

ORIGINAL ARTICLE



Second primary cancer following primary oral squamous cell carcinoma: a population-based, retrospective study

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ABSTRACT

Background: Second primary cancer (SPC), defined as a metachronous solid cancer resulting from neither a recurrence of the primary cancer nor a metastasis, is a leading long-term cause of death for survivors of primary oral squamous cell carcinoma (OSCC). This study examined the risk of SPC following treatment of primary OSCC.

Materials and Methods: This semi-national, population-based, retrospective study included all patients with primary OSCC treated with curative intent in Eastern Denmark in 2000–2014. The presence of SPC was confirmed from medical records and the Danish Pathology Data Bank. The rate of SPC was compared to the occurrence of any cancer in the Eastern Danish population using data from the Danish Cancer Registry.

Results: A total of 936 patients with primary OSCC were enrolled. Of these, 219 patients (23%) were diagnosed with SPC during the follow-up (median 8.9 years, IQR: 5.4–12.6 years). The rate of SPC was four times higher than the occurrence of any cancer among the Eastern Danish population i.e., with a standardized incidence ratio (SIR) of 4.13 (95%CI: 3.55–4.80). SPCs were most frequently found in head and neck region ($n=97$, SIR = 43.6), lower respiratory organs ($n=38$, SIR = 5.6) and gastrointestinal organs ($n=33$, SIR = 3.2) with increased SPC rates in all locations. Among patients who developed SPC within the study period the median time from OSCC to the first SPC was 4.4 years (IQR: 2.5–6.2). Significant associations were found between both smoking and excessive alcohol consumption after treatment of OSCC and the risk of SPC.

Conclusions: A noteworthy increased rate of SPC following treatment of primary OSCC was found, especially in the head and neck region and in the lungs. Healthcare professionals should be aware of this increased risk.

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KEYWORDS

Second primary cancer; oral cancer; squamous cell carcinoma; OSCC

Background

Worldwide, oral cavity cancer is the most common head and neck cancer (HNC) accounting for 40% of all new HNCs and 2% of all diagnosed malignancies with an incidence of more than 350,000 new cases a year [1]. Oral squamous cell carcinomas (OSCC) constitute the vast majority of cancers in the oral cavity. In Denmark, oral cavity cancer (excluding lip cancer) is the second most common head and neck cancer i.e., only oropharyngeal cancer is more common due to the impact of HPV [2]. Both the incidence and survival rates of OSCC have increased in the past decades in Denmark [2,3] comparable with other countries [4,5]. Due to improvements in survival and the aging population, the occurrence of second primary cancer (SPC) has risen considerably [6]. SPC is a leading long term cause of death for survivors of primary OSCC [7,8], and data from Europe and Northern America indicates that the risk of developing SPC among HNC patients is twice the risk of developing any cancer among the general population [9–11]. Several potential risk factors

in developing SPC following primary OSCC are identified and include smoking [12–14], alcohol [12,13], genetic susceptibility [15] and possibly previous radiotherapy [16].

All Danish citizens have free access to diagnostics and treatments at public university cancer centers, financed by general tax revenue. As registration in the Danish Pathology Data Bank is mandatory, we have an ideal basis for retrospective and large cohort analyses. In Denmark, it is recommended for patients treated for OSCC to have follow-up visits for at least a five-year period according to the guidelines of The Danish Head and Neck cancer Study Group (DAHANCA).

The purpose of this study was to evaluate the risk of SPC following a primary OSCC treated with curative intent and assess baseline characteristics for patients with and without SPC.

Material and methods

This retrospective study included all patients diagnosed with primary OSCC receiving treatment with a curative intent in

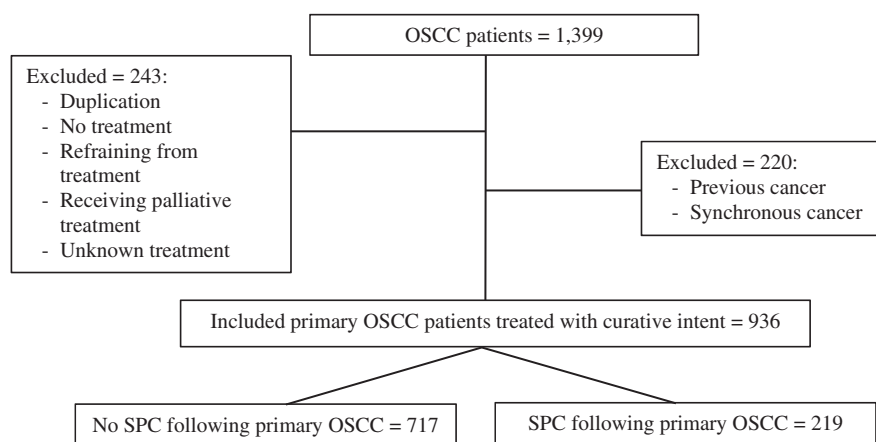


Figure 1. Flowchart of included patients from the Copenhagen Oral Cavity Squamous Cell Carcinoma database (COrCa) with reasons for exclusion.

the Eastern Region of Denmark, primarily at Rigshospitalet, in the period 2000–2014. Information on these patients was obtained from the Copenhagen Oral Cavity Squamous Cell Carcinoma (COrCa) database [17]. Registered OSCC patients with any previous or synchronous cancer (i.e., simultaneously or within six months of the primary tumor) were excluded (Figure 1).

SPC in any location was defined as a metachronous solid cancer (i.e., more than six months after diagnosis of OSCC) and not as a result of neither a recurrence of the primary OSCC nor a metastasis [18]:

- Metachronous secondary cancer developing in a different location than the oral cavity (and not being a metastasis) or being of non-squamous cell origin was diagnosed as a SPC.
- Locally recurrent OSCC was excluded using the Odense-Birmingham definition [19]. If the metachronous secondary cancer was a squamous cell carcinoma and located in the oral cavity it was diagnosed as a SPC if occurring more than three centimeters from the primary OSCC separated by healthy tissue (and not being a metastasis) or occurring more than three years after the primary OSCC at the same tumor site [19].

Data from the COrCa database comprised baseline information of the patients at time of diagnosis. The data included the following information: sex, age at diagnosis, subsite of OSCC (floor of mouth, oral tongue, gingiva and 'other subsite'), TNM classification, Union for International Cancer Control (UICC) stage (7th edition), treatment, tobacco smoking (before and after treatment of OSCC), alcohol consumption (before and after treatment of OSCC), and Charlson Comorbidity Index (CCI). The CCI index is a comorbidity summary measure, providing a single number description of the overall comorbidity status for the patient, excluding the primary OSCC diagnosis. The CCI was calculated for each patient based on data from the Danish National Patient Register, comprising diagnoses registered during hospital visits [20].

Patients with SPC were further examined providing data on the SPC location and subdivided into head and neck,

lower respiratory area and intrathoracic region, gastrointestinal organs, reproductive organs, skin (excluding basal-cell carcinoma) and "other locations" (incl. cancer in breast, urinary tract, bones and lymphomas). Second primary cancer in the head and neck region was further subdivided into oral cavity, pharynx, larynx and sinuses. Further, data included the time from OSCC to SPC and the time from SPC to either death or end of follow-up monitoring. Data on SPC obtained from the database was validated by reviewing the medical records and the Danish Pathology Data Bank.

Statistical analysis

Statistical analyses were performed using R software (version 3.6.1). Patients with SPC following a diagnosis of primary OSCC were compared to patients without SPC to examine the differences in baseline characteristics of the two groups.

Categorical variables were reported as frequencies and continuous variables as median values with an interquartile range (IQR). Potential associations were expressed as Hazard Ratios (HR) using univariate and multivariate cox regression analysis. The multivariate cox regression analysis included the variables of sex, age at diagnosis, subsite of OSCC (i.e., floor of mouth, oral tongue, gingiva, and others), tobacco smoking (before and after treatment of OSCC), alcohol consumption (before and after treatment of OSCC), as well as the CCI and UICC stage.

A Standardized Incidence Ratio (SIR) with 95% confidence intervals [95% CI] was calculated overall and for different SPC locations (head and neck, lower respiratory and intrathoracic region, gastrointestinal organs, reproductive organs, skin and "other locations") with data from the Danish Cancer Registry (Danish Health Data Authority) [21]. The risk among patients treated for primary OSCC were calculated six months from diagnosis (SPC is impossible within the first six months due to the exclusion of synchronous cancer) until either date of death, end of follow-up monitoring or diagnosis of a SPC. The expected number of cancers in the Eastern Denmark population during 2000–2014 was used as a reference and estimated with data from the Danish Cancer Registry [21]. The number of cases for the population of Eastern Denmark was estimated by filtering number of

malignancies per 100,000 inhabitants for different types of cancer in different calendar years for the population of Eastern Denmark in the Danish Cancer Registry. Standardized Incidence Ratio (SIR) was obtained by dividing the observed number of cases of SPC by the number expected in the population of Eastern Denmark. This provided an estimate of the rate of OSCC patients developing a SPC relative to the occurrence of cancer in the Eastern Danish population. The probability of overall survival (1-, 3- and 5-year survival proportion) following the patients' first diagnosis of SPC was estimated by using a Kaplan-Meier analysis.

Results

Baseline characteristics

A total of 936 patients diagnosed with primary OSCC and treated with curative intent were included (Figure 1), with a median age of 61 years (IQR 54–69 years, range 25–95 years). The majority was men (64%, $n = 596$) and the median follow-up time was 8.9 years (IQR 5.4–12.6 years, range 1.89–18.3 years). Most patients were treated with surgery as single-modality treatment, ($n = 443$, 47%), or surgery with adjuvant radiotherapy ($n = 338$, 36%) (Table 1).

SPC following OSCC

Of the 936 included patients a total of 219 patients (23%) were diagnosed with SPC (Table 2). The majority of the 219 patients was diagnosed with a single SPC in the study period (83%, $n = 182$), as the rest was diagnosed with two or more SPCs (17%, $n = 37$). The median follow-up time after diagnosis of OSCC for patients with SPC was 10.2 years (IQR 6.8–13.2, range 2.2–18.3). Among patients who developed SPC within the study period, the median time from OSCC to the first SPC was 4.4 years (IQR 2.5–6.2, range 0.5–14.4).

The most frequent location of the first SPC for the 219 patients were the head and neck region (44%, $n = 97$), especially secondary oral cancer (32%, $n = 69$) and pharyngeal cancer (11%, $n = 23$) (Table 2). The majority of the secondary oral cancer occurred more than three years after primary OSCC ($n = 63$) and most frequently in a different oral subsite than the primary OSCC ($n = 44$).

The univariate analysis showed a significant association between the risk of SPC after treatment of OSCC and smoking and excessive alcohol consumption, respectively (Table 1). This association was not found in the multivariate analysis. Both the univariate and the multivariate analysis showed a significant association between advanced stage cancer (UICC IV) and a lower risk of SPC. No association was found between the risk of SPC and CCI (Table 1).

The 1-year overall survival proportion after diagnosis of SPC following a primary OSCC was 60.2% (95%CI 53.9–67.2), while the 3- and 5-year overall survival proportion was respectively 41.8% (95%CI 35.3–49.5) and 32.8% (95%CI 26.3–41.0) (Table 2, Supplementary Figure 1).

The rate of SPC

The rate of SPC was four times higher than the occurrence of any cancer in the Eastern Danish population with an SIR of 4.13 (95%CI: 3.55–4.80) (Table 2). The rate of SPC was increased in multiple locations, especially in the head and neck region, but also in the lungs and gastrointestinal organs.

During the follow-up 97 patients developed SPC in the head and neck region which was an increased rate compared to the occurrence of head and neck cancer in the Eastern Danish population with a SIR of 43.61 (95%CI: 37.48–50.73). An increased rate of cancer was also found in the lower respiratory area (SIR 5.57, 95%CI: 4.79–6.48) and gastrointestinal organs (SIR 3.17, 95%CI: 2.72–3.69) (Table 2).

Discussion

This study found a four-fold increased rate of SPC following primary OSCC compared to the occurrence of any cancer among the Eastern Danish population. Previous studies have also showed increased rate of SPC following diagnosis of OSCC with a variation in different populations from SIR 1.47 in Korea [22] to 1.85 in Finland [23]. The higher rate in our study might be explained by the inclusion of only patients treated with curative intent as well as the longer follow-up monitoring. Similar to previous studies, SPCs following a primary OSCC were most commonly found in the head and neck region (the majority being a secondary OSCC) and in the lungs [9–11]. We observed a noteworthy increased rate of head and neck cancer (SIR 43.6) in accordance with previous findings (SIR 26.2) [24]. The higher rate of SPC in the head and neck region in our study might be explained partly by the inclusion of only patients treated with curative intent and mostly because of the difference in SPC definition. We defined SPC in the oral cavity as either occurring more than three centimeters from the primary OSCC or occurring more than three years after primary OSCC (and not being a metastasis) [19], while others defined SPC in oral cavity without a distance criteria and only if occurring more than 5 years after primary OSCC [24].

Previous studies have found an increased risk of SPC following primary OSCC for patients with high intakes of alcohol and tobacco, especially for current smokers who smoked more than 20 cigarettes per day [13,14] and for patients continuing to use tobacco and alcohol after treatment of a HNC [12]. Our study found similar significant associations in the univariate analysis for patients continuing the use of tobacco and excessive alcohol consumption after treatment of primary OSCC. The multivariate analysis found no association between neither smoking status nor alcohol consumption (neither before nor after treatment of OSCC) and the risk of SPC. The lack of association in the multivariate analysis was unexpected since most SPCs appear in areas where smoking is a known risk factor of cancer, including lung cancer and various squamous cell carcinomas in the head and neck region [25]. A possible explanation for the lack of association in the multivariate analysis might be insufficient information

Table 1. Baseline characteristics of patients with and without second primary cancer following primary OSCC diagnosed at Rigshospitalet, Copenhagen, Denmark during the period 2000–2014.

Baseline Characteristics				
Data are either number (%) or median [IQR]				
	Without SPC (<i>n</i> = 717)	With SPC (<i>n</i> = 219)	HR [95%CI] for SPC Univariate	HR [95%CI] for SPC Multivariate
Sex				
Female	267 (37.2)	73 (33.3)	Ref	Ref
Male	450 (62.8)	146 (66.7)	1.16 [0.88–1.54]	1.30 [0.87–1.92]
Age at diagnosis	62 [54–69]	60 [55–67]	1.00 [0.99–1.01]	1.00 [0.99–1.02]
Follow-up period after OSCC (years)	8.5 [5.1–12.4]	10.2 [6.8–13.2]	–	–
Sublocation				
Floor of mouth	268 (37.4)	100 (45.7)	Ref	Ref
Oral tongue	259 (36.1)	71 (32.4)	0.75 [0.56–1.01]	0.68 [0.45–1.04]
Gingiva	81 (11.3)	22 (10.0)	0.86 [0.54–1.36]	0.84 [0.47–1.49]
Other sublocations	109 (15.2)	26 (11.9)	0.66 [0.43–1.02]	1.19 [0.65–2.19]
Smoking before treatment of OSCC				
Non-smokers	86 (12.0)	18 (8.2)	Ref	Ref
Smokers	460 (64.2)	158 (72.1)	1.25 [0.78–2.02]	0.99 [0.49–1.99]
Ex-smokers	105 (14.6)	30 (13.7)	1.29 [0.73–2.30]	1.12 [0.56–2.21]
Unknown	66 (9.2)	13 (5.9)	–	–
Smoking after treatment of OSCC				
No	242 (33.8)	67 (30.6)	Ref	Ref
Yes	278 (38.8)	106 (48.4)	1.45 [1.07–2.00]	1.36 [0.83–2.21]
Unknown	197 (27.5)	46 (21.0)	–	–
Alcohol consumption ^a before treatment of OSCC				
Normal intake	262 (36.5)	75 (34.2)	Ref	Ref
Excessive intake	262 (36.5)	92 (42.0)	1.10 [0.81–1.50]	1.08 [0.65–1.80]
Former excessive intake	108 (15.1)	35 (16.0)	1.07 [0.72–1.59]	1.13 [0.67–1.92]
Unknown	85 (11.9)	17 (7.8)	–	–
Excessive alcohol consumption ^a after treatment of OSCC				
No	316 (44.1)	87 (39.7)	Ref	Ref
Yes	155 (21.6)	74 (33.8)	1.40 [1.03–1.90]	1.25 [0.78–2.01]
Unknown	246 (34.3)	58 (26.5)	–	–
Treatment				
Surgery	325 (45.3)	118 (53.9)	–	–
Radiotherapy	95 (13.2)	16 (7.3)	–	–
Surgery and radiotherapy	263 (36.7)	75 (34.2)	–	–
Radiotherapy and chemotherapy	14 (2.0)	5 (2.3)	–	–
Surgery, radiotherapy and chemotherapy	20 (2.8)	5 (2.3)	–	–
CCI				
0	473 (66.0)	148 (67.6)	Ref	Ref
1	134 (18.7)	36 (16.4)	0.87 [0.60–1.25]	0.82 [0.50–1.32]
2	62 (8.6)	20 (9.1)	0.99 [0.62–1.57]	0.90 [0.47–1.70]
3 or above	48 (6.7)	15 (6.8)	1.04 [0.61–1.77]	1.24 [0.64–2.41]
T-stage				
1	216 (30.1)	82 (37.4)	–	–
2	216 (30.1)	61 (27.9)	–	–
3	52 (7.3)	20 (9.1)	–	–
4a/b/x	150 (20.9)	21 (9.6)	–	–
Unknown	83 (11.6)	35 (16.0)	–	–
N-stage				
0	401 (55.9)	134 (61.2)	–	–
1	107 (14.9)	30 (13.7)	–	–
2a/b/c	130 (18.1)	22 (10.0)	–	–
3	1 (0.1)	0 (0)	–	–
Unknown	78 (10.9)	33 (15.1)	–	–
UICC stage (I–IV)				
I	171 (23.8)	71 (32.4)	Ref	Ref
II	132 (18.4)	43 (19.6)	0.72 [0.50–1.05]	0.75 [0.47–1.20]
III	95 (13.2)	32 (14.6)	0.77 [0.51–1.17]	0.69 [0.42–1.14]
IVa/b/c/x	231 (32.2)	37 (16.9)	0.43 [0.29–0.64]	0.48 [0.30–0.77]
Unknown	88 (12.3)	36 (16.4)	–	–

IQR: Interquartile Range; OSCC: Oral Squamous Cell Carcinoma; CCI: Charlson Comorbidity Index; UICC: Union for International Cancer Control.

^aExcessive alcohol intake defined as above 14 units of alcohol per week for men and seven for women, in accordance with the recommendation from the Danish Health Authority [17].

on the amount of daily tobacco consumption and the duration of tobacco smoking. Likewise, this lack of information applies to alcohol consumption, which only differentiated between excessive, normal, and no alcohol consumption. Further, as seen in Table 1, a noteworthy part of patients

had an unknown alcohol (32%, *n* = 304) and smoking (26%, *n* = 243) status after treatment for OSCC.

Most patients were treated with surgery as single-modality treatment or with adjuvant radiotherapy. There was no statistical analysis on treatment and the risk of SPC, since

Table 2. Characteristics of SPC following primary OSCC diagnosed at Rigshospitalet, Copenhagen, Denmark during the period 2000–2014.

Second Primary Cancer		
Data is either expressed in numbers (%) or as a median [IQR], if not otherwise stated.		
	Number	SIR [95% CI]
Patients with SPC	219	4.13 [3.55–4.80]
Location of the first SPC		
Head and Neck:	97 (44.3)	43.61 [37.48–50.73]
Oral cavity	69 (31.5)	–
Pharyngeal area	23 (10.5)	–
Laryngeal area	4 (1.8)	–
Nose and sinuses	1 (0.5)	–
Lower respiratory and intrathoracic organs	38 (17.4)	5.57 [4.79–6.48]
Gastrointestinal organs	33 (15.1)	3.17 [2.72–3.69]
Reproductive organs (male and female)	10 (4.6)	0.59 [0.51–0.69]
Skin	21 (9.6)	3.04 [2.61–3.54]
Other location	18 (8.2)	–
Unknown topography	2 (0.9)	–
Number of SPCs per patient		
1	182 (83.1)	–
2	32 (14.6)	–
≥3	5 (2.3)	–
Survival time following first SPC		
1-year survival (%) [95%CI]	60.2 [53.9–67.2]	–
3-year survival (%) [95%CI]	41.8 [35.3–49.5]	–
5-year survival (%) [95%CI]	32.8 [26.3–41.0]	–

IQR: Interquartile Range; SIR: Standardized Incidence Ratio; OSCC: Oral Squamous Cell Carcinoma; SPC: Second Primary Cancer.

many factors influence the choice of treatment. Previous findings indicate that radiation therapy of primary OSCC might be a risk factor in the development of solid SPC, but not until 10 years of follow-up [16]. Therefore, this was not examined in this study.

An association was demonstrated between advanced stage cancer upon the diagnosis of OSCC and a lower risk of SPC. This might be explained by higher mortality related to advanced stage cancer [4].

It is well known that SPC is a leading long term cause of death for survivors of primary OSCC [7,8] with previous findings showing a median survival of 12 months after diagnosis of SPC following a primary HNC [26]. The overall survival proportion after diagnosis of SPC following primary OSCC in this study was more encouraging, with a 1-year survival proportion of 60%, a 3-year survival proportion of 42% and a 5-year survival proportion of 33%, which might be explained by the inclusion of only OSCC patients treated with curative intent.

A limitation to this study was the retrospective study design, which relied on the accuracy of the Danish Health Data Authority and the COrCa-database. There is a risk of misclassification of SPCs as metastases (underestimation) and vice versa (overestimation). The risk of overestimation was minimized by reviewing the medical records of patients with SPC, thereby validating the data on SPC obtained from the database. The follow-up period was relatively short (with a median of 8.9 years), although longer than most previous studies [27]. A short follow-up period lead to a risk of underestimating SPC but might be of less importance since previous studies have shown that most SPCs appear within five years from diagnosis of OSCC [23]. The noteworthy part of patients with unknown alcohol and smoking status after treatment of OSCC may have led to the lack of association between smoking and alcohol and the risk of SPC in the multivariate analysis.

The strengths of the study were the inclusion of all patients treated with curative intent in the Eastern Denmark region, comprising nearly half the approximately 5.8 million inhabitants. A further strength was the information on numerous parameters for all patients diagnosed and/or treated for OSCC in the COrCa-database.

With a median follow-up of nine years this study identified 219 cases (23%) with SPC among 936 patients with a primary OSCC treated with curative intent in Eastern Denmark in 2000–2014. OSCC patients showed a four-fold rate (SIR 4.13) of SPC compared to the occurrence of any cancer among the Eastern Danish population. Among patients who developed SPC within the study period, the median time from OSCC to the first SPC was 4.4 years. Healthcare professionals should be aware of the increased rate of SPC following primary OSCC, especially in the head and neck region and in the lungs.

Disclosure statement

No potential conflict of interest was reported by the authors.

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Data availability statement

Raw data were generated at Department of Otorhinolaryngology, Rigshospitalet, Denmark. Derived data supporting the findings of this study are available from the corresponding author, LØP, on request.

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