Journal of Dental Sciences 18 (2023) 1047–1054

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.e-jds.com

Original Article

Incidence of second primary cancers in oral and pharyngeal cancer patients using a large medical claims database in Japan

Masanori Matsui [a,b], Kahori Kawamura [b*], Keita Kano [b], Hideki Yoshimatsu [b], Takashi Doi [b], Tatsuro Miyake [b]

[a] *Graduate School of Dentistry (Department of Preventive and Community Dentistry), Osaka Dental University, Hirakata, Osaka, Japan*
[b] *Department of Preventive and Community Dentistry, Osaka Dental University, Hirakata, Osaka, Japan*

Received 27 October 2022; Final revision received 24 November 2022
Available online 9 December 2022

KEYWORDS
Claims database;
Oral and pharyngeal cancer;
Second primary cancers

Abstract *Background/purpose:* As the occurrence of second primary cancers (SPCs) is strongly related to the survival rate of patients with oral and pharyngeal cancers, early detection and treatment are important. Therefore, this study aimed to clarify the incidence of SPCs and their risk factors in patients with oral and pharyngeal cancer.
Materials and methods: This observational study was conducted using data from the administrative claims database of 21,736 participants with oral and pharyngeal cancer from January 2005 to December 2020. We evaluated the cumulative incidence of SPCs among patients with oral and pharyngeal cancers using the Kaplan–Meier method. The Cox proportional-hazard model was used for multivariate analysis.
Results: Of the 1633 patients with oral and pharyngeal cancer who qualified for analysis, 388 developed SPCs (incidence rate, 7.994/1000 person-months). The multivariate analysis showed that the risk of developing SPCs was affected by age at diagnosis of oral and pharyngeal cancer, cancer treatment, and anatomical site of the primary cancer.
Conclusion: Patients with oral and pharyngeal cancers are at a high risk of developing SPCs. The data from this study may be useful in providing accurate information to patients with oral and oropharyngeal cancer.

* Corresponding author. Department of Preventive and Community Dentistry, Osaka Dental University 8-1 Kuzuhahanazono-cho, Hirakata, Osaka 573-1121, Japan
E-mail address: kawamura@cc.osaka-dent.ac.jp (K. Kawamura).

https://doi.org/10.1016/j.jds.2022.11.025

Introduction

Oral and pharyngeal cancers have been reported in more than 700,000 cases and 380,000 deaths worldwide annually.[1] In Japan, more than 22,000 people are diagnosed with oral and pharyngeal cancer per year, and in 2020, there were approximately 7800 deaths; this figure is increasing every year.[2,3] Patients with head and neck cancer may be directly exposed to tobacco and alcohol carcinogens in their oral and pharyngeal regions. These patients are at an increased risk of local recurrence of head and neck, lung, esophagus, and other cancers called second primary cancers (SPCs), according to the "field cancerization" phenomenon.[4–6] In addition, the overall survival rate is lower in patients with SPCs than in those without SPCs, especially those with SPCs in the esophagus or lungs.[7–9]

Studies have also been conducted on the incidence of SPCs in relation to the age at diagnosis of head and neck cancer using the Japanese Cancer Registry Database. The cumulative incidence of secondary esophageal cancer is significantly higher among younger (<65 years) than among older individuals (≥65 years), whereas the cumulative incidence of other cancers is significantly lower among younger than among older individuals.[10] Another study on the risk of SPCs of the hypopharynx and esophagus in patients with primary oral and oropharyngeal cancer using mass screening data and cancer registry data in Taiwan suggested that compared with patients with lip cancer, those with cancer of the oropharynx, oral floor, and hard palate are at a higher risk for SPCs, and the risk varies by the anatomical site.[11]

As SPCs are strongly related to the survival rate of patients with oral and pharyngeal cancers, early detection and treatment are important. Detailed surveillance, including regular follow-up, is emphasized for the early diagnosis of SPCs; however, standard recommendations have not yet been determined. Therefore, this study aimed to clarify the incidence of SPC and its risk factors in patients with oral and pharyngeal cancer using a large medical claims database in Japan.

Materials and methods

Study design and data source

This retrospective study used the health insurance claims database provided by the Japan Medical Data Center (JMDC) Co., Ltd (Tokyo, Japan). The JMDC database consists of medical, dental, and pharmacy claims, including specific health checkup information from several health insurance societies in Japan. As of April 2022, the cumulative dataset comprises approximately 14 million employees of medium-to-large companies and their dependents, excluding individuals aged ≥75 years. In addition, the JMDC claims database is highly encrypted using irreversible anonymization technology and does not allow the identification of individuals. Diagnoses were recorded using the International Classification of Diseases 10th revision (ICD-10). The study protocol was approved by the ethics committee of Osaka Dental University (Number: 111163, May 31, 2021). The need for additional informed consent was waived by the committee, according to the guidelines.

Study population

Data of patients diagnosed with oral and pharyngeal cancer (ICD-10 codes C00-C14) from January 2005 to December 2020 were obtained from the JMDC database. The inclusion criterion was that the patient had received at least one therapy: surgery, radiotherapy, and chemotherapy. The exclusion criteria were as follows: suspected oral and pharyngeal cancer, diangosis within the first 6 months from the start of the observation, and diagnosis of cancer in other sites before oral and pharyngeal cancer treatment. This record included information concerning the patient's age, sex, insurance codes, and tumor sites. We assessed comorbid conditions before oral and pharyngeal cancer treatment, including hypertension (I10-I15), diabetes mellitus (E10-E14), cerebrovascular disease (I60-I69), ischemic heart disease (I20-I25), hyperlipidemia (E78), and renal disease (N00-N29). The treatment was identified using the original Japanese procedure codes.

Outcomes

The primary outcome was the cumulative incidence of SPCs (ICD-10 codes C15-C73) in patients with oral and pharyngeal cancer. We separated the SPCs of the digestive system (ICD-10 codes C15-25) from those of the respiratory system (ICD-10 codes C30-C34). We excluded the suspected disease codes for the diagnosis of SPCs. A synchronous SPC was defined as one that was diagnosed within 6 months of the initial primary oral and pharyngeal cancer, while a metachronous SPC was defined as one that was diagnosed at ≥6 months after the primary oral and pharyngeal cancer, according to the criteria of Warren and Gates.[12] We examined whether the incidence of SPC differed according to age, sex, working status, comorbidity, treatment of primary cancer, and anatomical site of the primary cancer.

Statistical analysis

Continuous variables are presented as means and standard deviations (SD) or as medians and ranges, depending on the type of data. Categorical variables are presented as numbers and percentages for analysis. The cumulative incidence of SPCs was estimated using the Kaplan–Meier method, and differences among anatomical subsites of the primary cancer were compared using the log-rank test. The Cox proportional-hazard regression model was used to calculate the hazard ratios (HRs) of SPCs in patients with oral and pharyngeal cancer. We performed a sensitivity analysis: SPCs were diagnosed after primary cancer and diagnosed 6 months after primary cancer. Data analysis was performed using SPSS software version 28 (IBM, Armonk, NY, USA). A two-sided value of $P < 0.01$ was used to determine statistical significance.

Results

Fig. 1 shows a flowchart of participant selection. We identified 21,736 patients diagnosed with oral and pharyngeal cancer. After excluding 20,103 patients based on our criteria, 1633 were eligible for analysis.

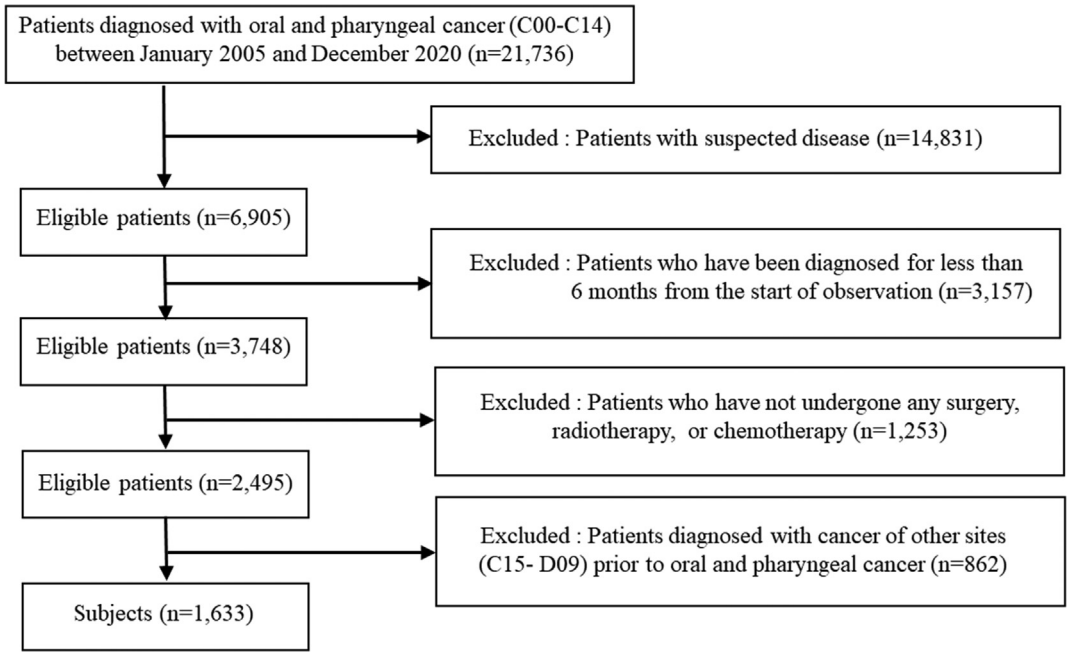

Figure 1 Flowchart of the inclusion and exclusion criteria for participation.

Table 1 shows the sociodemographic data of patients with oral and pharyngeal cancers divided into oral, salivary gland, and pharyngeal cancers based on the site of primary cancer. "Oral" includes the lip, tongue, gingiva, oral floor, plate, and buccal mucosa. "Salivary grand" includes the parotid, submandibular, and sublingual glands. "Pharynx" includes the nasopharynx, oropharynx, and hypopharynx.

Table 1 The sociodemographic data of patients, based on the site of primary cancer.

	Oral	Salivary gland	Pharynx
	N = 830	N = 221	N = 582
Age	53 (44–60)	51 (42–60)	58 (51–63)
Age-grouping (years)			
<45	217 (26.1)	64 (29.0)	60 (10.3)
45–54	234 (28.2)	66 (29.9)	152 (26.1)
55–64	274 (33.0)	72 (32.6)	259 (44.5)
≥65	105 (12.7)	19 (8.6)	111 (19.1)
Sex			
Male	563 (67.8)	131 (59.3)	488 (83.8)
Female	267 (32.2)	90 (40.7)	94 (16.2)
Working status			
Insured person	658 (79.3)	155 (70.1)	501 (86.1)
Family	172 (20.7)	66 (29.9)	81 (13.9)
Cancer treatment			
With surgery	698 (84.1)	167 (75.6)	182 (31.3)
With chemotherapy	281 (33.9)	60 (27.1)	460 (79.0)
With radiation therapy	216 (26.0)	98 (44.3)	438 (75.3)
Comorbidity			
Hypertension	220 (26.5)	48 (21.7)	184 (31.6)
Hyperlipidemia	180 (21.7)	36 (16.3)	122 (21.0)
Diabetes mellitus	153 (18.4)	26 (11.8)	121 (20.8)
Renal disease	46 (5.5)	13 (5.9)	38 (6.5)
Ischemic heart disease	37 (4.5)	11 (5.0)	31 (5.3)
Cerebrovascular disease	33 (4.0)	4 (1.8)	36 (6.2)

Age is expressed as median (interquartile range).
Categorical variables are presented as numbers (%).

Table 2 Second primary cancers (SPCs) by site of oral and pharyngeal cancer (including SPCs < 6 months after initial cancer diagnosis).

	Total N = 1633		Lip N = 16		Tongue N = 590		Gingiva N = 113		Oral floor N = 46		Palate N = 18		Buccal mucosa N = 47		Parotid gland N = 157		Submandibular grand/ Sublingual grand N = 64		Oro pharynx N = 233		Naso pharynx N = 81		Hypo pharynx N = 235		Others N = 33	
Age	55	(46–62)	52	(36–63)	51	(43–59)	57	(51–65)	58	(54–64)	47	(43–57)	58	(49–63)	51	(41–59)	53	(44–61)	56	(50–62)	51	(42–60)	60	(55–65)	59	(50–63)
Male	1182	(72.4)	7	(43.8)	398	(67.5)	76	(67.3)	40	(87.0)	11	(61.1)	31	(66.0)	91	(58.0)	40	(62.5)	184	(79.0)	62	(76.5)	214	(91.1)	28	(84.8)
Cancer treatment																										
Surgery	1047	(64.1)	14	(87.5)	520	(88.1)	74	(65.5)	36	(78.3)	16	(88.9)	38	(80.9)	121	(77.1)	40	(71.9)	88	(37.8)	12	(14.8)	69	(29.4)	13	(39.4)
Chemotherapy	801	(49.1)	2	(12.5)	178	(30.2)	61	(54.0)	18	(39.1)	2	(11.1)	20	(42.6)	35	(22.3)	25	(39.1)	177	(76.0)	70	(86.4)	193	(82.1)	20	(60.6)
Radiation therapy	752	(46.1)	2	(12.5)	127	(21.5)	50	(44.2)	18	(39.1)	5	(27.8)	14	(29.8)	75	(47.8)	23	(35.9)	152	(65.2)	64	(79.0)	197	(83.8)	25	(75.8)
Person-months at risk	48535		514		18001		2931		1279		432		1475		5266		2241		6564		3270		5620		942	
Anatomic site of SPCs																										
Esophagus	146	3.01	0	0.00	16	0.89	6	2.05	4	3.13	2	4.63	2	1.36	0	0.00	0	0.00	26	3.96	0	0.00	87	15.48	3	3.18
Lung	58	1.20	0	0.00	15	0.83	6	2.05	0	0.00	0	0.00	1	0.68	4	0.76	4	1.78	11	1.68	1	0.31	14	2.49	2	2.12
Larynx	54	1.11	0	0.00	4	0.22	0	0.00	1	0.78	0	0.00	0	0.00	0	0.00	0	0.00	8	1.22	0	0.00	31	5.52	10	10.62
Stomach	47	0.97	0	0.00	12	0.67	3	1.02	3	2.35	0	0.00	3	2.03	1	0.19	1	0.45	11	1.68	0	0.00	9	1.60	4	4.25
Nasal, paranasal sinus	30	0.62	0	0.00	0	0.00	15	5.12	0	0.00	2	4.63	2	1.36	2	0.38	1	0.45	3	0.46	4	1.22	1	0.18	0	0.00
Male genital organs	21	0.43	1	1.95	4	0.22	2	0.68	2	1.56	0	0.00	1	0.68	5	0.95	0	0.00	0	0.00	1	0.31	5	0.89	0	0.00
Large intestine	20	0.41	0	0.00	2	0.11	3	1.02	2	1.56	0	0.00	0	0.00	0	0.00	1	0.45	5	0.76	0	0.00	4	0.71	3	3.18
Thyroid gland	20	0.41	0	0.00	7	0.39	0	0.00	0	0.00	0	0.00	0	0.00	3	0.57	0	0.00	2	0.30	1	0.31	5	0.89	1	1.06
Bone, articular cartilage and spinal cord	16	0.33	0	0.00	2	0.11	7	2.39	1	0.78	1	2.31	2	1.36	0	0.00	0	0.00	0	0.00	2	0.61	1	0.18	0	0.00
Renal urinary tract	11	0.23	0	0.00	4	0.22	1	0.34	1	0.78	0	0.00	0	0.00	2	0.38	0	0.00	2	0.30	0	0.00	1	0.18	0	0.00
Pancreas	10	0.21	0	0.00	1	0.06	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	1	0.45	2	0.30	1	0.31	5	0.89	0	0.00
Mesothelium	10	0.21	0	0.00	1	0.06	2	0.68	0	0.00	0	0.00	3	2.03	0	0.00	0	0.00	1	0.15	1	0.31	1	0.18	1	1.06

and soft tissue																									
Breast	9	0.19	0	0.00	3	0.17	1	0.34	0	0.00	1	2.31	0	0.00	2	0.38	1	0.45	0	0.00	1	0.31	0	0.00	0	0.00
Liver	7	0.14	0	0.00	0	0.00	0	0.00	1	0.78	0	0.00	0	0.00	0	0.00	1	0.45	2	0.30	1	0.31	1	0.18	1	1.06
Skin	6	0.12	1	1.95	2	0.11	1	0.34	0	0.00	0	0.00	1	0.68	0	0.00	0	0.00	0	0.00	1	0.31	0	0.00	0	0.00
Gallbladder, biliary tract	5	0.10	0	0.00	2	0.11	0	0.00	0	0.00	0	0.00	1	0.68	0	0.00	0	0.00	0	0.00	0	0.00	2	0.36	0	0.00
Brain, central nervous system	3	0.06	1	1.95	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	1	0.45	0	0.00	0	0.00	1	0.18	0	0.00
Small intestine	2	0.04	0	0.00	0	0.00	0	0.00	1	0.78	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	1	0.18	0	0.00
Female genital organs	2	0.04	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	1	0.19	0	0.00	0	0.00	1	0.31	0	0.00	0	0.00
No. of SPCs of the digestive system	207	4.26	0	0.00	27	1.50	10	3.41	10	7.82	2	4.63	3	2.03	1	0.19	4	1.78	41	6.25	2	0.61	98	17.44	9	9.55
No. of SPCs of the respiratory system	137	2.82	0	0.00	19	1.06	21	7.16	1	0.78	2	4.63	3	2.03	6	1.14	5	2.23	20	3.05	5	1.53	43	7.65	12	12.74
No. of SPCs	388	7.99	3	5.84	66	3.67	40	13.65	13	10.16	5	11.57	10	6.78	18	3.42	10	4.46	61	9.29	13	3.98	131	23.31	18	19.11

In total, most patients were male (72.4%), 37.0% were aged 55—64 years, and 80.5% were working during cancer therapy. In addition, we indicated the percentages of cancer treatment types and the prevalence of comorbidities. Surgery (64.1%) was more common than chemotherapy (49.1%) or radiation therapy (46.1%). The most common complication was hypertension (27.7%), followed by hyperlipidemia (20.7%) and diabetes mellitus (18.4%).

Table 2 shows the incidence of SPCs by the anatomical site of the primary oral and pharyngeal cancer. Of the 1633 patients with oral and pharyngeal cancer, 388 developed SPCs (incidence rate, 7.99/1000 person-months). Of the SPC sites, the esophagus (146 cases) was the most common site, followed by the lungs (58 cases) and larynx (54 cases).

In the overall SPCs, the incidence was highest in the hypopharynx (23.31), followed by the gingiva (13.65) and palate (11.57). The parotid gland (3.42) had the lowest incidence. In SPCs of the digestive system, the incidence was highest in the hypopharynx (17.44), followed by the oral floor (7.82) and oropharynx (6.25). In SPCs of the respiratory system, the incidence was highest in the hypopharynx (7.65), followed by the gingiva (7.16) and palate (4.63). The cumulative incidence of SPCs in patients whose initial cancers were in different sites of oral and pharyngeal cancer is presented in Fig. 2.

The univariate and multivariate Cox proportional-hazard models for the risk of developing SPCs among patients with oral and pharyngeal cancer are shown in Table 3. Multivariate analysis showed that age, cancer treatment, and the anatomical site of the primary cancer affected the development of SPCs. Age (≥55 years), chemotherapy, radiation therapy, and development of primary cancer on the oral floor, gingiva, or hypopharynx increased the risk of SPCs. However, surgery and the development of primary cancer of the tongue reduced the risk of SPCs.

Discussion

In this study, we examined the incidence of and factors associated with SPCs among patients with oral and pharyngeal cancer using an administrative claims database in Japan. Patients with oral and pharyngeal cancers are at a higher risk of developing SPCs. According to a systematic review by Coca-Pelaz et al.,[13] the average morbidity rate of second primary tumors, including synchronous and metachronous tumors, in patients treated for head and neck cancer was 13.2% (2.4—27.7%), with large discrepancies. In the present study, the morbidity rate of SPCs, including both synchronous and metachronous tumors, was 23.8%. In addition, as shown in Supplementary Table 1, the morbidity of metachronous tumors (SPCs) at 6 months after the primary cancer diagnosis was 9.3% (153 cases). We performed a sensitivity analysis of the characteristics noted in the claims data to confirm the occurrence of the outcome (Supplementary Table 1). Although there is a wide range in the incidence rate between immediately after the diagnosis of the primary tumor and at 6 months after the diagnosis, the results complement those of previous studies.[5,10]

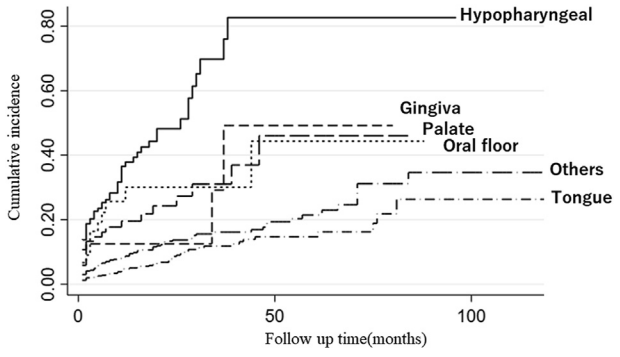

Figure 2 Cumulative incidence of second primary cancers (SPCs) by site of oral and pharyngeal cancer.

After adjusting for several covariates, the results showed that the risk of developing SPCs was affected by age at diagnosis of oral and pharyngeal cancer, cancer treatment, and the anatomical site of the primary cancer. The same trend was observed regarding the factors contributing to the occurrence of second primary cancers between the incidence immediately after the primary-tumor diagnosis and that after 6 months (Supplementary Table 2).

It is generally believed that cancer morbidity increases with age, as shown in a study by Hori et al. using the Japanese cancer registry.[14] It has been reported that the morbidity of SPC increases with age,[5,15] while there are also reports that younger people are at an increased risk for SPC,[16,17] with some studies reporting different results. In this study, older age (≥55 years) resulted in a higher risk of SPC. Younger and older patients were defined based on a median age of 55 years, which is the median age of the entire patient population. The database did not include patients aged >75 years, which resulted in a relatively low median age. Patients aged 55—64 years, which represented 37% of the total eligible population, were included in this study as older adults. It is likely that the risk of developing SPCs differs depending on the age used as the criterion for defining younger and older patients.

To the best of our knowledge, no study to date has examined the onset and comorbidity of SPCs using a large claims database. Multivariate analysis showed that comorbidities were not associated with the risk of developing SPC. The ability to obtain information on comorbidities other than cancer is an advantage of using a health insurance claims database.

In the treatment of primary cancer, radiation therapy has been reported to increase the risk of SPCs by field cancerization of the upper respiratory tract due to exposure-induced DNA strand breaks, chromosomal aberrations, mutations, and overall genetic instability.[18] Conversely, the effect of radiation on the incidence of SPCs is much more controversial, as studies of different designs and methods have yielded conflicting results in the analysis of SPC risk in patients treated with radiation therapy.[19,20] In this study, multivariate analysis showed that patients treated with radiation therapy or chemotherapy were at a higher risk of developing SPC. However, the medical claims database lacks information, such as radiation dose. Chemotherapy and radiotherapy for the treatment of oral and pharyngeal cancers may only be applied in severe cases.

Table 3 Cox proportional hazard model for risk of developing second primary cancers.

Variables		Univariable			Multivariable		
		HR	95%CI	*P*-value	HR	95%CI	*P*-value
Age	≥55 years	2.141	1.734–2.644	<0.001	1.435	1.140–1.805	0.002
Sex	Male	1.541	1.206–1.969	<0.001	0.932	0.641–1.355	0.712
Working status	Working	0.905	0.794–1.033	0.139	1.065	0.719–1.579	0.752
Comorbidity	Hypertension	1.561	1.267–1.923	<0.001	1.271	1.006–1.607	0.044
	Hyperlipidemia	1.09	0.856–1.388	0.485	0.851	0.644–1.125	0.258
	Diabetes mellitus	1.322	1.035–1.688	0.025	1.127	0.857–1.483	0.392
	Renal disease	0.905	0.583–1.406	0.658	0.789	0.499–1.248	0.311
	Ischemic heart disease	1.231	0.793–1.912	0.354	0.927	0.579–1.483	0.752
	Cerebrovascular disease	1.515	1.003–2.291	0.049	1.100	0.703–1.721	0.676
Cancer treatment	With surgery	0.349	0.285–0.427	<0.001	0.755	0.590–0.968	0.026
	With chemotherapy	3.331	2.654–4.180	<0.001	1.703	1.280–2.265	<0.001
	With radiation therapy	3.295	2.646–4.103	<0.001	1.644	1.243–2.173	<0.001
Anatomic site of the primary cancer	Tongue	1.000		<0.001	1.000		<0.001
	Parotid gland	1.005	0.597–1.693	0.984	0.906	0.532–1.544	0.717
	Nasopharynx	1.324	0.730–2.401	0.356	0.626	0.335–1.173	0.144
	Submandibular grand/ Sublingual grand	1.348	0.693–2.623	0.378	1.168	0.598–2.280	0.650
	Lip	1.706	0.536–5.427	0.366	2.169	0.678–6.941	0.192
	Buccal mucosa	2.072	1.065–4.030	0.032	1.547	0.790–3.030	0.203
	Oropharynx	2.672	1.886–3.786	<0.001	1.392	0.949–2.040	0.090
	Palate	2.823	1.137–7.009	0.025	3.086	1.229–7.754	0.016
	Oral floor	2.930	1.616–5.313	<0.001	2.258	1.234–4.131	0.008
	Gingva	4.086	2.756–6.059	<0.001	2.834	1.882–4.267	<0.001
	Hypopharyngeal	7.508	5.567–10.127	<0.001	3.323	2.336–4.727	<0.001

HR, hazard ratio; CI, confidence interval.

Previous studies have shown that patients with oropharyngeal and hypopharyngeal primary cancers have an increased incidence of SPCs compared with those with cancers at other sites.[21,22] In a study on the risk of a second primary hypopharyngeal and esophageal cancer after an initial primary oral and oropharyngeal cancer in Taiwan,[11] the oral cavity was subdivided by site, with the lips having the lowest incidence as the criterion; the highest relative risk was in the oropharynx (21.85), followed by the oral floor (12.11) and palate (8.74). In the present study, compared with the tongue, the highest risk was observed in the hypopharyngeal region, followed by the gingiva, oral floor, palate, and oropharynx. Interestingly, the risk of developing SPC depended on the anatomical site of the primary cancer.

To the best of our knowledge, this is the first study to examine the incidence of SPCs and associated factors in a large and diverse population of patients treated for oral and pharyngeal cancer in Japan. The advantage of the health insurance claims database that we used is that it can provide information on diagnosis and treatment even if participants switch to other healthcare providers.[23] However, our study had several limitations. Owing to the nature of the administrative claims database, only medical and dental services in health insurance could be included. Reports have shown that the severity of oral and pharyngeal cancers affects the development of SPCs.[4,24] However, tumor staging was not performed in this study. Although alcohol consumption and smoking have been reported to be factors associated with the development of SPCs, alcohol consumption and smoking status could not be ascertained.[10,25–27]

In conclusion, patients with oral and pharyngeal cancer are at a higher risk of developing SPCs. Age, cancer treatment, and the anatomical subsite of the initial cancer may influence its incidence. The data obtained in this study may be useful to provide information on the risk of SPCs in patients with oral and oropharyngeal cancer.

Declaration of competing interest

None.

Acknowledgments

This research was supported by Grant-in-Aid for Young Scientists (KAKENHI grant number: 21K17204). We would like to thank Korenori Arai of Osaka Dental University for providing us with valuable advice for our study.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jds.2022.11.025.

References

1. Global Burden of Disease 2019 Cancer Collaboration, Kocarnik JM, Compton K, et al. Cancer incidence, mortality, years of life lost, years lived with disability, and disability-

adjusted life years for 29 cancer groups from 2010 to 2019: a systematic analysis for the global burden of disease study 2019. *JAMA Oncol* 2022;8:420—44.
2. *Vital statistics Japan (Ministry of health, Labour and Welfare)*. Available at: https://ganjoho.jp/reg_stat/statistics/index.html. [Date accessed 31 July 2022.
3. Katanoda K, Hori M, Saito E, et al. Updated trends in cancer in Japan: incidence in 1985—2015 and mortality in 1958—2018—a sign of decrease in cancer incidence. *J Epidemiol* 2021;31:426—50.
4. Diaz DA, Reis IM, Weed DT, Elsayyad N, Samuels M, Abramowitz MC. Head and neck second primary cancer rates in the human papillomavirus era: a population-based analysis. *Head Neck* 2016;38:E873—83.
5. Tabuchi T, Ito Y, Ioka A, Miyashiro I, Tsukuma H. Incidence of metachronous second primary cancers in Osaka, Japan: update of analyses using population-based cancer registry data. *Cancer Sci* 2012;103:1111—20.
6. Simple M, Suresh A, Das D, Kuriakose MA. Cancer stem cells and field cancerization of oral squamous cell carcinoma. *Oral Oncol* 2015;51:643—51.
7. Chuang SC, Scelo G, Tonita JM, et al. Risk of second primary cancer among patients with head and neck cancers: a pooled analysis of 13 cancer registries. *Int J Cancer* 2008;123:2390—6.
8. Baxi SS, Pinheiro LC, Patil SM, Pfister DG, Oeffinger KC, Elkin EB. Causes of death in long-term survivors of head and neck cancer. *Cancer* 2014;120:1507—13.
9. Chen MC, Huang WC, Chan CH, Chen PT, Lee KD. Impact of second primary esophageal or lung cancer on survival of patients with head and neck cancer. *Oral Oncol* 2010;46:249—54.
10. Iwatsubo T, Ishihara R, Morishima T, et al. Impact of age at diagnosis of head and neck cancer on incidence of metachronous cancer. *BMC Cancer* 2019;19:3.
11. Su WW, Chuang SL, Yen AM, et al. Risk for a second primary hypopharyngeal and esophageal cancer after an initial primary oral cancer. *Oral Dis* 2019;25:1067—75.
12. Warren S, Gates O. Multiple malignant tumors: a survey of literature and statistical study. *Am J Cancer* 1932;16:1358—414.
13. Coca-Pelaz A, Rodrigo JP, Suárez C, et al. The risk of second primary tumors in head and neck cancer: a systematic review. *Head Neck* 2020;42:456—66.
14. Hori M, Matsuda T, Shibata A, et al. Cancer incidence and incidence rates in Japan in 2009: a study of 32 population-based cancer registries for the Monitoring of Cancer Incidence in Japan (MCIJ) project. *Jpn J Clin Oncol* 2015;45:884—91.
15. Mochizuki Y, Harada H, Ikuta M, et al. Clinical characteristics of multiple primary carcinomas of the oral cavity. *Oral Oncol* 2015;51:182—9.
16. Chen MC, Chen PT, Chan CH, et al. Second primary esophageal or lung cancer in patients with head and neck carcinoma in Taiwan: incidence and risk in relation to primary index tumor site. *J Cancer Res Clin Oncol* 2011;137:115—23.
17. Chen PT, Kuan FC, Huang CE, et al. Incidence and patterns of second primary malignancies following oral cavity cancers in a prevalent area of betel-nut chewing: a population-based cohort of 26,166 patients in Taiwan. *Jpn J Clin Oncol* 2011;41:1336—43.
18. Hashibe M, Ritz B, Le AD, Li G, Sankaranarayanan R, Zhang ZF. Radiotherapy for oral cancer as a risk factor for second primary cancers. *Cancer Lett* 2005;220:185—95.
19. Min SK, Choi SW, Lim J, Park JY, Jung KW, Won YJ. Second primary cancers in patients with oral cavity cancer included in the Korea Central Cancer Registry. *Oral Oncol* 2019;95:16—28.
20. Ben Arie G, Shafat T, Belochitski O, El-Saied S, Joshua BZ. Treatment modality and second primary tumors of the head and neck. *ORL J Otorhinolaryngol Relat Spec* 2021;83:420—7.
21. Morris LG, Sikora AG, Patel SG, Hayes RB, Ganly I. Second primary cancers after an index head and neck cancer: subsite-specific trends in the era of human papillomavirus-associated oropharyngeal cancer. *J Clin Oncol* 2011;29:739—46.
22. Tiwana MS, Hay J, Wu J, Wong F, Cheung W, Olson RA. Incidence of second metachronous head and neck cancers: population-based outcomes over 25 years. *Laryngoscope* 2014;124:2287—91.
23. Tanaka S, Seto K, Kawakami K. Pharmacoepidemiology in Japan: medical databases and research achievements. *J Pharm Health Care Sci* 2015;1:16.
24. Rennemo E, Zätterström U, Boysen M. Impact of second primary tumors on survival in head and neck cancer: an analysis of 2,063 cases. *Laryngoscope* 2008;118:1350—6.
25. Tabuchi T, Ito Y, Ioka A, Nakayama T, Miyashiro I, Tsukuma H. Tobacco smoking and the risk of subsequent primary cancer among cancer survivors: a retrospective cohort study. *Ann Oncol* 2013;24:2699—704.
26. León X, Del Prado Venegas M, Orús C, Kolañczak K, García J, Quer M. Metachronous second primary tumours in the aero-digestive tract in patients with early stage head and neck squamous cell carcinomas. *Eur Arch Oto-Rhino-Laryngol* 2005;262:905—9.
27. Day GL, Blot WJ, Shore RE, et al. Second cancers following oral and pharyngeal cancers: role of tobacco and alcohol. *J Natl Cancer Inst* 1994;86:131—7.