Oral Oncology 95 (2019) 16–28

Contents lists available at ScienceDirect

Oral Oncology

journal homepage: www.elsevier.com/locate/oraloncology

Second primary cancers in patients with oral cavity cancer included in the Korea Central Cancer Registry

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ARTICLE INFO

Keywords:
Oral cavity cancer
Second primary cancer
Korea Central Cancer Registry
Standardized incidence ratio

ABSTRACT

Objectives: The improved survival of patients with oral cavity cancer (OCC) has generated interest in factors affecting survivorship, particularly among second primary cancer (SPC) patients. This study aimed to assess the incidence, patterns, and risk factors for SPC after OCC treatment in the Korean population.

Materials and methods: Data from 15,261 patients with OCC (ICD-O: C01–C06) identified between 1993 and 2014 were extracted from the Korean Central Cancer Registry. The standardized incidence ratio (SIR) for SPC after index OCC was calculated, and Poisson regression analysis was performed to evaluate the risk factors for SPC among survivors.

Results: The overall SIR for SPC among OCC survivors was 1.47 (95% confidence interval [CI] 1.39–1.56). SIR differed by sex (male: 1.51 vs. female: 1.37), age at diagnosis (< 45 years: 2.47 vs. 45–64 years: 1.68 vs. ≥ 65 years: 1.10), index OCC subsite (floor of mouth: 1.95 vs. gum: 1.30), follow-up duration (6–23 months: 1.64 vs. 24–59 months: 1.51 vs. 60–119 months: 1.48 vs. ≥ 120 months: 1.24), histological OCC type (salivary gland malignancy: 1.77 vs. squamous cell carcinoma: 1.44 vs. others: 1.47), and radiation history (any: 1.94 vs. no radiation: 1.37). The risk factors for SPC development among OCC survivors included younger age at diagnosis and history of radiation therapy.

Conclusion: OCC survivors have significantly increased risks of SPCs, exhibiting distinctive site distributions and chronological patterns. These patients would benefit from an SPC surveillance protocol.

Introduction

Advances in surgical techniques and radiation therapies have significantly improved survival among patients with oral cavity cancer (OCC). A recent study found that > 60% of Korean patients with OCC are expected to survive for at least 5 years [1]. Most deaths caused by primary OCC occur within 2 years after diagnosis and treatment. Accordingly, the conditional 5-year relative survival rate increased to 81.4% after 2 years of survival. Moreover, after an additional 3 years of survival, the rate remains similar at 86.5%. This finding suggests that OCC survivors have significant and sustained risks of death as compared with the general population. Second primary cancer (SPC) has been speculated to be a major potential cause of this risk in OCC survivors, leading to increased clinical and patient interest in SPC.

Previous studies examining SPC after OCC have dealt mostly with head and neck cancer in general rather than focusing on OCC [2,3], and therefore, these studies have overlooked the specific properties of OCC. In fact, all head and neck cancer subsets have distinctive characteristics that deserve individualized attention. For example, etiological factors, such as the contributions of the Epstein–Barr virus to nasopharyngeal cancer or human papilloma virus to oropharyngeal cancer, are not prominent causative factors for OCC [4–6]. Furthermore, the relatively low and high 5-year survival rates of patients with hypopharyngeal cancer and laryngeal cancer, respectively, may differently affect the incidence of SPC as compared to that of OCC [2]. Most importantly, OCCs itself includes malignancies with distinct histologic features and

Abbreviations: KCCR, Korean Central Cancer Registry; OCC, oral cavity cancer; PYR, person year risk; RRR, relative risk ratio; SEER, Surveillance Epidemiology, and End Results; SIR, standardized incidence ratio; SPC, second primary cancer

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https://doi.org/10.1016/j.oraloncology.2019.05.025
Received 3 August 2018; Received in revised form 26 May 2019; Accepted 27 May 2019
Available online 04 June 2019

Table 1
Characteristics of patients with oral cavity cancer.

	Oral cavity					
	Male and female		Male		Female	
	No.	%	No.	%	No.	%
No. of patients	15,261	100	10,116	100	5,145	100
No. of patients with subsequent cancer	1,096	7.19	843	8.33	253	4.92
No. of patients with one subsequent cancer	1,008	6.61	769	7.6	239	4.65
No. of patients with two subsequent cancers	81	0.53	68	0.67	13	0.25
No. of patients with three or more subsequent cancers	7	0.05	6	0.06	1	0.02
Mean follow-up, years (SD)†	4.94	5.19	4.64	5.02	5.52	5.45
Mean age at index diagnosis, years (SD)†	58.46	14.35	58.31	13.10	58.76	16.54
Mean age at event diagnosis, years (SD)†	64.83	11.77	65.29	11.00	63.32	13.98
Age at diagnosis						
< 45	2,468	16.17	1,425	14.09	1,043	20.27
45–64	7,222	47.32	5,278	52.17	1,944	37.78
≥65	5,571	36.5	3,413	33.74	2,158	41.94
Year at diagnosis						
1993–2000	4,097	26.85	2,883	28.5	1,214	23.6
2001–2007	5,033	32.98	3,330	32.92	1,703	33.1
2008–2014	6,131	40.17	3,903	38.58	2,228	43.3

† Mean years are inscribed in the No. columns and standard deviation (SD) in the % columns.

distributions. For example, minor salivary gland cancers more frequently involve the palate rather than other subsites of the oral cavity [7]. These findings indicate the need for SPC assessment with a specific focus on OCC survivors.

OCC survivors who develop SPC have worse survival outcomes than those without SPC [8], and SPC has been identified as the leading cause of death among long-term survivors [9]. Investigation regarding the sites at risk, incidence, patterns, and risk factors of SPC may improve survivorship in OCC survivors. These data would serve as a basis for an efficient SPC surveillance protocol that can benefit OCC survivors. Therefore, this study aimed to analyze the types and patterns of SPC among patients with OCC who were identified from the Korea Central Cancer Registry (KCCR). Additionally, we conducted a multivariate analysis of the potential risk factors for SPC among patients with OCC and surveyed index cancers preceding the second primary OCC among patients in the registry.

Materials and methods

The KCCR uses the ICD-O-3 code to classify the site/subsite and histology of cancer, and to standardize the database. The study subjects with OCC had cancer of the following anatomic sites: lips, tongue, gum, floor of mouth, palate, and other parts of mouth (ICD-O-3: C00–C06). Based on these sites, all cases that showed invasive histology were used for the analysis. We defined an SPC as a cancer occurring at least six months after the index cancer. Because SPC detected within the first 6 months after diagnosis of the initial cancer was considered a synchronous primary cancer, the cases were excluded. Additionally, to calculate the standardized incidence ratio (SIR) for the secondary primary OCC, any preceding first primary invasive cancers that matched the second OCC were selected as index cancers.

SIRs and corresponding 95% confidence intervals (CIs) of subsequent cancers among patients with OCC were analyzed to quantify relative risk compared with that among the general population. SIRs were calculated as the ratio of the observed-to-expected number of cases, which was obtained by assuming that these patients experienced the same cancer incidence as the corresponding general population based on the 5-year age, 1-year calendar period, and sex specificity by cancer type. The mid-year population reported by Statistics Korea, available at http://kosis.kr/, was used as a general reference population in this study.

The number of person-years at risk (PYR) was calculated from 6 months after the diagnosis of the first primary cancer to the date of loss to follow-up, date of death, or end date of the study (December 31, 2014), whichever occurred first. For individuals with two or more subsequent cancers, each was analyzed independently. CIs of SIRs were based on the assumption of a Poisson distribution for patients with SPC. A 2-sided p-value < 0.05 was considered statistically significant.

Using the multivariate Poisson regression analysis, relative risk ratios (RRRs) of SPCs for each possible related factor were estimated by adjusting for possible confounding variables such as sex, age at initial diagnosis, year of diagnosis, follow-up period, oral cavity subsite, histology, and receipt of radiation therapy.

To compute SIRs and their 95% CIs, we used the “MP-SIR” session of SEER*Stat (version 8.3.5; SEER Program, National Cancer Institute, Bethesda, MD). RRR analyses using the multivariate Poisson regression analyses were performed using SAS (version 9.4; SAS Institute, Cary, NC).

The National Cancer Center Institutional Review Board approved this study (NCC2018-0142).

Results

A total of 15,261 patients with OCC were identified from the KCCR between 1993 and 2014. The mean age at OCC diagnosis was 58.46 years, and patients were followed up for a mean duration of 4.94 years. Eventually, 1,096 patients developed 1,191 metachronous SPCs during follow-up; among them, 81 patients developed two SPCs and seven patients developed three SPCs. The mean age at SPC diagnosis was 64.83 years (Table 1).

OCC survivors exhibited a significant excess risk of subsequent metachronous SPC (SIR = 1.47, 95% CI: 1.39–1.56) compared with the general population (Table 2). The risk of subsequent oral SPCs was higher (SIR = 16.25, 95% CI: 13.04–20.02) than that of non-oral SPCs (SIR = 1.37, 95% CI: 1.29–1.45) in index OCC patients (Table 2). Lip, tongue, gums, floor of mouth, palate, ‘other and unspecified parts of mouth’, tonsil, oropharynx, hypopharynx, salivary gland, esophagus, nose, nasal cavity, ear, larynx, lung, bronchus, bone, joints, soft tissue (including heart), and melanoma of skin (anatomic sites follows the SEER scheme except for the first six subsites of the oral cavity) were the anatomic locations with significant excess risk of SPC after an index OCC. Sites harboring fewer than expected SPCs included the colon and prostate (Figure 1).

During follow-up, the overall SIR was highest between 6 and

Table 2
Risk of second primary cancers after oral cavity cancer by follow-up, 1993–2014.

	6–23 months			24–59 months			60–119 months			120 months			Total		
Other primary tumour	O	SIR	CI	O	SIR	CI	O	SIR	CI	O	SIR	CI	O	SIR	CI
All types	276	1.64#	1.46–1.85	346	1.51#	1.35–1.67	359	1.48#	1.33–1.64	210	1.24#	1.07–1.42	1,191*	1.47#	1.39–1.56
All types(except oral cavity)	241	1.45#	1.27–1.64	325	1.42#	1.27–1.59	337	1.40#	1.26–1.56	200	1.18#	1.03–1.36	1,103	1.37#	1.29–1.45
Oral cavity	35	29.43#	20.50–40.92	21	13.31#	8.24–20.34	22	13.80#	8.65–20.90	10	9.50#	4.55–17.46	88	16.25#	13.04–20.02
Lips	< 5	35.71#	4.32–129.00	0	0	0–49.61	< 5	12.92	0.33–72.01	0	0	0–73.08	< 5	11.62#	2.40–33.95
Tongue	18	34.14#	20.23–53.96	8	11.43#	4.94–22.53	7	9.91#	3.98–20.42	< 5	6.45#	1.33–18.86	36	15.01#	10.51–20.78
Gums	0	0	0–30.73	< 5	6.12	0.15–34.08	< 5	17.68#	3.65–51.68	< 5	8.18	0.21–45.57	5	8.69#	2.82–20.28
Floor of mouth	5	42.11#	13.67–98.27	< 5	26.91#	7.33–68.89	< 5	21.99#	4.54–64.28	< 5	13.02	0.33–72.52	13	27.05#	14.40–46.25
Palate	< 5	7.33	0.19–40.85	0	0	0–20.31	< 5	11.01#	1.33–39.78	< 5	25.52#	5.26–74.57	6	9.72#	3.57–21.16
Other and unspecified parts of mouth	9	38.96#	17.81–73.96	8	25.80#	11.14–50.84	6	18.61#	6.83–40.50	< 5	9.05#	1.10–32.68	25	23.05#	14.92–34.03
Pharynx and Salivary gland	21	12.35#	7.64–18.87	30	13.31#	8.98–19.00	21	9.28#	5.75–14.19	8	5.54#	2.39–10.92	80	10.44#	8.28–12.99
Nasopharynx	0	0	0–10.85	< 5	4.55	0.55–16.43	0	0	0–8.82	< 5	8.27#	1.00–29.87	< 5	2.78	0.76–7.11
Tonsil	< 5	6.15	0.74–22.22	5	11.30#	3.67–26.38	5	11.04#	3.59–25.78	0	0	0–12.41	12	7.91#	4.09–13.81
Oropharynx	8	63.16#	27.27–124.44	6	37.13#	13.63–80.82	< 5	18.67#	3.85–54.56	0	0	0–37.25	17	31.02#	18.07–49.67
Hypopharynx	< 5	6.60#	1.80–16.90	11	13.73#	6.86–24.58	9	11.08#	5.07–21.03	5	9.57#	3.11–22.33	29	10.58#	7.08–15.19
Salivary gland	7	23.11#	9.29–47.61	6	14.64#	5.37–31.87	< 5	9.56#	2.60–24.47	< 5	3.53	0.09–19.67	18	12.72#	7.54–20.11
Digestive system	80	0.9	0.72–1.12	138	1.15	0.97–1.36	168	1.35#	1.15–1.57	73	0.86	0.68–1.08	459	1.1	1.00–1.20
Esophagus	17	4.67#	2.72–7.48	35	7.30#	5.08–10.15	31	6.43#	4.37–9.12	9	2.93#	1.34–5.55	92	5.63#	4.54–6.91
Stomach	27	0.82	0.54–1.19	38	0.86	0.61–1.18	61	1.36#	1.04–1.75	17	0.58#	0.34–0.93	143	0.95	0.80–1.11
Small intestine	0	0	0–6.24	0	0	0–4.56	< 5	1.18	0.03–6.60	< 5	1.69	0.04–9.40	< 5	0.7	0.09–2.55
Colon	11	0.88	0.44–1.58	12	0.68	0.35–1.19	15	0.77	0.43–1.27	7	0.48#	0.19–0.99	45	0.70#	0.51–0.94
Rectum, rectosigmoid junction	5	0.48	0.16–1.12	9	0.62	0.28–1.18	15	0.97	0.54–1.60	9	0.84	0.38–1.60	38	0.74	0.53–1.02
Rectum	5	0.58	0.19–1.34	9	0.75	0.34–1.43	12	0.95	0.49–1.65	8	0.93	0.40–1.83	34	0.81	0.56–1.13
Anus, anal canal	0	0	0–16.60	0	0	0–12.35	0	0	0–11.77	< 5	4.59	0.12–25.56	< 5	0.95	0.02–5.30
Liver	9	0.63	0.29–1.20	19	1.03	0.62–1.60	23	1.29	0.82–1.93	8	0.74	0.32–1.46	59	0.96	0.73–1.24
Gallbladder	< 5	0.89	0.11–3.22	< 5	0.64	0.08–2.33	< 5	1.19	0.32–3.05	< 5	1.23	0.25–3.58	11	0.99	0.49–1.76
Bile ducts, other biliary	6	0.88	0.32–1.93	11	1.18	0.59–2.10	7	0.7	0.28–1.44	9	1.23	0.56–2.33	33	0.98	0.68–1.38
Pancreas	< 5	0.61	0.13–1.79	12	1.76	0.91–3.08	11	1.5	0.75–2.68	9	1.66	0.76–3.16	35	1.43	1.00–1.99
Respiratory system	71	2.46#	1.92–3.11	87	2.22#	1.78–2.74	89	2.14#	1.72–2.64	66	2.25#	1.74–2.86	313	2.25#	2.01–2.52
Nose, nasal cavity, ear	11	33.39#	16.67–59.75	< 5	6.91#	1.43–20.20	< 5	9.25#	2.52–23.69	< 5	14.34#	3.91–36.72	22	14.92#	9.35–22.59
Larynx	9	4.72#	2.16–8.95	10	4.05#	1.94–7.45	9	3.72#	1.70–7.07	8	5.44#	2.35–10.72	36	4.36#	3.05–6.03
Lung, bronchus	50	1.89#	1.40–2.50	72	1.99#	1.56–2.51	75	1.95#	1.53–2.44	53	1.93#	1.45–2.53	250	1.95#	1.71–2.20
Female Breast	< 5	0.97	0.26–2.48	6	1.02	0.37–2.21	5	0.81	0.26–1.89	< 5	0.69	0.14–2.03	18	0.88	0.52–1.39
Female genital system	< 5	0.3	0.01–1.66	< 5	0.65	0.13–1.90	< 5	0.66	0.14–1.92	< 5	0.69	0.08–2.48	9	0.58	0.27–1.11
Cervix uteri	< 5	0.54	0.01–3.02	< 5	0.41	0.01–2.26	< 5	0.86	0.10–3.09	0	0	0–2.70	< 5	0.5	0.14–1.28
Corpus uteri	0	0	0–6.43	0	0	0–4.45	< 5	1.15	0.03–6.43	0	0	0–6.12	< 5	0.35	0.01–1.94
Ovary	0	0	0–4.91	< 5	0.95	0.02–5.27	0	0	0–3.38	< 5	1.34	0.03–7.47	< 5	0.55	0.07–1.98
Vagina	0	0	0–94.03	0	0	0–68.68	0	0	0–65.71	0	0	0–93.88	0	0	0–19.58
Vulva	0	0	0–58.66	< 5	11.07	0.28–61.70	0	0	0–37.58	< 5	13.46	0.34–75.02	< 5	6.14	0.74–22.19
Male genital system	5	0.5	0.16–1.17	9	0.62	0.28–1.18	10	0.59	0.28–1.09	10	0.72	0.34–1.32	34	0.62#	0.43–0.86
Prostate	< 5	0.41	0.11–1.05	9	0.64	0.29–1.21	10	0.6	0.29–1.11	10	0.73	0.35–1.34	33	0.61#	0.42–0.86
Testis	0	0	0–79.48	0	0	0–63.12	0	0	0–69.11	0	0	0–117.66	0	0	0–19.46
Male Breast	0	0	0–44.86	0	0	0–33.12	0	0	0–31.89	0	0	0–45.73	0	0	0–9.46
Urinary system	7	0.82	0.33–1.69	9	0.77	0.35–1.46	9	0.72	0.33–1.37	7	0.78	0.31–1.60	32	0.77	0.52–1.08
Urinary bladder	< 5	0.85	0.23–2.18	7	1.09	0.44–2.25	5	0.73	0.24–1.70	5	1.02	0.33–2.37	21	0.92	0.57–1.40
Kidney parenchyma	< 5	1.02	0.21–2.99	< 5	0.5	0.06–1.79	< 5	0.47	0.06–1.70	< 5	0.33	0.01–1.86	8	0.56	0.24–1.11
Renal pelvis, other urinary	0	0	0–4.04	0	0	0–2.88	< 5	1.43	0.17–5.17	< 5	0.92	0.02–5.15	< 5	0.64	0.13–1.88
Ureter	0	0	0–8.47	0	0	0–5.97	< 5	1.46	0.04–8.12	0	0	0–6.75	< 5	0.44	0.01–2.44
Bone, joints	< 5	18.10#	4.93–46.34	0	0	0–12.90	< 5	10.75#	2.22–31.41	0	0	0–20.86	7	7.27#	2.92–14.98
Soft tissue including heart	8	13.87#	5.99–27.33	< 5	3.81	0.79–11.15	0	0	0–4.51	< 5	1.72	0.04–9.58	12	4.34#	2.24–7.59
Kaposi sarcoma	0	0	0–68.61	0	0	0–48.57	0	0	0–43.22	0	0	0–49.60	0	0	0–12.74
Melanoma of skin	< 5	10.92#	2.97–27.95	< 5	1.97	0.05–10.96	< 5	1.82	0.05–10.12	0	0	0–9.12	6	3.28#	1.20–7.14
Eye, orbit	< 5	16.07	0.41–89.54	0	0	0–43.38	0	0	0–42.58	0	0	0–61.25	< 5	3.4	0.09–18.94
Brain, central, nervous system	0	0	0–3.64	< 5	0.73	0.02–4.07	< 5	1.43	0.17–5.16	< 5	2.11	0.26–7.61	5	1.06	0.34–2.47
Thyroid	14	1.74	0.95–2.93	10	0.87	0.42–1.59	10	0.81	0.39–1.49	9	1.01	0.46–1.91	43	1.05	0.76–1.42
Lymphatic, hematopoietic	7	1.22	0.49–2.52	11	1.4	0.70–2.51	5	0.61	0.20–1.41	7	1.19	0.48–2.46	30	1.08	0.73–1.55
Hodgkin lymphoma	0	0	0–30.00	0	0	0–22.48	< 5	12.14#	1.47–43.86	0	0	0–34.56	< 5	3.58	0.43–12.94
Non-Hodgkin lymphoma	< 5	1.33	0.36–3.40	< 5	0.97	0.26–2.48	< 5	0.46	0.06–1.67	5	1.62	0.53–3.79	15	1.03	0.58–1.70

(*continued on next page*)

Table 2 (*continued*)

Other primary tumour	6–23 months			24–59 months			60–119 months			120 months			Total		
	O	SIR	CI	O	SIR	CI	O	SIR	CI	O	SIR	CI	O	SIR	CI
Myeloma	< 5	1.02	0.03–5.68	< 5	1.46	0.18–5.27	< 5	1.36	0.16–4.90	< 5	0.92	0.02–5.10	6	1.22	0.45–2.66
Leukemia	< 5	1.15	0.14–4.16	5	2.12	0.69–4.94	< 5	0.41	0.01–2.27	< 5	0.59	0.01–3.28	9	1.09	0.50–2.07
Acute lymphocytic	0	0	0–30.37	0	0	0–23.07	0	0	0–23.95	0	0	0–38.91	0	0	0–6.96
Chronic lymphocytic	0	0	0–35.79	0	0	0–25.59	0	0	0–23.54	0	0	0–32.09	0	0	0–7.11
Acute non-lymphocytic	< 5	1.81	0.22–6.54	< 5	2.67	0.73–6.84	0	0	0–2.38	< 5	0.93	0.02–5.20	7	1.34	0.54–2.76
Chronic myeloid	0	0	0–11.73	< 5	2.34	0.06–13.04	< 5	2.27	0.06–12.67	0	0	0–11.92	< 5	1.34	0.16–4.85

is significant at Alpha = 0.05; O: Observed number of second primary malignancies; SIR: Standardized Incidence Ratio; CI: Confidence Interval.
* Sum of the number of patients with one, two, three or more subsequent cancers; 1,191 = 1,008 + (81 × 2) + (7 × 3).

23 months after index OCC (SIR = 1.64, 95% CI: 1.46–1.85), and decreased gradually thereafter. However, some peculiar patterns were observed. The SIR for the second primary esophageal cancer was highest between 24 and 59 months (SIR = 7.30, 95% CI: 5.08–10.15), whereas a high risk of stomach SPC was only observed during the 60 to 119 month period (SIR = 1.36, 95% CI: 1.04–1.75), after which the risk was lower than that for the general population (SIR = 0.58, 95% CI: 0.34–0.93) (Table 2).

The overall SIR was higher in male OCC survivors (SIR = 1.51, 95% CI: 1.41–1.61) than in female OCC survivors (SIR = 1.37, 95% CI: 1.21–1.54). Among male OCC survivors, SPCs most frequently occurred in the lung, bronchus, stomach, and esophagus. The risk of developing cancer in lung, bronchus and esophagus in OCC male survivors was higher than that in the matched general population. Among female OCC survivors, SPCs most frequently occurred in the thyroid, lung, bronchus and stomach. Only the lung and bronchus showed significantly elevated SIRs; the stomach showed a significantly lower SIR (Table 3). Furthermore, OCC survivors aged < 45 years had the highest overall SIR (SIR = 2.47, 95% CI: 2.04–2.95), followed by those aged 45–64 years (SIR = 1.68, 95% CI: 1.56–1.81). The SIR of survivors aged > 65 years failed to reach significance for an increased risk relative to the general population (SIR = 1.1, 95% CI: 0.99–1.21) (Table 3).

When OCCs were classified according to subsites, the floor of mouth had the highest SIR (SIR = 1.95, 95% CI: 1.65–2.29) for a subsequent metachronous SPC, followed by the palate (SIR = 1.78, 95% CI: 1.53–2.07). In contrast, the gums had the lowest SIR (SIR = 1.30, 95% CI: 1.05–1.60). Noticeably, survivors of cancer of the floor of mouth had a high SIR for SPC of the lung and bronchus (SIR = 3.08, 95% CI: 2.21–4.18) which far exceeded that for the whole cohort (SIR = 1.95, 95% CI: 1.65–2.29). Survivors of gum cancer had a lower risk of

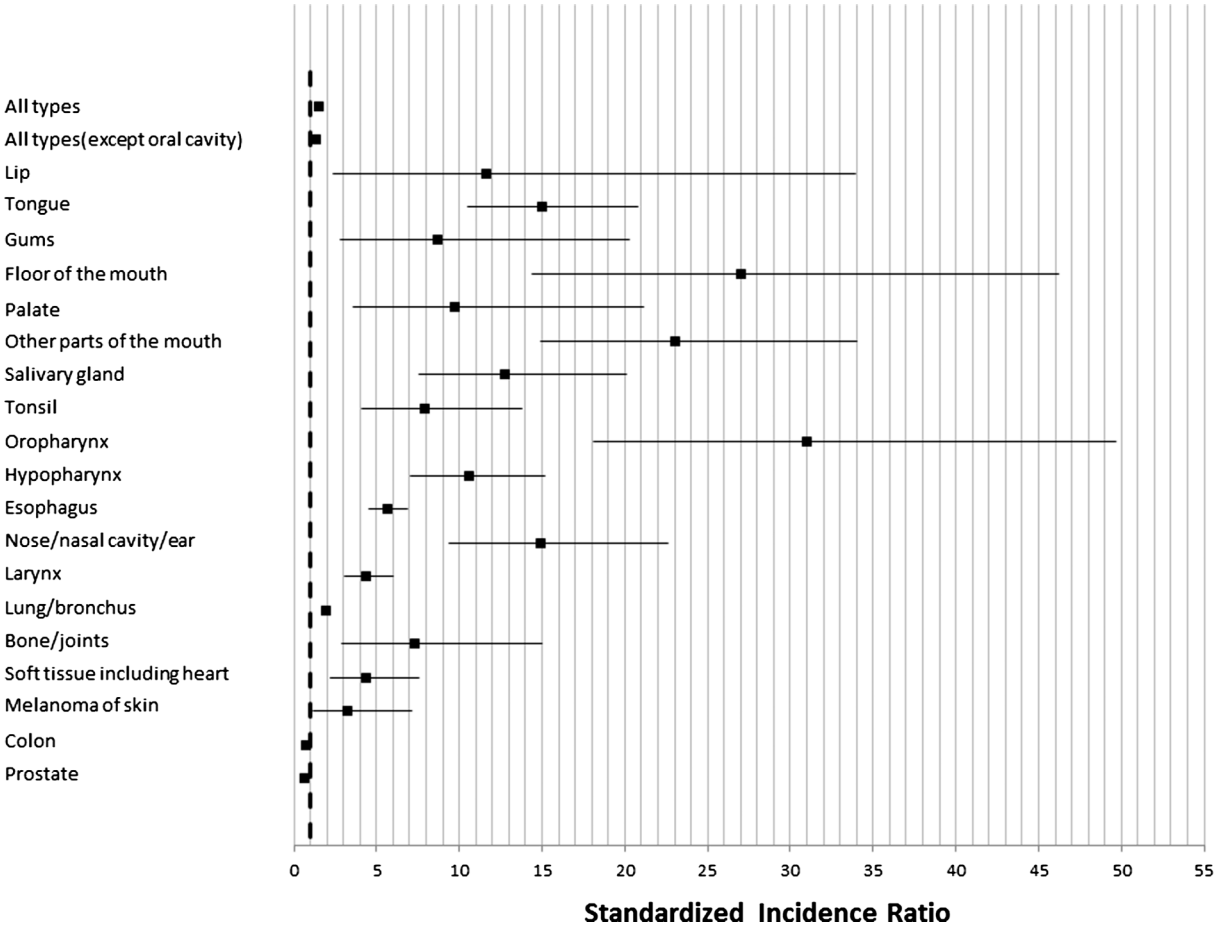

Fig. 1. Risk of second primary cancers after oral cavity cancer, 1993–2014.

Table 3
Risk of second primary cancers after oral cavity cancer by sex and age, 1993–2014.

	Sex						Age								
	Male			Female			< 45 years			45–64 years			≥ 65 years		
Other primary tumour	O	SIR	CI	O	SIR	CI	O	SIR	CI	O	SIR	CI	O	SIR	CI
All types	923	1.51#	1.41–1.61	268	1.37#	1.21–1.54	119	2.47#	2.04–2.95	679	1.68#	1.56–1.81	393	1.1	0.99–1.21
All types (except oral cavity)	870	1.43#	1.34–1.53	233	1.19#	1.04–1.36	105	2.19#	1.79–2.65	628	1.57#	1.45–1.69	370	1.04	0.94–1.15
Oral cavity	53	12.10#	9.06–15.83	35	33.83#	23.57–47.06	14	49.41#	27.01–82.90	51	17.81#	13.26–23.42	23	10.14#	6.43–15.22
Lips	< 5	15.02#	3.10–43.89	0	0	0–63.08	0	0	0–649.23	< 5	17.28#	2.09–62.43	< 5	7.31	0.19–40.73
Tongue	22	11.32#	7.09–17.14	14	30.81#	16.84–51.69	< 5	24.10#	6.57–61.70	21	15.90#	9.84–24.31	11	12.07#	6.02–21.59
Gums	< 5	4.66	0.56–16.85	< 5	20.45#	4.22–59.77	0	0	0–175.12	< 5	7.01	0.85–25.31	< 5	11.15#	2.30–32.60
Floor of mouth	7	15.93#	6.40–32.81	6	146.08#	53.61–317.96	< 5	146.55#	30.22–428.28	6	20.75#	7.61–45.16	< 5	23.39#	6.37–59.90
Palate	< 5	6.05#	1.25–17.69	< 5	24.66#	5.09–72.06	< 5	71.22#	8.63–257.29	< 5	12.45#	3.39–31.88	0	0	0–13.77
Other and unspecified parts of mouth	16	18.34#	10.48–29.78	9	42.43#	19.40–80.55	5	118.86#	38.59–277.38	16	30.12#	17.22–48.92	< 5	7.82#	2.13–20.03
Pharynx and Salivary gland	66	9.51#	7.35–12.10	14	19.43#	10.62–32.60	10	21.41#	10.27–39.38	50	11.39#	8.45–15.02	20	7.13#	4.36–11.01
Nasopharynx	< 5	2.4	0.49–7.01	< 5	5.3	0.13–29.54	0	0	0–23.65	< 5	3.43	0.71–10.02	< 5	2.44	0.06–13.61
Tonsil	9	6.37#	2.91–12.10	< 5	28.44#	5.86–83.10	< 5	27.51#	5.67–80.39	< 5	4.22#	1.15–10.81	5	10.84#	3.52–25.29
Oropharynx	15	28.69#	16.06–47.33	< 5	79.35#	9.61–286.64	0	0	0–224.96	13	42.91#	22.85–73.38	< 5	17.49#	4.77–44.79
Hypopharynx	28	10.46#	6.95–15.11	< 5	15.66	0.40–87.23	< 5	50.56#	10.43–147.75	20	13.29#	8.12–20.53	6	5.09#	1.87–11.08
Salivary gland	11	10.21#	5.10–18.27	7	20.75#	8.34–42.75	< 5	31.68#	8.63–81.12	10	13.14#	6.30–24.17	< 5	7.58#	2.07–19.42
Digestive system	393	1.18#	1.06–1.30	66	0.78#	0.60–0.99	26	1.46	0.95–2.14	272	1.26#	1.11–1.42	161	0.87	0.74–1.02
Esophagus	85	5.42#	4.33–6.70	7	11.02#	4.43–22.72	10	32.88#	15.77–60.47	62	7.19#	5.51–9.21	20	2.70#	1.65–4.17
Stomach	127	1.02	0.85–1.22	16	0.59#	0.34–0.96	6	0.89	0.33–1.94	86	1.09	0.87–1.35	51	0.78	0.58–1.02
Small intestine	< 5	0.95	0.11–3.43	0	0	0–5.06	0	0	0–25.39	< 5	0.71	0.02–3.96	< 5	0.78	0.02–4.34
Colon	36	0.75	0.53–1.04	9	0.55	0.25–1.05	< 5	0.41	0.01–2.29	22	0.69	0.43–1.05	22	0.74	0.46–1.12
Rectum, rectosigmoid junction	30	0.76	0.51–1.08	8	0.69	0.30–1.36	< 5	0.4	0.01–2.25	23	0.86	0.54–1.29	14	0.64	0.35–1.08
Rectum	26	0.8	0.52–1.18	8	0.84	0.36–1.65	< 5	0.48	0.01–2.65	22	1	0.62–1.51	11	0.62	0.31–1.11
Anus, anal canal	< 5	1.45	0.04–8.06	0	0	0–10.21	0	0	0–80.34	< 5	2.04	0.05–11.39	0	0	0–7.13
Liver	51	0.96	0.71–1.26	8	0.99	0.43–1.96	< 5	0.75	0.15–2.18	36	0.99	0.69–1.37	20	0.96	0.59–1.48
Gallbladder	8	1.15	0.50–2.27	< 5	0.71	0.15–2.08	0	0	0–16.32	5	1.07	0.35–2.49	6	0.96	0.35–2.09
Bile ducts, other biliary	30	1.19	0.80–1.69	< 5	0.37	0.08–1.07	< 5	4.29	0.88–12.53	20	1.34	0.82–2.07	10	0.56	0.27–1.03
Pancreas	23	1.32	0.83–1.97	12	1.72	0.89–3.00	< 5	3.09	0.37–11.16	16	1.43	0.82–2.33	17	1.34	0.78–2.15
Respiratory system	266	2.22#	1.96–2.50	47	2.48#	1.83–3.30	23	8.41#	5.33–12.62	176	2.74#	2.35–3.17	114	1.59#	1.31–1.90
Nose, nasal cavity, ear	9	7.79#	3.56–14.80	13	40.61#	21.62–69.44	< 5	35.82#	7.39–104.68	15	19.78#	11.07–32.62	< 5	6.32#	1.72–16.19
Larynx	34	4.25#	2.94–5.94	< 5	7.7	0.93–27.81	< 5	15.92#	3.28–46.52	21	4.61#	2.85–7.04	12	3.41#	1.76–5.96
Lung, bronchus	218	1.98#	1.72–2.26	32	1.76#	1.20–2.48	15	6.19#	3.47–10.22	137	2.34#	1.96–2.76	98	1.45#	1.18–1.77
Female Breast	0	0	0–0	18	0.88	0.52–1.39	6	0.99	0.37–2.17	11	1.03	0.51–1.84	< 5	0.26	0.01–1.47
Female genital system	0	0	0–0	9	0.58	0.27–1.11	0	0	0–1.27	7	0.91	0.37–1.88	< 5	0.41	0.05–1.47
Cervix uteri	0	0	0–0	< 5	0.5	0.14–1.28	0	0	0–2.42	< 5	0.53	0.06–1.91	< 5	0.74	0.09–2.67
Corpus uteri	0	0	0–0	< 5	0.35	0.01–1.94	0	0	0–5.98	< 5	0.6	0.02–3.33	0	0	0–6.32
Ovary	0	0	0–0	< 5	0.55	0.07–1.98	0	0	0–5.86	< 5	1.11	0.13–4.01	0	0	0–3.03
Vagina	0	0	0–0	0	0	0–19.58	0	0	0–280.46	0	0	0–45.29	0	0	0–39.34
Vulva	0	0	0–0	< 5	6.14	0.74–22.19	0	0	0–192.49	< 5	15.91#	1.93–57.47	0	0	0–20.41
Male genital system	34	0.62#	0.43–0.86	0	0	0–0	0	0	0–6.71	18	0.73	0.43–1.15	16	0.53#	0.31–0.87
Prostate	33	0.61#	0.42–0.86	0	0	0–0	0	0	0–8.06	17	0.7	0.41–1.12	16	0.54#	0.31–0.88
Testis	0	0	0–19.46	0	0	0–0	0	0	0–52.77	0	0	0–46.58	0	0	0–91.12
Male Breast	0	0	0–9.46	0	0	0–0	0	0	0–215.54	0	0	0–19.84	0	0	0–19.74
Urinary system	29	0.81	0.54–1.16	< 5	0.51	0.11–1.49	< 5	0.62	0.02–3.45	16	0.8	0.46–1.30	15	0.74	0.42–1.23
Urinary bladder	21	1.02	0.63–1.56	0	0	0–1.56	< 5	2.06	0.05–11.45	10	1	0.48–1.84	10	0.81	0.39–1.48
Kidney parenchyma	6	0.52	0.19–1.12	< 5	0.77	0.09–2.79	0	0	0–3.58	5	0.64	0.21–1.48	< 5	0.56	0.12–1.64
Renal pelvis, other urinary	< 5	0.54	0.06–1.94	< 5	1.07	0.03–5.94	0	0	0–37.41	< 5	0.46	0.01–2.59	< 5	0.83	0.10–2.99
Ureter	< 5	0.56	0.01–3.12	0	0	0–7.37	0	0	0–104.86	0	0	0–3.62	< 5	0.81	0.02–4.53
Bone, joints	6	9.26#	3.40–20.15	< 5	3.18	0.08–17.70	< 5	33.36#	9.09–85.40	< 5	6.13#	1.26–17.91	0	0	0–10.43
Soft tissue including heart	6	2.96#	1.08–6.43	6	8.18#	3.00–17.80	6	24.55#	9.01–53.43	5	3.68#	1.19–8.59	< 5	0.86	0.02–4.80
Kaposi sarcoma	0	0	0–14.40	0	0	0–110.62	0	0	0–527.26	0	0	0–35.44	0	0	0–20.68

(*continued on next page*)

Table 3 (*continued*)

	Sex						Age									
	Male			Female			< 45 years			45–64 years			≥ 65 years			
Other primary tumour	O	SIR	CI	O	SIR	CI	O	SIR	CI	O	SIR	CI	O	SIR	CI	
Melanoma of skin	5	4.14#	1.34–9.65	< 5	1.61	0.04–8.98	0	0	0–36.50	5	5.75#	1.87–13.43	< 5	1.16	0.03–6.48	
Eye, orbit	0	0	0–18.41	< 5	10.67	0.27–59.46	0	0	0–164.60	< 5	6.84	0.17–38.13	0	0	0–29.38	
Brain, central, nervous system	< 5	1.24	0.34–3.18	< 5	0.66	0.02–3.68	< 5	2.19	0.06–12.23	< 5	0.83	0.10–3.02	< 5	1.06	0.13–3.84	
Thyroid	10	0.85	0.41–1.57	33	1.13	0.78–1.59	14	1.16	0.63–1.94	21	0.92	0.57–1.41	8	1.34	0.58–2.64	
Lymphatic, hematopoietic	21	1.04	0.65–1.60	9	1.19	0.54–2.26	7	3.65#	1.47–7.53	14	1	0.55–1.68	9	0.76	0.35–1.45	
Hodgkin lymphoma	< 5	2.22	0.06–12.38	< 5	9.23	0.23–51.44	0	0	0–55.09	< 5	3.3	0.08–18.41	< 5	5.29	0.13–29.49	
Non-Hodgkin lymphoma	11	1.04	0.52–1.85	< 5	1.02	0.28–2.60	< 5	3.84#	1.05–9.83	10	1.35	0.65–2.48	< 5	0.16#	0–0.91	
Myeloma	< 5	0.57	0.07–2.06	< 5	2.84	0.77–7.28	< 5	5.82	0.15–32.40	< 5	0.79	0.10–2.87	< 5	1.35	0.28–3.94	
Leukemia	8	1.33	0.57–2.62	< 5	0.45	0.01–2.49	< 5	2.84	0.34–10.26	< 5	0.49	0.06–1.78	5	1.43	0.47–3.35	
Acute lymphocytic	0	0	0–10.47	0	0	0–20.72	0	0	0–36.96	0	0	0–13.28	0	0	0–24.18	
Chronic lymphocytic	0	0	0–9.48	0	0	0–28.42	0	0	0–211.29	0	0	0–14.09	0	0	0–15.39	
Acute non-lymphocytic	7	1.86	0.75–3.84	0	0	0–2.51	< 5	5.15	0.62–18.61	< 5	0.4	0.01–2.23	< 5	1.71	0.47–4.38	
Chronic myeloid	< 5	0.88	0.02–4.89	< 5	2.84	0.07–15.84	0	0	0–23.44	< 5	1.31	0.03–7.29	< 5	1.76	0.04–9.79	

is significant at Alpha = 0.05; CI: Confidence Interval; SIR: Standardized Incidence Ratio; O: Observed number of second primary malignancies.

stomach cancer than did the general population (SIR = 0.46, 95% CI: 0.17–1.00) (Table 4).

When OCC survivors were stratified by index OCC histology, survivors of salivary gland malignancies had higher SIRs (SIR = 1.77, 95% CI: 1.47–2.11) than those of squamous cell carcinoma (SIR = 1.44, 95% CI: 1.35–1.53) or other cancers (SIR = 1.47, 95% CI: 1.24–1.74) (Table 5).

When stratified by the history of any radiation therapy, survivors who received radiation had a higher SIR (SIR = 1.94, 95% CI: 1.71–2.18) than those who did not receive any radiation (SIR = 1.37, 95% CI: 1.29–1.47) (Table 5).

Next, we performed univariate and multivariate Poisson regression analyses to investigate risk factors for SPC among OCC survivors. The univariate analysis revealed that a diagnosis during 2001–2007 (relative to 1993–2000), salivary gland malignancies (relative to squamous cell carcinoma), subsites of the floor of mouth and palate (relative to the tongue), and radiation history significantly increased the risk of SPC. However, an age of ≥ 45 years and follow-up duration of ≥ 120 months decreased the risk of SPC among OCC survivors (Table 6). In the adjusted multivariate analysis, male sex also increased the risk of SPC, while a follow-up period of 60–119 months reduced the risk. The increased risk associated with a salivary gland malignancy did not remain significant after the adjustment (Table 6). When we classified SPCs into head and neck vs. non-head and neck cancers, we observed different effects of covariates. Most noticeably, the hazard ratio for males compared with that for females was significantly lower for SPCs of the head and neck (Supple. Table 1).

Additionally, we analyzed cancers that preceded second primary OCCs. When all index cancers were considered, the risk of second primary OCC corresponded to a SIR of 1.56 (95% CI: 1.47–1.66) (Supple. Table 2). Index sites associated with an excess risk of second primary OCC included the lips, tongue, gums, floor of mouth, palate, 'other and unspecified parts of mouth', nasopharynx, tonsil, oropharynx, hypopharynx, salivary gland, esophagus, nose, nasal cavity, ear, larynx, bone, joints, soft tissue (including heart), melanoma of the skin, non-Hodgkin lymphoma, and leukemia. In contrast, index cancers in the rectum and rectosigmoid junction were associated with a reduced risk of oral cavity SPC. Among oral cavity subsites, the floor of mouth showed the highest SIR for SPC (SIR = 1.82, 95% CI: 1.48–2.22) (Supple. Table 3).

Discussion

The increased survival after the treatment of various cancers has resulted in an increased frequency of subsequent SPCs, which have now become a major focus of research. Overall SIRs for SPCs vary significantly according to the preceding index cancers; for example, gastric or colorectal index cancers are associated with considerably higher risks of SPC, with respective overall SIRs of 1.46 and 1.28 [10,11]. In contrast, overall SIRs for thyroid, cervical, and kidney index cancer were 1.06, 1.08, and 1.13, respectively, suggesting only moderate increases in the risks of SPC [12–14]. Notably, some index cancers are even associated with a lower risk of subsequent SPC, such as in the case of prostate cancer (overall SIR for SPC = 0.75) [15].

OCC patients have a relatively high risk of a subsequent SPC. Institution-based studies have reported overall SPC rates of 13.2–18.4% among OCC patients [16–18], and population-based studies reported that 6.9–13.4% of OCC patients eventually developed SPCs [8,19,20]. The rates from the latter two reports coincided with SIRs of 2.03 and 3.11 when compared with the general population. Our data, which were based on the Korean population, yielded an overall SPC rate of 7.1% and SIR of 1.47. However, comparisons of these rates should be based on the comprehension of differences in the constitutions and etiologies of OCCs in each study. For instance, lip cancer accounted for a significant portion of cases in a report from Scotland but not in our report; similarly, betel nut chewing is a popular habit in Taiwan but not

Table 4
Risk of second primary cancers after oral cavity cancer by subsite, 1993–2014.

	Lips			Tongue			Gums		
Other primary tumour	O	SIR	CI	O	SIR	CI	O	SIR	CI
All types	91	1.37#	1.10–1.68	482	1.35#	1.23–1.48	92	1.30#	1.05–1.60
All types(except oral cavity)	89	1.35#	1.08–1.66	435	1.23#	1.11–1.35	83	1.18	0.94–1.47
Oral cavity	< 5	4.55	0.55–16.42	47	19.67#	14.45–26.16	9	19.26#	8.81–36.55
Lips	0	0	0–154.42	< 5	18.39#	2.23–66.43	0	0	0–159.07
Tongue	< 5	10.73#	1.30–38.77	5	4.63#	1.50–10.81	7	34.23#	13.76–70.52
Gums	0	0	0–76.46	5	19.95#	6.48–46.55	0	0	0–71.58
Floor of mouth	0	0	0–98.13	11	52.17#	26.04–93.35	0	0	0–94.07
Palate	0	0	0–72.48	< 5	14.93#	4.07–38.23	0	0	0–69.18
Other and unspecified parts of mouth	0	0	0–39.64	20	42.40#	25.90–65.49	< 5	20.92#	2.53–75.57
Pharynx and Salivary gland	< 5	5.03#	1.04–14.69	27	7.89#	5.20–11.47	8	12.64#	5.46–24.90
Nasopharynx	0	0	0–36.52	< 5	4.5	0.93–13.16	0	0	0–31.71
Tonsil	0	0	0–33.99	< 5	5.69#	1.55–14.56	< 5	8.04	0.20–44.81
Oropharynx	0	0	0–79.81	5	21.13#	6.86–49.32	< 5	65.90#	13.59–192.58
Hypopharynx	< 5	4.28	0.11–23.85	11	9.34#	4.66–16.71	< 5	4.43	0.11–24.66
Salivary gland	< 5	18.64#	2.26–67.33	< 5	6.25#	1.70–16.00	< 5	24.82#	5.12–72.54
Digestive system	38	1.09	0.77–1.50	190	1.03	0.89–1.19	29	0.79	0.53–1.14
Esophagus	8	5.64#	2.44–11.12	39	5.60#	3.98–7.65	< 5	2.21	0.46–6.45
Stomach	9	0.72	0.33–1.36	70	1.06	0.82–1.33	6	0.46#	0.17–1.00
Small intestine	< 5	4.24	0.11–23.60	0	0	0–2.95	0	0	0–14.58
Colon	6	1.11	0.41–2.43	20	0.71	0.43–1.10	< 5	0.52	0.11–1.52
Rectum, rectosigmoid junction	< 5	0.48	0.06–1.74	13	0.57#	0.31–0.98	< 5	0.89	0.24–2.28
Rectum	< 5	0.59	0.07–2.11	12	0.65	0.33–1.13	< 5	1.09	0.30–2.78
Anus, anal canal	0	0	0–40.18	0	0	0–8.04	0	0	0–38.54
Liver	5	1.08	0.35–2.51	18	0.65	0.38–1.03	10	1.95	0.94–3.59
Gallbladder	< 5	1.94	0.23–6.99	< 5	0.63	0.13–1.84	< 5	0.94	0.02–5.24
Bile ducts, other biliary	< 5	0.98	0.20–2.87	11	0.77	0.38–1.37	0	0	0–1.21
Pancreas	< 5	0.92	0.11–3.32	16	1.51	0.86–2.46	< 5	0.89	0.11–3.20
Respiratory system	15	1.19	0.67–1.97	125	2.11#	1.76–2.52	27	2.22#	1.47–3.23
Nose, nasal cavity, ear	0	0	0–30.55	< 5	1.54	0.04–8.58	6	46.55#	17.08–101.32
Larynx	< 5	1.42	0.04–7.94	18	5.07#	3.00–8.01	< 5	2.94	0.36–10.63
Lung, bronchus	13	1.11	0.59–1.90	102	1.87#	1.52–2.27	19	1.68#	1.01–2.63
Female Breast	0	0	0–3.84	11	1.1	0.55–1.97	< 5	0.58	0.01–3.24
Female genital system	< 5	1.06	0.03–5.92	< 5	0.56	0.15–1.43	0	0	0–2.53
Cervix uteri	0	0	0–7.26	< 5	0.81	0.17–2.38	0	0	0–4.83
Corpus uteri	0	0	0–26.57	0	0	0–2.67	0	0	0–14.75
Ovary	0	0	0–16.20	< 5	0.59	0.02–3.30	0	0	0–10.56
Vagina	0	0	0–245.81	0	0	0–44.42	0	0	0–182.89
Vulva	< 5	36.2	0.92–201.67	0	0	0–25.81	0	0	0–103.07
Male genital system	5	0.98	0.32–2.30	13	0.55#	0.29–0.94	< 5	0.63	0.13–1.85
Prostate	5	1	0.33–2.34	13	0.56#	0.30–0.96	< 5	0.65	0.13–1.89
Testis	0	0	0–343.35	0	0	0–37.83	0	0	0–259.30
Male Breast	0	0	0–106.93	0	0	0–21.67	0	0	0–114.99
Urinary system	< 5	0.82	0.17–2.41	17	0.93	0.54–1.49	0	0	0–1.02
Urinary bladder	< 5	1.4	0.29–4.10	10	1.03	0.49–1.89	0	0	0–1.85
Kidney parenchyma	0	0	0–3.40	5	0.77	0.25–1.80	0	0	0–3.03
Renal pelvis, other urinary	0	0	0–8.89	< 5	0.99	0.12–3.58	0	0	0–8.76
Ureter	0	0	0–17.83	0	0	0–3.76	0	0	0–17.63
Bone, joints	< 5	13.82	0.35–76.98	0	0	0–8.47	< 5	47.86#	13.04–122.55

(*continued on next page*)

Table 4 (*continued*)

Other primary tumour	Lips			Tongue			Gums		
	O	SIR	CI	O	SIR	CI	O	SIR	CI
Soft tissue including heart	0	0	0–16.83	< 5	0.81	0.02–4.49	< 5	12.40#	2.56–36.24
Kaposi sarcoma	0	0	0–128.91	0	0	0–29.83	0	0	0–143.55
Melanoma of skin	0	0	0–24.00	0	0	0–4.58	< 5	5.97	0.15–33.28
Eye, orbit	0	0	0–152.62	0	0	0–28.12	0	0	0–141.37
Brain, central, nervous system	0	0	0–10.16	< 5	0.94	0.11–3.39	< 5	4.78	0.58–17.27
Thyroid	6	3.23#	1.18–7.02	21	1.02	0.63–1.57	< 5	0.62	0.08–2.25
Lymphatic, hematopoietic	< 5	0.45	0.01–2.53	11	0.89	0.44–1.59	< 5	0.82	0.10–2.95
Hodgkin lymphoma	< 5	24.68	0.62–137.50	0	0	0–14.40	0	0	0–78.22
Non-Hodgkin lymphoma	0	0	0–3.21	5	0.77	0.25–1.79	0	0	0–2.88
Myeloma	< 5	2.5	0.06–13.95	< 5	0.92	0.11–3.34	< 5	4.49	0.54–16.22
Leukemia	0	0	0–5.64	< 5	1.09	0.30–2.78	0	0	0–5.08
Acute lymphocytic	0	0	0–105.25	0	0	0–15.06	0	0	0–82.27
Chronic lymphocytic	0	0	0–84.97	0	0	0–16.25	0	0	0–78.91
Acute non-lymphocytic	0	0	0–8.67	< 5	1.3	0.27–3.79	0	0	0–7.94
Chronic myeloid	0	0	0–32.76	< 5	1.47	0.04–8.20	0	0	0–28.81

Other primary tumour	Floor of mouth			Palate			Other and unspecified parts of mouth		
	O	SIR	CI	O	SIR	CI	O	SIR	CI
All types	152	1.95#	1.65–2.29	173	1.78#	1.53–2.07	201	1.43#	1.24–1.64
All types(except oral cavity)	146	1.89#	1.60–2.22	164	1.70#	1.45–1.98	186	1.33#	1.15–1.54
Oral cavity	6	10.72#	3.93–23.33	9	14.41#	6.59–27.36	15	16.08#	9.00–26.52
Lips	0	0	0–142.42	0	0	0–121.78	< 5	21.65	0.55–120.62
Tongue	6	24.35#	8.94–53.00	8	29.08#	12.55–57.29	8	19.70#	8.51–38.82
Gums	0	0	0–65.93	0	0	0–54.10	0	0	0–36.57
Floor of mouth	0	0	0–63.85	0	0	0–69.50	< 5	24.35#	2.95–87.96
Palate	0	0	0–57.38	< 5	13.78	0.35–76.79	< 5	9.24	0.23–51.48
Other and unspecified parts of mouth	0	0	0–33.68	0	0	0–29.48	< 5	15.82#	3.26–46.25
Pharynx and Salivary gland	14	16.40#	8.97–27.51	17	20.08#	11.7–32.15	11	8.41#	4.20–15.05
Nasopharynx	0	0	0–23.42	< 5	6.14	0.16–34.23	0	0	0–15.60
Tonsil	< 5	5.92	0.15–32.99	< 5	12.46#	1.51–45.02	< 5	15.88#	4.33–40.66
Oropharynx	< 5	15.39	0.39–85.73	< 5	67.29#	18.33–172.29	< 5	42.02#	11.45–107.58
Hypopharynx	8	24.58#	10.61–48.43	7	23.78#	9.56–48.99	< 5	2.06	0.05–11.49
Salivary gland	< 5	29.24#	7.97–74.86	< 5	17.69#	3.65–51.69	< 5	8.34#	1.01–30.12
Digestive system	65	1.54#	1.19–1.96	57	1.18	0.89–1.53	80	1.11	0.88–1.38
Esophagus	17	8.88#	5.17–14.22	13	7.37#	3.92–12.60	12	4.13#	2.13–7.21
Stomach	19	1.21	0.73–1.89	15	0.86	0.48–1.42	24	0.92	0.59–1.36
Small intestine	0	0	0–13.78	< 5	2.97	0.08–16.53	0	0	0–7.50
Colon	5	0.83	0.27–1.95	< 5	0.4	0.08–1.16	8	0.72	0.31–1.42
Rectum, rectosigmoid junction	< 5	0.6	0.12–1.76	8	1.34	0.58–2.64	8	0.91	0.39–1.79
Rectum	< 5	0.24	0.01–1.35	8	1.63	0.70–3.20	7	0.97	0.39–2.00
Anus, anal canal	0	0	0–39.89	0	0	0–28.26	< 5	5.47	0.14–30.47
Liver	7	1.03	0.41–2.12	7	1.03	0.41–2.11	12	1.17	0.61–2.05
Gallbladder	< 5	2.09	0.25–7.56	< 5	0.72	0.02–4.04	< 5	1.02	0.12–3.67

(*continued on next page*)

Table 4 (*continued*)

Other primary tumour	Floor of mouth			Palate			Other and unspecified parts of mouth		
	O	SIR	CI	O	SIR	CI	O	SIR	CI
Bile ducts, other biliary	7	2.2	0.88–4.52	< 5	0.76	0.16–2.24	9	1.52	0.69–2.88
Pancreas	5	2.22	0.72–5.17	6	2.07	0.76–4.50	< 5	0.93	0.25–2.39
Respiratory system	47	3.24#	2.38–4.31	55	3.51#	2.65–4.57	44	1.76#	1.28–2.37
Nose, nasal cavity, ear	0	0	0–24.81	9	52.17#	23.86–99.04	6	23.57#	8.65–51.31
Larynx	6	6.05#	2.22–13.16	6	6.77#	2.49–14.74	< 5	2.07	0.43–6.05
Lung, bronchus	41	3.08#	2.21–4.18	40	2.75#	1.97–3.75	35	1.51#	1.05–2.11
Female Breast	< 5	2.54	0.31–9.18	< 5	0.26	0.01–1.47	< 5	0.91	0.19–2.67
Female genital system	< 5	1.6	0.04–8.93	< 5	0.73	0.09–2.64	< 5	0.4	0.01–2.21
Cervix uteri	0	0	0–11.23	0	0	0–2.60	< 5	0.76	0.02–4.25
Corpus uteri	0	0	0–32.94	< 5	1.91	0.05–10.62	0	0	0–7.93
Ovary	< 5	6.84	0.17–38.13	0	0	0–5.79	0	0	0–6.16
Vagina	0	0	0–466.76	0	0	0–120.88	0	0	0–116.26
Vulva	0	0	0–273.03	< 5	19.51	0.49–108.69	0	0	0–67.66
Male genital system	< 5	0.17#	0–0.95	< 5	0.68	0.19–1.75	8	0.79	0.34–1.56
Prostate	< 5	0.17#	0–0.97	< 5	0.7	0.19–1.79	7	0.71	0.28–1.45
Testis	0	0	0–230.18	0	0	0–164.70	0	0	0–128.63
Male Breast	0	0	0–85.17	0	0	0–90.00	0	0	0–53.60
Urinary system	< 5	0.94	0.26–2.41	< 5	0.21	0.01–1.19	7	0.95	0.38–1.96
Urinary bladder	< 5	1.68	0.46–4.30	< 5	0.4	0.01–2.20	< 5	0.73	0.15–2.13
Kidney parenchyma	0	0	0–2.61	0	0	0–2.27	< 5	1.24	0.26–3.63
Renal pelvis, other urinary	0	0	0–8.10	0	0	0–6.91	< 5	1.21	0.03–6.73
Ureter	0	0	0–16.93	0	0	0–14.05	< 5	2.45	0.06–13.68
Bone, joints	< 5	11.58	0.29–64.54	< 5	8.12	0.21–45.23	0	0	0–22.80
Soft tissue including heart	0	0	0–14.60	< 5	11.90#	3.24–30.46	< 5	8.44#	2.30–21.62
Kaposi sarcoma	0	0	0–137.41	0	0	0–115.29	0	0	0–70.08
Melanoma of skin	0	0	0–23.02	< 5	17.73#	4.83–45.4	< 5	3.15	0.08–17.54
Eye, orbit	0	0	0–141.11	< 5	27.54	0.70–153.44	0	0	0–73.48
Brain, central, nervous system	< 5	2.36	0.06–13.18	0	0	0–6.24	0	0	0–4.60
Thyroid	< 5	1.35	0.28–3.95	5	0.76	0.25–1.77	6	0.93	0.34–2.03
Lymphatic, hematopoietic	< 5	0.78	0.09–2.82	< 5	0.9	0.18–2.62	11	2.31#	1.15–4.13
Hodgkin lymphoma	0	0	0–67.00	< 5	15.1	0.38–84.14	0	0	0–39.48
Non-Hodgkin lymphoma	0	0	0–2.73	< 5	1.14	0.14–4.12	8	3.21#	1.38–6.32
Myeloma	< 5	2.18	0.06–12.17	0	0	0–6.25	0	0	0–4.30
Leukemia	< 5	1.32	0.03–7.33	< 5	0.99	0.03–5.53	< 5	2.11	0.44–6.18
Acute lymphocytic	0	0	0–81.20	0	0	0–51.81	0	0	0–41.60
Chronic lymphocytic	0	0	0–74.46	0	0	0–60.37	0	0	0–40.51
Acute non-lymphocytic	< 5	2.08	0.05–11.58	0	0	0–5.78	< 5	3.32	0.68–9.71
Chronic myeloid	0	0	0–26.68	< 5	5.57	0.14–31.06	0	0	0–14.58

is significant at Alpha = 0.05; O: Observed number of second primary malignancies; SIR: Standardized Incidence Ratio; CI: Confidence Interval.

Table 5
Risk of second primary cancers after oral cavity cancer by histology and radiation, 1993–2014.

	Histology									Radiation					
	Squamous cell carcinoma			Salivary gland malignancies			Others			Any radiation			No radiation		
Other primary tumour	O	SIR	CI	O	SIR	CI	O	SIR	CI	O	SIR	CI	O	SIR	CI
All types	927	1.44#	1.35–1.53	125	1.77#	1.47–2.11	139	1.47#	1.24–1.74	271	1.94#	1.71–2.18	920	1.37#	1.29–1.47
All types (except oral cavity)	864	1.35#	1.26–1.44	110	1.57#	1.29–1.89	129	1.38#	1.15–1.64	243	1.75#	1.54–1.98	860	1.29#	1.21–1.38
Oral cavity	63	14.40#	11.07–18.42	15	35.34#	19.78–58.29	10	16.26#	7.80–29.90	28	29.64#	19.70–42.84	60	13.42#	10.24–17.28
Lips	< 5	9.63#	1.17–34.79	0	0	0–193.22	< 5	31.77	0.80–177.03	< 5	23.07	0.58–128.56	< 5	9.31#	1.13–33.62
Tongue	23	11.89#	7.54–17.85	9	46.17#	21.11–87.65	< 5	14.84#	4.04–38.00	13	30.65#	16.32–52.42	23	11.65#	7.39–17.48
Gums	5	10.87#	3.53–25.37	0	0	0–77.31	0	0	0–54.48	0	0	0–37.53	5	10.48#	3.40–24.46
Floor of mouth	9	22.61#	10.34–42.91	< 5	31.29	0.79–174.31	< 5	59.34#	12.24–173.43	< 5	46.55#	12.68–119.19	9	22.80#	10.43–43.29
Palate	< 5	8.04#	2.19–20.58	< 5	40.78#	4.94–147.31	0	0	0–52.30	< 5	9.35	0.24–52.08	5	9.80#	3.18–22.87
Other and unspecified parts of mouth	20	22.79#	13.92–35.19	< 5	36.72#	7.57–107.31	< 5	15.98#	1.93–57.71	9	48.38#	22.12–91.83	16	17.81#	10.18–28.92
Pharynx and Salivary gland	64	10.14#	7.81–12.95	13	23.80#	12.67–40.70	< 5	3.72	0.77–10.87	23	16.70#	10.59–25.06	57	9.07#	6.87–11.75
Nasopharynx	< 5	1.72	0.21–6.21	< 5	8.44	0.21–47.04	< 5	6.34	0.16–35.35	< 5	3.81	0.10–21.25	< 5	2.55	0.53–7.44
Tonsil	9	7.16#	3.27–13.59	< 5	18.65#	2.26–67.37	< 5	6.53	0.17–36.38	< 5	3.56	0.09–19.81	11	8.90#	4.44–15.92
Oropharynx	15	32.69#	18.3–53.92	< 5	30.57	0.77–170.35	< 5	17.71	0.45–98.69	5	51.21#	16.63–119.50	12	26.65#	13.77–46.55
Hypopharynx	29	12.56#	8.41–18.04	0	0	0–23.31	0	0	0–13.42	10	20.54#	9.85–37.78	19	8.43#	5.07–13.16
Salivary gland	9	8.03#	3.67–15.25	9	69.45#	31.76–131.84	0	0	0–22.44	6	24.07#	8.83–52.39	12	10.30#	5.32–17.99
Digestive system	379	1.12#	1.01–1.24	33	1.01	0.69–1.41	47	0.98	0.72–1.30	89	1.22	0.98–1.51	370	1.07	0.96–1.19
Esophagus	91	6.64#	5.34–8.15	0	0	0–3.90	< 5	0.6	0.02–3.34	24	8.35#	5.35–12.42	68	5.05#	3.92–6.41
Stomach	111	0.91	0.75–1.09	13	1.12	0.60–1.92	19	1.11	0.67–1.73	35	1.32	0.92–1.84	108	0.87	0.71–1.04
Small intestine	< 5	0.89	0.11–3.20	0	0	0–15.19	0	0	0–10.88	0	0	0–7.53	< 5	0.85	0.10–3.08
Colon	32	0.63#	0.43–0.88	8	1.49	0.64–2.94	5	0.66	0.22–1.55	8	0.73	0.31–1.43	37	0.70#	0.49–0.96
Rectum, rectosigmoid junction	29	0.71	0.47–1.02	< 5	0.94	0.26–2.42	5	0.84	0.27–1.97	< 5	0.34#	0.07–0.98	35	0.83	0.58–1.15
Rectum	25	0.74	0.48–1.10	< 5	1.14	0.31–2.93	5	1.02	0.33–2.39	< 5	0.41	0.08–1.20	31	0.9	0.61–1.27
Anus, anal canal	< 5	1.22	0.03–6.79	0	0	0–37.85	0	0	0–27.46	0	0	0–20.85	< 5	1.14	0.03–6.37
Liver	49	0.98	0.72–1.29	< 5	0.87	0.24–2.22	6	0.89	0.33–1.94	7	0.64	0.26–1.31	52	1.03	0.77–1.35
Gallbladder	10	1.15	0.55–2.12	0	0	0–3.70	< 5	0.68	0.02–3.76	< 5	0.54	0.01–3.04	10	1.07	0.51–1.97
Bile ducts, other biliary	27	1	0.66–1.46	< 5	1.16	0.24–3.39	< 5	0.74	0.15–2.16	9	1.6	0.73–3.04	24	0.86	0.55–1.28
Pancreas	27	1.39	0.91–2.02	< 5	0.5	0.01–2.77	7	2.33	0.94–4.80	< 5	0.49	0.06–1.75	33	1.62#	1.12–2.28
Respiratory system	255	2.23#	1.97–2.53	30	3.21#	2.16–4.58	28	1.81#	1.20–2.62	78	3.28#	2.59–4.10	235	2.04#	1.79–2.32
Nose, nasal cavity, ear	10	8.47#	4.06–15.58	10	83.06#	39.83–152.75	< 5	11.52#	1.39–41.60	< 5	11.69#	2.41–34.17	19	15.60#	9.39–24.36
Larynx	31	4.47#	3.03–6.34	< 5	2.09	0.05–11.65	< 5	4.74#	1.29–12.15	6	4.09#	1.50–8.90	30	4.41#	2.98–6.30
Lung, bronchus	211	2.00#	1.74–2.29	18	2.07#	1.23–3.27	21	1.46	0.91–2.24	68	3.10#	2.41–3.93	182	1.71#	1.47–1.97
Female Breast	12	0.94	0.49–1.65	5	1.06	0.35–2.48	< 5	0.32	0.01–1.80	< 5	0.58	0.07–2.09	16	0.94	0.54–1.52
Female genital system	6	0.62	0.23–1.35	< 5	0.64	0.08–2.30	< 5	0.38	0.01–2.12	< 5	0.79	0.10–2.84	7	0.54	0.22–1.12
Cervix uteri	< 5	0.6	0.12–1.76	0	0	0–2.29	< 5	0.71	0.02–3.93	0	0	0–2.82	< 5	0.6	0.16–1.53
Corpus uteri	0	0	0–2.05	< 5	1.58	0.04–8.80	0	0	0–8.39	< 5	2.03	0.05–11.31	0	0	0–1.55
Ovary	< 5	0.43	0.01–2.41	< 5	1.37	0.03–7.65	0	0	0–6.07	< 5	1.68	0.04–9.34	< 5	0.33	0.01–1.83
Vagina	0	0	0–30.06	0	0	0–116.32	0	0	0–108.63	0	0	0–124.64	0	0	0–23.23
Vulva	< 5	9.28#	1.12–33.52	0	0	0–70.54	0	0	0–63.85	0	0	0–73.32	< 5	7.26	0.88–26.24
Male genital system	25	0.53#	0.35–0.79	< 5	0.68	0.08–2.44	7	1.27	0.51–2.62	< 5	0.42	0.11–1.07	30	0.66#	0.44–0.94
Prostate	24	0.52#	0.34–0.78	< 5	0.69	0.08–2.50	7	1.3	0.52–2.68	< 5	0.43	0.12–1.10	29	0.65#	0.43–0.93
Testis	0	0	0–25.11	0	0	0–185.77	0	0	0–161.73	0	0	0–106.61	0	0	0–23.80
Male Breast	0	0	0–11.24	0	0	0–168.67	0	0	0–92.79	0	0	0–53.93	0	0	0–11.47
Urinary system	25	0.73	0.47–1.08	< 5	1.02	0.21–2.98	< 5	0.86	0.23–2.20	8	1.11	0.48–2.19	24	0.69	0.44–1.03
Urinary bladder	17	0.9	0.52–1.44	< 5	1.39	0.17–5.04	< 5	0.79	0.10–2.85	5	1.29	0.42–3.00	16	0.84	0.48–1.37
Kidney parenchyma	6	0.52	0.19–1.14	< 5	0.86	0.02–4.76	< 5	0.63	0.02–3.54	< 5	1.18	0.24–3.46	5	0.43#	0.14–1.00
Renal pelvis, other urinary	< 5	0.53	0.06–1.91	0	0	0–10.77	< 5	1.86	0.05–10.34	0	0	0–4.65	< 5	0.77	0.16–2.26
Ureter	< 5	0.54	0.01–3.01	0	0	0–21.87	0	0	0–13.80	0	0	0–9.57	< 5	0.53	0.01–2.93
Bone, joints	< 5	4.08	0.84–11.93	< 5	9.73	0.25–54.20	< 5	23.96#	4.94–70.02	< 5	6.01	0.15–33.50	6	7.53#	2.76–16.39
Soft tissue including heart	< 5	1.38	0.28–4.03	< 5	3.89	0.10–21.69	8	24.05#	10.38–47.38	< 5	6.30#	1.30–18.42	9	3.93#	1.80–7.47
Kaposi sarcoma	0	0	0–15.46	0	0	0–203.63	0	0	0–112.69	0	0	0–77.81	0	0	0–15.24

(*continued on next page*)

Table 5 (*continued*)

Other primary tumour	Histology								Radiation					
	Squamous cell carcinoma			Salivary gland malignancies			Others		Any radiation			No radiation		
	O	SIR	CI	O	SIR	CI	O	SIR	CI	O	SIR	CI	O	SIR	CI
Melanoma of skin	0	0	0–2.58	0	0	0–21.35	6	26.25#	9.63–57.13	< 5	9.69#	2.00–28.32	< 5	1.97	0.41–5.77
Eye, orbit	0	0	0–16.10	< 5	35.48	0.90–197.68	0	0	0–100.20	< 5	19.82	0.50–110.43	0	0	0–15.14
Brain, central, nervous system	< 5	0.82	0.17–2.39	< 5	2.1	0.05–11.72	< 5	1.69	0.04–9.40	0	0	0–4.52	5	1.28	0.41–2.98
Thyroid	30	1.08	0.73–1.54	11	1.4	0.70–2.51	< 5	0.38	0.05–1.38	6	0.83	0.30–1.80	37	1.1	0.78–1.52
Lymphatic, hematopoietic	20	0.92	0.56–1.41	< 5	0.39	0.01–2.20	9	2.71#	1.24–5.15	7	1.46	0.59–3.01	23	1	0.64–1.51
Hodgkin lymphoma	< 5	2.26	0.06–12.58	0	0	0–72.37	< 5	15.47	0.39–86.20	0	0	0–37.01	< 5	4.36	0.53–15.75
Non-Hodgkin lymphoma	10	0.87	0.42–1.60	< 5	0.75	0.02–4.18	< 5	2.31	0.63–5.92	5	1.98	0.64–4.63	10	0.83	0.40–1.53
Myeloma	< 5	1.03	0.28–2.63	0	0	0–8.51	< 5	3.41	0.41–12.33	< 5	1.18	0.03–6.56	5	1.23	0.40–2.87
Leukemia	6	0.93	0.34–2.02	0	0	0–4.79	< 5	2.98	0.61–8.71	< 5	0.7	0.02–3.92	8	1.17	0.51–2.31
Acute lymphocytic	0	0	0–9.35	0	0	0–57.80	0	0	0–51.29	0	0	0–39.86	0	0	0–8.43
Chronic lymphocytic	0	0	0–8.89	0	0	0–85.63	0	0	0–60.69	0	0	0–40.87	0	0	0–8.61
Acute non-lymphocytic	6	1.46	0.54–3.18	0	0	0–7.69	< 5	1.56	0.04–8.68	< 5	1.12	0.03–6.24	6	1.39	0.51–3.02
Chronic myeloid	0	0	0–3.14	0	0	0–26.45	< 5	11.41#	1.38–41.22	0	0	0–14.12	< 5	1.63	0.20–5.87

is significant at Alpha = 0.05; O: Observed number of second primary malignancies; SIR: Standardized Incidence Ratio; CI: Confidence Interval.

in Korea.

Hypothetically, inhaled or ingested carcinogens may influence several adjacent and related anatomic sites of the alimentary canal and respiratory system. The resultant theory of “field cancerization” or “multi-centric origin of epidermoid carcinoma” has been widely accepted as a concept to explain the frequent occurrence of SPC after OCC [21,22]. Inevitably, the oral cavity itself was a preferred site of SPC after OCC in our study, with a 10-fold higher SIR compared with non-oral sites. However, these data should be carefully interpreted, as low expectations of OCC in the general Korean population could potentially cause an exacerbation of SIR values. In fact, lung, bronchus, stomach, and esophagus were the most frequent sites of SPC, far exceeding any of the oral cavity subsites. Additionally, some observed cases of SPC within the oral cavity could have been registered as SPCs erroneously. The significantly high SIRs for the tonsil, oropharynx, hypopharynx, nose, nasal cavity, ear, and larynx could also be attributed to the vicinities of these sites to the oral cavity. Although the esophagus and lung/bronchus may be considered relatively more distant, their designation as constant sites of SPC after OCC has also been attributed to the major etiological factor of smoking [8,20,23]. Notably, most of the aforementioned SPC sites were also identified as significant index cancer sites preceding a second primary OCC, which supports the concepts of common carcinogens and field cancerization.

One exception was lip cancer. Actinic damage from sunlight is considered to be a major cause of lip cancer. In our registry, lips were the only subsite of the oral cavity that did not show increased SIRs for SPC of the lung and bronchus. This finding might suggest that actinic damage was the cause of lip cancer. However, the extreme rarity of lip cancer in Korea does not allow us to make any definite inference.

Even though the actual incidence was rare, this study also identified risks of SPC of the bone, joints, soft tissue (including heart), and melanoma of skin after OCC. A previous report from Taiwan also described high SIR for bone cancer after OCC [8]. Additionally, index cancers in these sites can increase the risk of a second primary OCC. Altogether, these findings suggest that the indicated sites share a currently unknown etiological factor.

We also studied the risk factors for SPC after OCC with the intent to propose an efficient surveillance strategy for OCC survivors. The two most robust factors related to the risk of SPC, regardless of the location, were age at OCC diagnosis and history of radiation therapy. Regarding the former, the increased risk of SPC among younger patients might be attributed to their longer life expectancy [1]; simply, the longer a patient survives, the higher the chance of SPC. It remains unclear whether various susceptibility genes associated with a younger onset of OCC might also affect the incidence of SPC.

In contrast, the role of radiation in the incidence of SPC is much more controversial because analyses of the risk of additional SPC among irradiated patients in studies with different designs and methodologies have yielded conflicting results [17–19,24]. In our multivariate Poisson regression analyses, we found that radiation correlated with increased risks of both head and neck SPCs and to a lesser extent, non-head and neck SPCs. Generally, SPC caused by radiation occurs within or near irradiated fields and requires at least 5–10 years to develop [25]. Correspondingly, sites with increased SIRs in the irradiated group included the tongue, floor of mouth, ‘other and unspecified parts of mouth’, oropharynx, hypopharynx, salivary glands, esophagus, and lungs and bronchus. Most of these anatomic sites are within or near the irradiated fields. Noticeably, the lungs and bronchus are the areas where most SPCs developed in the irradiated group, which suggests an aberrant radiation-induced bystander effect that results in SPC [24,26].

However, the debate is further complicated by contradicting views regarding the interactions among radiation, smoking continuation, and SPC occurrence [18,24]. According to previous studies, patients who receive a less complicated primary treatment tend to continue smoking [27,28], suggesting that patients treated with radiation alone would most likely continue smoking, followed by those treated with surgery

Table 6
Univariate and multivariate Poisson regression analysis results for risk of second primary cancer by factors, 1993–2014.

		Univariate			Multivariate		
		RRR	CI	p-value	RRR	CI	p-value
Sex	Female	1.00	–		1.00	–	
	Male	1.11	0.97–1.27	0.1462	1.17	1.01–1.35	0.0343
Age group of diagnosis	< 45	1.00	–		1.00	–	
	45–64	0.71	0.58–0.86	0.0006	0.63	0.51–0.78	< 0.0001
	≥65	0.46	0.38–0.57	< 0.0001	0.39	0.31–0.49	< 0.0001
Year group of diagnosis	1993–2000	1.00	–		1.00	–	
	2001–2007	1.23	1.08–1.40	0.0014	1.21	1.06–1.39	0.0062
	2008–2014	1.04	0.89–1.23	0.6087	1.02	0.85–1.23	0.8272
Histology group	Squamous cell carcinoma	1.00	–		1.00	–	
	Salivary gland malignancies	1.23	1.02–1.48	0.0329	1.06	0.86–1.30	0.5835
	Others	1.01	0.84–1.20	0.9470	1.03	0.86–1.23	0.7711
Follow-up	6–23 months	1.00	–		1.00	–	
	24–59 months	0.93	0.79–1.09	0.3748	0.89	0.76–1.05	0.1578
	60–119 months	0.92	0.78–1.07	0.2829	0.82	0.69–0.97	0.0189
	120 + months	0.76	0.64–0.92	0.0035	0.68	0.55–0.83	0.0002
Subsite	Tongue	1.00	–		1.00	–	
	Lips	0.99	0.79–1.25	0.9600	1.15	0.91–1.45	0.2304
	Gums	0.96	0.77–1.20	0.7039	1.03	0.83–1.29	0.7758
	Floor of mouth	1.45	1.21–1.74	< 0.0001	1.45	1.21–1.75	< 0.0001
	Palate	1.32	1.11–1.57	0.0020	1.32	1.09–1.59	0.0037
	Others	1.06	0.90–1.25	0.4789	1.12	0.95–1.32	0.1849
Radiation therapy	No radiation	1.00	–		1.00	–	
	Any radiation	1.39	1.22–1.60	< 0.0001	1.34	1.17–1.54	< 0.0001

RRR: Relative Risk Ratio; CI: Confidence Interval.

alone. In contrast, patients treated with a combination of surgery and postoperative radiation are most likely to stop smoking. Therefore, smoking continuation might be an important mediator of the increased risk of SPC among patients who received primary treatment comprising radiation alone. Although we were unable to determine conclusively whether radiation was a major direct cause of SPCs in our dataset, our findings suggest that OCC patients with a history of radiation therapy may benefit from stricter SPC surveillance.

Although we did not test a screening protocol, our study results support a strict surveillance protocol for the detection of upper aerodigestive tract SPCs after OCC treatment. However, the optimal modality [e.g., panendoscopy or an imaging study such as combined 18F-fluorodeoxyglucose-positron emission tomography and computed tomography (PET-CT)] for SPC surveillance after OCC treatment exceeds the scope of the current article [29,30]. Additionally, the surveillance methods can be affected by resource availability, cost efficiency, and government policies (e.g., the format of national medical insurance). In the context of restricted resources (e.g., where PET-CT is not available for follow-up surveillance), a follow-up period-guided endoscopy protocol may be the best choice. For instance, a protocol based on our study results would suggest that esophageal endoscopies should be performed more frequently in the follow-up period of 24–119 months, which is associated with the highest risk of esophageal SPCs. Similarly, stomach endoscopy during the follow-up period of 60–119 months might also be cost-efficient. In contrast, lung cancer screening should be continuous and may involve low-dose chest CT.

Our study has some limitations. First, KCCR did not include lifestyle information such as smoking history or drinking history. These data would have helped to elucidate the relationship between OCC and subsequent SPCs. Second, patients who developed a second malignancy within the first 6 months of follow-up were excluded, because these tumors are considered synchronous rather than metachronous. The increased cancer surveillance after the diagnosis of OCC may have created bias, thereby affecting the results of this study. However, there may not be a fully accurate and efficient way to remove unavoidable cases from the cancer registration. Thirdly, the radiation therapy variable was evaluated by calculating the number of patients who received it within the initial 4 months of treatment. As a result, the purpose of radiation treatment was not differentiated in terms of definitive vs adjuvant therapy. Radiation therapy was mostly confined to first-line therapy. Fourth, we did not evaluate age at radiation exposure or attained age directly for analysis.

Conclusions

OCC survivors have an increased risk of SPC. SPCs occur at sites where possible common etiological factors are shared. These sites also differ with chronological intervals in the highest risk of SPC occurrence. A younger age at diagnosis and radiation therapy were identified as risk factors of SPC. A tailored SPC surveillance program will improve survivorship of OCC patients.

Declaration of Competing Interest

The authors declare that they have no conflicts of interest.

Acknowledgements

This study was supported by the National Cancer Center Grant (No. 1610201), Republic of Korea.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.oraloncology.2019.05.025.

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