidities among the OTSCC patients, while OPSCC patients are increasingly influenced by HPV.

The present study included patients from consecutive series of OPSCC and OTSCC patients during the time period when the incidence of HPV-related OPSCC was rising in Finland. All patients received diagnostic evaluation and treatment at a public tertiary care center, and the impact of socio-economic factors in the management of these patients remains minor which is a strength. However, the retrospective setting of this study partially complicated recoding of the data, as some information remained inexact or unmentioned in the medical records. Thus, the sample sizes used in the statistical analyses were limited, which is a weakness in our study. Finally, it should be mentioned that HPV vaccinations are expected to reduce the number of OPSCC cases in the future [42]. However, beyond those young generations now being vaccinated there remain many age groups with risk for developing HPV-related cancer. Focus should thus be placed on careful clinical oral and oropharyngeal examination to identify any suspicious lesions.

Conclusion

In conclusion, the differences in dental health between the OPSCC and OTSCC patients remained relatively limited with some factors indicating better dental health among OTSCC patients. These findings call for further validation in larger cohorts with a case-control or longitudinal setting.

Author Contributions

Conceptualization: Antti Mäkitie, Jukka H. Meurman.

Data curation: Lauri Jouhi, Jenna Sikiö, Rayan Mroueh, Jukka H. Meurman.

Formal analysis: Lauri Jouhi, Anni Suomalainen, Antti Mäkitie.

Funding acquisition: Jukka H. Meurman.

Investigation: Lauri Jouhi, Jenna Sikiö, Anni Suomalainen, Rayan Mroueh, Antti Mäkitie, Jukka H. Meurman.

Project administration: Antti Mäkitie, Jukka H. Meurman.

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Writing – review & editing: Lauri Jouhi, Jenna Sikiö, Anni Suomalainen, Rayan Mroueh, Antti Mäkitie, Jukka H. Meurman.

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