Risk of second primary cancer in oral squamous cell carcinoma

Short title: Second primary cancer after OSCC

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ABSTRACT

BACKGROUND: The incidence and survival of oral squamous cell carcinoma (OSCC) patients have increased in recent years. Understanding their long-term survival aspects is essential for optimal treatment and follow-up planning. Almost one in five cancers diagnosed occurs nowadays in individuals with a previous diagnosis of cancer.

METHODS: Patients diagnosed with primary OSCC during 1953-2015 were retrieved from the Finnish Cancer Registry. Both standardized incidence ratios (SIR) and excess absolute risk (EAR) per 1,000 person-years at risk (PYR) of second primary cancer (SPC) were calculated relative to the general population.

RESULTS: Among 6,602 first primary OSCC patients there were 640 (10%) SPCs. The SIR for SPCs was 1.85 (95% CI: 1.71-1.99, $P < .001$) corresponding to an EAR of 8.78 (95% CI: 7.29-10.26).

CONCLUSIONS: Health-care professionals should be aware of the second primary cancer risk after management of primary OSCC and patients need to be counselled about this phenomenon.

Introduction

Oral cancer, including lip cancer, accounts for approximately 2% of all diagnosed malignancies worldwide (1). The global burden is expected to further increase not only as a consequence of the growth and aging of the population (2) but also due to unknown etiological factors (3,4). Squamous cell carcinoma (SCC) accounts for 80-90% of all malignancies in the oral cavity and the tongue remains the most common location, covering approximatively 25 % of the cases (5,6). Incidence rates for oral squamous cell carcinoma (OSCC) vary markedly (0.43-20.4 per 100,000 per year) around the world, due to diverse risk profiles among populations (1,6,7). It is for instance widely prevalent in India and Bangladesh (5,8), whereas in Finland OSCC is the 16th most common cancer (http://www.cancerregistry.fi). While its incidence is not as high as that of other cancers, it still poses significant morbidity and mortality in patients, particularly when advanced disease is present (9).

The term second primary cancer (SPC), or second primary malignancy, is used to designate a new primary cancer arising in a person who has been diagnosed with cancer in the past. SPCs are considered to occur independently, and not as a result of resurgence or metastasis of the original primary cancer, at any time after the primary cancer was diagnosed and treated. (10) SPCs are defined as synchronous when diagnosed simultaneously or within six months of the primary tumor and as metachronous when diagnosed more than six months after the primary tumor (11). The concept of SPC was put forward by Billroth in 1889 (12) and it has evolved from a rare medical condition to one of the leading causes of morbidity and mortality today (13).

Improvements in early detection, supportive care, and treatment outcome have resulted in an increase in the number of cancer survivors, a substantial proportion of whom will be diagnosed with a new cancer (14). In general, almost one in five cancers diagnosed occurs nowadays in individuals with a

previous diagnosis of cancer (13). Based on an international meta-analysis from 1992, head and neck cancer (HNC) survivors, including OSCC survivors, have SPC rates of 14.2% when followed up for more than five years (15). As in the case of primary cancers, SPCs can be a result of lifestyle factors, environmental exposures to carcinogenic substances, such as tobacco, and inherited gene mutations. Studies have also reported genetic susceptibility and radiotherapy as potential risk factors for SPCs after treatment of OSCC (16-18).

The survival of patients with OSCC has improved in recent years and the need to understand the long-term survival aspects of this population has become essential (9,19,20). However, there is a dearth of research on SPCs arising after treatment of primary OSCC. Moreover, to our knowledge, no comprehensive data on subsite-specific differences in SPC risk after primary OSCC based on a large patient cohort have been published. The purpose of this study was to evaluate the risk of any SPC and the risk of site-specific SPC in a large nationwide OSCC cohort and to describe risk changes over time with long-term follow-up time obtained from the Finnish Cancer Registry. We also aimed at finding out whether this risk would differ from the published risk of SPC for other head and neck cancer subsites because of the impact that this finding might have on the planning of appropriate follow-up recommendations for this patient population.

Patients and Methods

OSCC comprises squamous cell carcinomas located in the buccal mucosa, the gingiva, the hard palate, the tongue and the floor of the mouth, as defined by the 8th edition of the Union for International Cancer Control's (UICC) TNM classification (21). ICD-O-3 topographical codes were used to retrieve OSCC patients from the nationwide cancer registry in Finland.

The classification of SPC established in 1932 by Warren and Gates was adhered to: both primary and second primary tumors must be malignant and separated by non-neoplastic mucosa, and it should be established that the second tumor is not a metastasis of the first tumor (10). Nevertheless, a small percentage of local, or even distant, recurrences could theoretically be misclassified as a SPC and vice versa. To minimize the risk of misclassification, SPC was described in our study as a metachronous malignant cancer developing later than six months after diagnosis of primary OSCC. SPCs diagnosed less than six months after diagnosis of primary OSCC were thus excluded. For SPCs arising in locally adjacent anatomical structures, the risk of misclassification is undoubtedly present despite this 6-month cut-off. Still, we decided to report the results, as this issue is unavoidable in clinical practise.

Data from the Finnish Cancer Registry (FCR) were retrieved to identify an epidemiological series of patients diagnosed with primary OSCC in Finland during 1953–2015. The FCR includes all new primary cancers diagnosed in Finland since 1953 with complete follow-up until death or emigration. Quality assessment studies have shown high coverage (96% of solid tumors) and accuracy of diagnosis (22). Follow-up time for the risk of SPC was calculated from the date of diagnosis of the first primary tumor of OSCC to the diagnosis of any or site-specific SPC. All cases with primary SCCs located in the oral cavity were included. Patients with any previous cancer, except for basal-cell carcinoma of the skin, were excluded. Research permission for the study design was granted by the National Institute for Health and Welfare in Finland (Dnro THL/264/5.05.00/2015). For data privacy reasons, we do not report observed or expected values, if less than five cases were reported in a certain site.

Two statistical quantities were calculated to describe the risk of SPC among the OSCC patients. Standardized incidence ratios (SIRs) were employed to quantify the risk of SPC in OSCC patients relative to general population (23). The SIR estimates the risk of a cancer patient developing a SPC relative to the first occurrence of cancer among the general population. SIR is thus a ratio of observed SPC to expected cancers, in which the expected number of first cancers was calculated for the general population. The SIRs were stratified according to site of the primary tumor, age group, gender, extent of disease and time period. The excess absolute risk (EAR) is an absolute measure of SPC risk and describes the difference in absolute risk of cancer between the OSCC patient population and the general population (observed cases – expected cases) per 1,000 person-years at risk (or PYR). The EAR estimates the absolute number of additional cancers attributable to primary OSCC and thus measures the burden of SPCs to health care in a given population.

All analyses were conducted using R and the popEpi –package. P-values and confidence intervals for SIRs were computed using normal approximation for Poisson-model coefficient. P-values were adjusted for multiple comparisons by Holm's method. Confidence intervals for EARs were calculated using normal approximation.

Results

Between the 1st of January 1953 and the 31st of December 2015, 6,996 occurrences of OSCC were registered in the Finnish Cancer Registry. Age-adjusted incidence rate of OSCC in Finland is presented in Figure 1. A total of 6,602 OSCC patients with no previous cancers (except for basal-cell carcinoma of the skin) were eligible for our study, which contributed 33,395 person-years of follow-up. The tongue and the floor of the mouth comprised 48% and 22% of all the cases in this study

cohort, respectively. OSCC located in the hard palate was rare, with only 24 cases (0.4%) reported. during the 63-year period.

A metachronous SPC was observed in 640 (10%) OSCC patients of the study cohort. SPCs (41%) were most commonly diagnosed within five years of diagnosis of primary OSCC; only 9% (n=231) were reported after 20 years. Of all metachronous SPCs arising in the mouth or pharynx (n=73), 23 (31%) were diagnosed within 0.5 to 5 years after diagnosis of the primary OSCC. Synchronous SPCs were reported for 70 patients (1%), the majority of which occurred in the respiratory (n=26, 37%) and digestives organs (n=12, 17%). Synchronous SPCs were excluded from the following statistical analyses. The incidence of SPCs arising after OSCC, has been steadily rising in Finland, as shown in Figure 2.

Among patients with OSCC, the SIR for SPC was 1.85 (95% CI: 1.71-1.99, P < .001), corresponding to 8.78 excess SPCs per 1,000 PYR (95% CI: 7.29-10.26). The risk was elevated in both sexes and in all age groups in comparison to the general population. The extent of the primary disease did not markedly influence the SIR, as both localized and advanced disease had a comparable SIR (1.81 versus 1.86, SIR-ratio 0.973, CI: 0.77-1.24). The SIR for SPC was elevated after diagnosis of primary OSCC in each follow-up interval, as well as throughout each 15-year period (or 17-year period for the first) of first diagnosis. The SIRs and EARs for SPCs, for the different stratified categories and subsites are summarized in Table 1.

There were differences in the relative risk and absolute number of excess SPCs between subsites of OSCC. The highest relative risk for SPC at any site was observed in patients with a primary SCC in the floor of mouth (SIR 2.38, 95% CI: 2.04-2.77, P < .001), followed by gingival SCC (SIR 2.22, 95% CI: 1.36-3.37, P< .001). Similarly, the highest absolute number of excess SPCs per 1,000 PYR

was observed in patients with gingival SCC (EAR 15.27, 95% CI: 2.75-27.79), followed by floor of the mouth SCC (EAR 14.56, 95% CI: 10.73-18.39).

For all OSCC patients combined, the highest SIRs were for SPCs in mouth or pharynx (SIR 10.90, 95% CI: 8.59-13.60, P < .001 and EAR 1.99, 95% CI: 1.48-2.49), in bone (SIR 8.04, 95% CI: 2.59-24.94, P < .001 and EAR 0.08, 95% CI: -0.02-0.18) and in respiratory or intrathoracic organs (SIR 3.43, 95% CI: 2.89-4.02, P < .001 and EAR 3.03, 95% CI: 2.33-3.73), as shown in Figure 3. The relative risk for SPCs in mouth or pharynx and in respiratory organs was elevated in each follow-up interval. Women had a higher relative risk than men for SPCs in mouth or pharynx (SIR 17.1, 95% CI 12.6-23.2, P < .001 versus 7.46, 95% CI 5.27-10.5, P < .001). No substantial differences in SIRs and EARs between OSCC and oral tongue squamous cell carcinoma (OTSCC) patients could be noted. Therefore, only values for OSCC are reported. SIRs for SPCs by site and stratified by time of diagnosis of SPC and by age, are outlined in Figures 4 and 5, respectively.

For tongue and floor of the mouth SCC, the highest EAR of SPCs occurred in the respiratory or intrathoracic organs (EAR 2.75, 95% CI: 1.82-3.69 and 5.75, 95% CI: 3.74-7.78, respectively), followed by the mouth or pharynx for tongue SCC (EAR 1.72, 95% CI: 1.06-2.37) and digestive organs for floor of the mouth SCC (EAR 3.58, 95% CI: 1.72-5.44). Similarly, for these subsites, the highest statistically significant SIRs for SPC (with more than one observed occurrence) were observed in the mouth or pharynx: 9.93 (95% CI: 6.91-13.71, P < .001) for tongue and 14.90 (95% CI: 9.61-23.10, P < .001) for floor of the mouth SCC. For gingival and buccal mucosa SCC, the highest SIRs (39.10, 95% CI: 17.57-87.03, P < .001 for gingival and 7.51, 95% CI: 4.23-12.16, P < .001 for buccal mucosa SCC), and EAR (8.56, 95% CI: 1.53-15.60 for gingival and 1.38, 95% CI: -0.55-2.22 for buccal mucosa SCC) were observed in the mouth or pharynx. However, only six SPCs

(19 in total) after gingival SCC were observed in this location. No cases of SPC were reported following primary OSCC originating in the hard palate.

Discussion

The results of this study confirm that patients with OSCC have an 85% excess risk of developing a SPC compared with the underlying incidence rates experienced in the Finnish population. Among all the different primary subsites of the oral cavity, the respiratory organs and intrathoracic organs (22% of all SPCs) and digestive organs (21%) are the commonest sites for SPCs in our data. The highest relative risks for SPC were in the mouth and pharynx (SIR 10.90, 95% CI: 8.59-13.60) and the risk remained constantly elevated after five years.

In contrast to single-institution or pooled-data studies, which are hampered by cohort size or heterogeneity of registries, the foremost strength of our study is the large and population-based series of OSCC patients. Data addressing subsite-specific risks and trends over time may be helpful in the rational application of follow-up protocols and patient counselling in primary OSCC patients after treatment.

In Finland, the incidence of OSCC has been progressively rising, among others, as a consequence of the growing and ageing of the population (24). Tobacco products and heavy alcohol consumption are well-documented etiologic risk factors. Additionally, other suspected risk factors for the development of OSCC, such as poor oral hygiene, chronic irritation, viral infections, and consumption of processed meat products have been identified. (25-27) Advancements in diagnostic and therapeutic management of cancer patients have resulted in an increased population of cancer survivors, for whom one of the

most serious events will be the diagnosis of a new cancer (14). This issue is equally relevant for OSCC patients: with the rising incidence and prolongation of survival time of primary OSCC patients, the incidence of SPCs is similarly growing (9).

In our study cohort, the cumulative risk for synchronous SPC was 1%, which is comparable to the 2.4% rate observed in HNC patients (28). A metachronous SPC was diagnosed in 10% of the patients, which is in alignment with the range of 9% to 14.2% reported by other studies of HNC patients (15,29-31). For other cancer patient populations, different rates of SPC have been reported: while Bradford et al. (32) observed that 12% of melanoma patients subsequently developed a SPC, Murakami et al. (33) reported a 3.6% incidence of SPCs for patients with primary breast cancer, and Ikeda et al. (34) a 4.2% incidence of SPCs for gastric cancer patients.

The SIR of developing a SPC was 1.85 (95% CI: 1.71-2.00), which is lower than the SIR of 2.82 (95% CI: 2.74-2.90) and 2.8 (95% CI: 2.70-2.90) for oral cancer patients reported by Morris et al. (35) and Day et al. (36), respectively, in the USA. The differences could be due to inclusion criteria: for example, in the study of Day et al. pharyngeal cancer patients were also included, and also, only SPCs developing within two months (versus 6 months in our study) of the diagnosis of the primary cancer were excluded. For SPCs arising in the oral cavity or pharynx in oral cancer patients, Morris et al. reported a SIR of 31.68 (95% CI: 30.08-33.33), and only cases diagnosed after five years were included (35). The rate is higher than in our study, where the corresponding relative risk remained between 12.8-13.8 (95% CI 6.01-24.5) during each follow-up interval after five years. Our result is in line with the SIR of 1.86 (95% CI: 1.83-1.90) for HNC patients observed in a pooled international multicenter analysis consisting of 99 257 patients (37). Also, in a study recently conducted in South Korea (38), the authors reported an overall SIR of 1.47 (95% CI 1.39-1.56) for SPC among oral cavity cancer survivors (SPCs diagnosed after six months were included, as in our study). Interestingly,

similar to our findings, the relative risk for SPCs arising in the oral cavity was higher for women (SIR 33.83, 95% CI 23.57-47.06, p < .005) than for men (SIR 12.10, 95% CI 9.06-15.83, p<.005). OSCC, and other HNCs, can carry a higher relative risk for SPC than most other cancers (35,39). Thus, it is essential to pay close attention to the risk for SPC during the follow-up of this patient population. While there was some variation in the estimated relative risks, a fairly constant pattern of increased risk following primary OSCC was seen for both males and females, and across all age groups (except for 75-year-old patients) at first diagnosis, and follow-up intervals. Floor of the mouth SCC carried a higher relative risk for SPC than OTSCC or oral mucosa SCC, an observation earlier reported in a study by de Vries et al. (1986) (40).

OSCC has been most strongly associated with SPCs in the head and neck area, as confirmed also by our study (35,40). These findings are not unexpected, as these different SPC sites share a partially common etiology with OSCC, mainly tobacco smoking and alcohol consumption (25,41). Moreover, it has been reported that continuance of tobacco and alcohol use after treatment of primary HNSCC had a significant impact on the development of a SPC (42). Genetic predisposition could also play a critical role. Studies have indeed identified genetic aberrations involving HNCs. For example, SCC of the lungs and the head and neck show a high frequency of genetic alteration in the fibroblast growth factor receptor 1 (FGFR1) gene located on chromosome 8. FGFR1 acts as the cell surface receptor for fibroblast growth factors and is involved, among others, in the regulation of cell proliferation and differentiation. (43-46)

A noteworthy observation was that bone cancer had also an elevated SIR of 8.04, even though observed cases were few and subsequently the confidence interval large (95% CI: 2.59-24.94, P = 0.009). Nevertheless, it is plausible that some bone sarcomas of the jaw were classified in the FCR as HNC or oral cancers and the incidence could consequently be slightly higher. These SPCs can be

the manifestation of the late sequelae of treatment. Indeed, one epidemiological study established an association between previous radiation exposure and bone sarcoma (47). In Finland, 21 patients were treated for craniomaxillofacial osteosarcoma between 1992 and 2009 and in four patients (19%) the osteosarcoma developed in a previously irradiated area (48). Tucker et al. similarly reported an association between radiation exposure and alkylating agents, used in chemotherapy, and bone sarcoma in childhood cancer survivors (49). It should be stressed that the platinum-containing anticancer agents cisplatin and carboplatin, commonly used in the chemotherapeutic treatment of advanced HNCs, are not alkylating agents. Still, in multivariate analyses, cisplatin was associated with an increased risk of leukaemia following treatment of ovarian and testicular cancer (50,51). It seems reasonable to expect that a SPC caused by the primary treatment would occur many years after the diagnosis and treatment of the primary tumor. Still, in our study the relative risk for SPC was consistent during each follow-up interval. Information on radiation exposure as part of treatment and chemotherapy was not reliably available in the FCR and was thus omitted from analyses.

In addition to exposure to common carcinogens and genetic susceptibility, cancer survivors may have a lower threshold for the detection of SPCs due to more frequent and effective follow-up methods. More sensitive imaging modalities may have led to improved detection of SPCs. Small lesions may be more frequently identified. Some lesions previously classified as metastases could be also more often classified adequately as SPCs due to greater awareness and understanding of SPCs and improved biopsy techniques. The last three decades of our study period show a higher relative risk for SPC compared with the first decade. This can be due not only to the aforementioned causes but also to the improved surveillance of patients and treatment modalities. In combination with these factors, increased survival rates allow for a longer time for the development of SPCs.

Certain weaknesses of our study should be pointed out. One limitation in our registry-based study is the lack of information on key etiological factors, such as tobacco and alcohol consumption, and the limited information available on primary treatment. We could thus not evaluate the relation of these risk factors to SPCs. Also, as mentioned previously, some distant metastases could have been erroneously classified as SPCs and vice versa. Most SPCs occurred in the head and neck region and in the respiratory organs and the anatomical proximity of these sites might have led to a misdiagnosis of local spread or distant metastasis as SPCs. On the other hand, this diagnostic bias is not likely to be entirely responsible for the association between OSCC and SPC, as the relative risk was still elevated after 10 years from diagnosis of the primary tumor, also for SPCs arising in the mouth and pharynx and in the respiratory organs. One study concluded that a significant number (50%, n=20) of squamous cell lung cancers clinically diagnosed as metastases were, in fact, suggested to be SPCs according to loss of heterozygosity analysis evaluating clonal relationship between tumors (52). However, the clinical diagnostic criteria for a SPC could vary among different treatment centers, with some centers having more conservative criteria than others.

Other caveats in our study are related to the precise definition and potential misclassification of SPC being, in fact, a residue of the first primary cancer (10). Contemporary studies have proposed the concept of field cancerization, which involves cancer stem cells as the primary units, and their presence in the mucosa adjacent to the tumor may be an indicator for later development of SPC (53). SPCs can subsequently share some or all the genetic markers with the primary tumor, a sign that both tumors are descendants from a common cell clone. (54) Some SPCs can be recurrences of the primary disease in a pre-existing patch of field cancerization. This may, at least partially, explain the high SIR observed for SPCs originating in the mouth or pharynx. The carcinogenic effects of tobacco smoking and alcohol consumption can act simultaneously on multiple parts of this region and lead to the development of a cancerization field. The definition of SPC will most certainly be redefined in the

future. However, due to the nature and purpose of the study, the clinical definition of SPC had to be adhered to.

The SIR of developing a SPC for OSCC patients (1.85) does not markedly differ from the SIR for other HNC patients reported in the literature, with the head and neck area and respiratory organs being the primary SPC sites for these cancers (37). OSCC represents the commonest HNC, with as many as 303 cases diagnosed in Finland in 2015. Therefore, frequent clinical and imaging examinations for the detection of indolent SPCs for such a large patient population may involve high healthcare costs and increased radiation exposure for patients. Alternatively, OSCC survivors, and also primary health care professionals, should be counselled of the risk of SPC. Patients should be advised to be vigilant and consult with a healthcare professional in the event of symptoms associated with a potential SPC. Encouragement of cessation of both tobacco smoking and heavy alcohol consumption should also be an essential part of the treatment protocol, as the risk for SPCs has been shown to be elevated in this patient population. Important opportunities for future research include the identification of patient subgroups that might be at an increased predisposition of SPC and the development of diagnostic tools for the detection of field cancerization.

Conclusion

We conclude, that patients with OSSC as primary cancer have an 85% excess of risk for a SPC and this excess risk remained even 20 years after the diagnosis of the first primary cancer. Health-care professionals should be aware of the second primary risk after management of primary OSCC and patients need to be counselled about this phenomenon.

Statement of author contributions

MR, NA, HA, PJ, ST and MA conceived and designed the study. NA conceived the data. MR and NA analyzed the data. MR devised the manuscript. All authors contributed to the revision of the manuscript and had final approval of the submitted and published versions.

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Figure 1. Age-adjusted incidence rate of oral squamous cell carcinoma in Finland between 1953-2016 (incidence data were available until the 31st of December 2016).

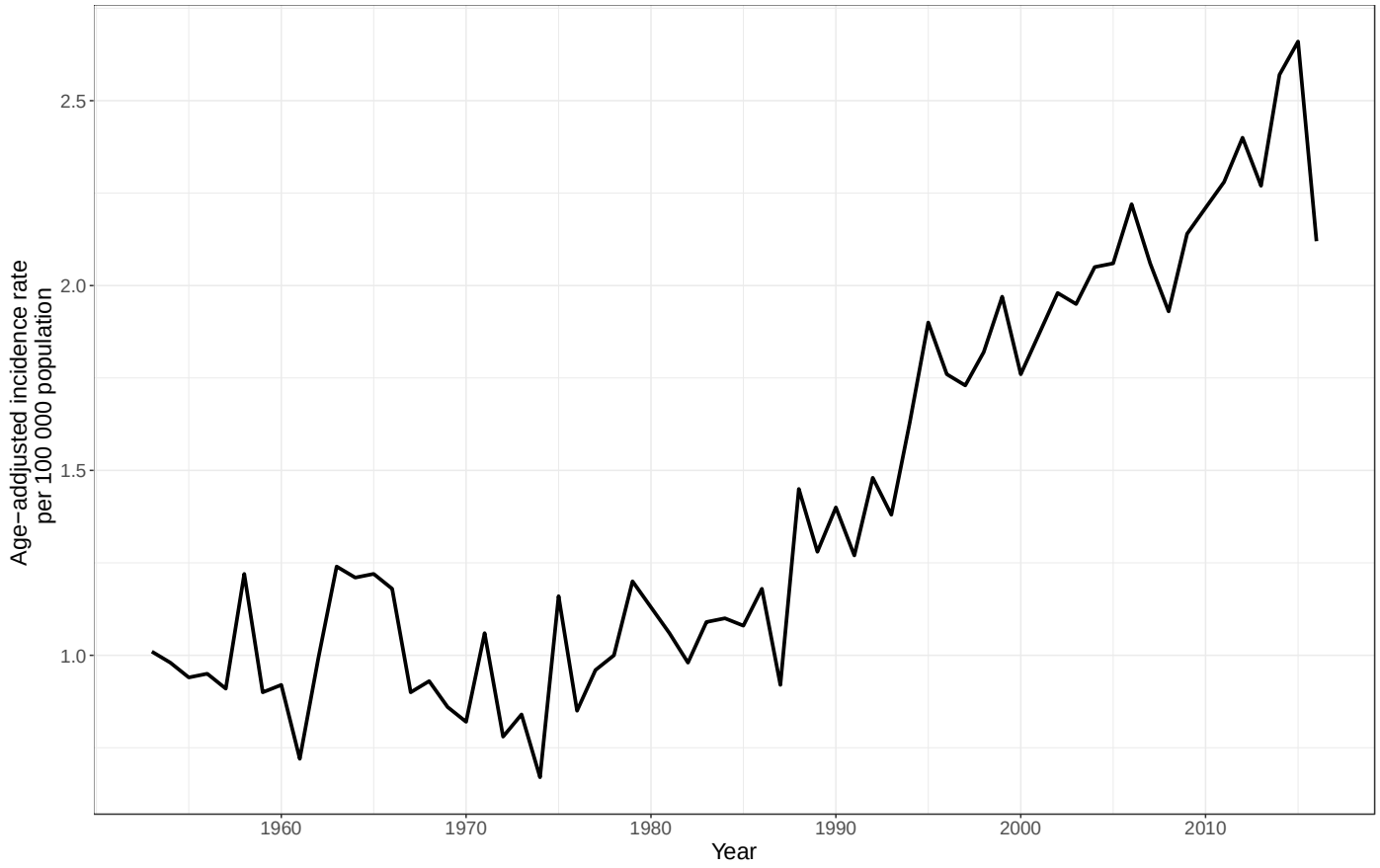


Figure 2. Annual incidence of any metachronous secondary primary cancer among 6602 oral squamous cell carcinoma (OSCC) patients diagnosed in Finland during 1953-2015.

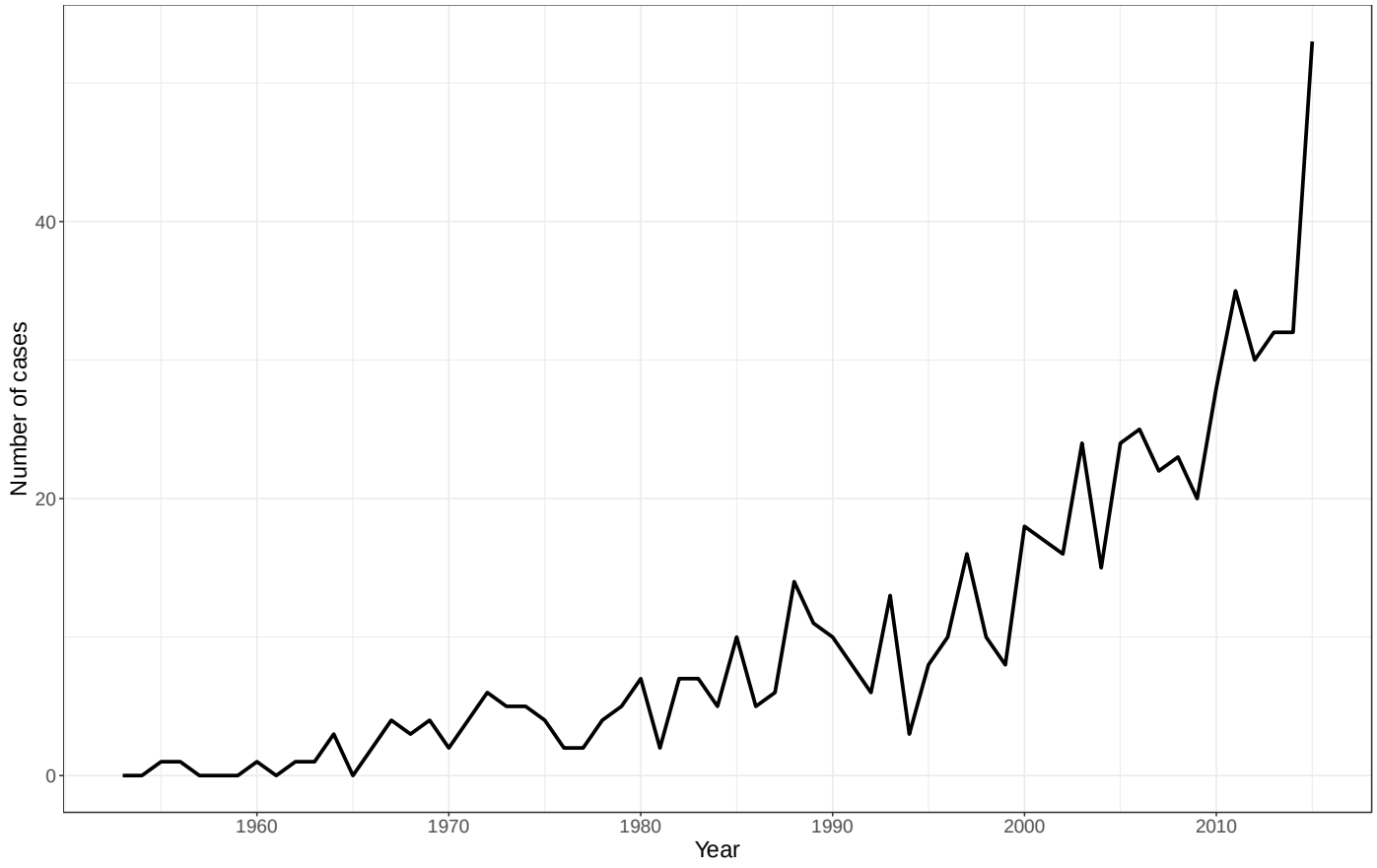
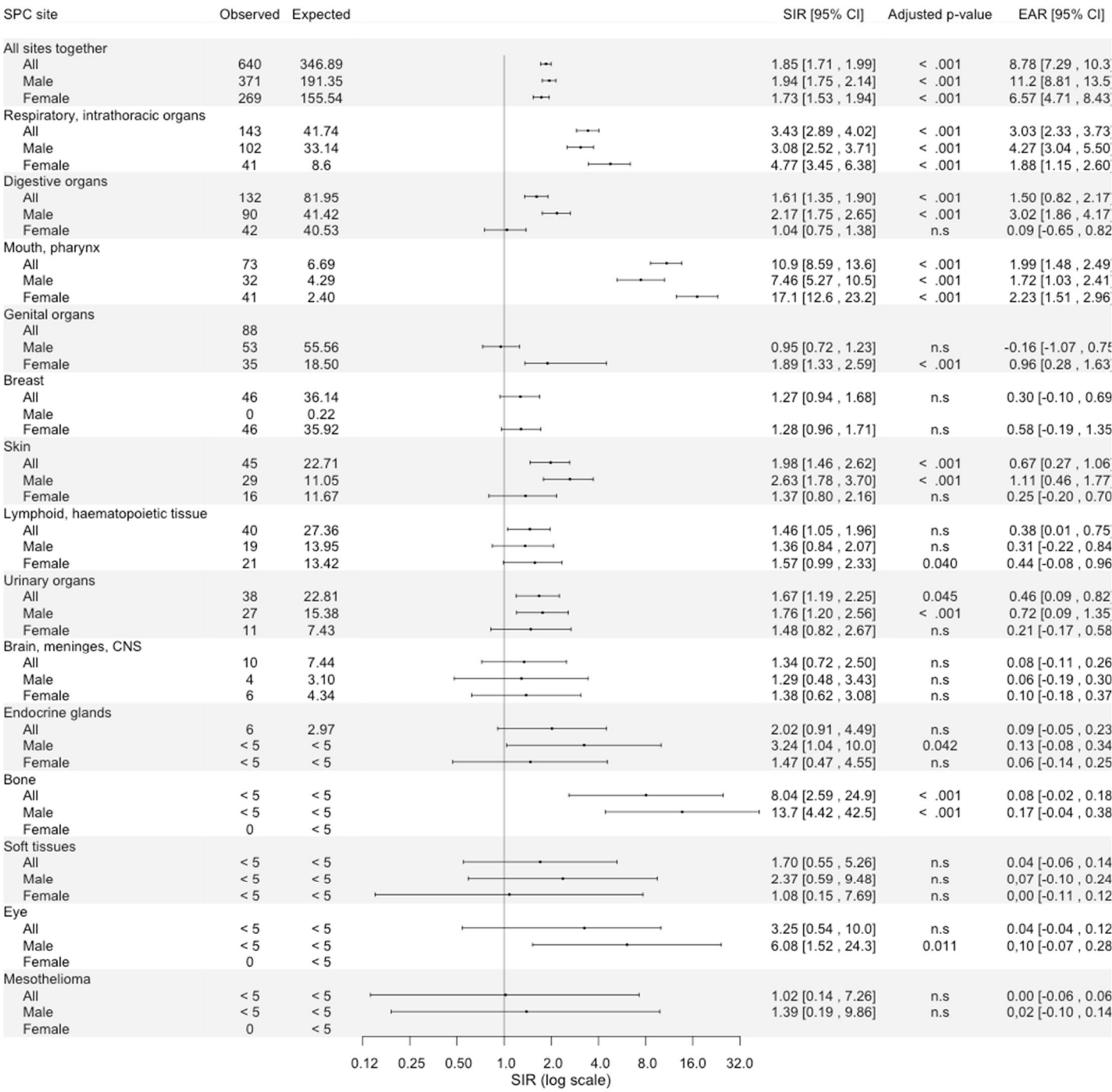


Table 1. Standardized incidence Ratios (SIR) for any metachronous second primary cancer among 6602 oral squamous cell carcinoma (OSCC) patients diagnosed in Finland during 1953-2015.

	First cancers		Second cancers						
	No. of cancers	%	Observed no. of cancers	Expected no. of cancers	PYR	SIR	95% CI	Adjusted p-value	EAR
Sex									
All	6,602	100	640	346.8	33,395	1.85	1.71 - 1.99	< .001	8.8
Male	3,442	52	371	191.3	16,114	1.94	1.75 - 2.14	< .001	11.1
Female	3,160	48	269	155.5	17,281	1.73	1.53 - 1.94	< .001	6.6
Age at diagnosis									
<40	346	5	21	12.2	4,238	1.72	1.12 - 2.63	0.317	2.1
40-54	1,263	19	149	65.6	9,631	2.27	1.94 - 2.67	< .001	8.7
55-64	1,717	26	204	99.3	9,028	2.06	1.79 - 2.36	< .001	11.6
65-74	1,680	25	178	104.3	6,871	1.71	1.47 - 1.98	< .001	10.7
>75	1,596	24	88	65.6	3,627	1.34	1.09 - 1.65	0.145	6.2
Year of diagnosis									
1953-69	803	12	81	52.1	5,457	1.55	1.24 - 1.92	0.002	5.3
1970-84	904	14	98	62.8	5,862	1.56	1.27 - 1.89	< .001	6.0
1985-1999	1,632	25	230	114.8	11,120	2.00	1.76 - 2.27	< .001	10.4
2000-15	3,263	49	231	117.2	10,957	1.97	1.73 - 2.24	< .001	10.4
Time of diagnosis of SPM									
0,5 - 5 years			263	145.2	14,964	1.81	1.60 - 2.04	< .001	7.9
5 - 10 years			161	89.4	8,664	1.80	1.60 - 2.09	< .001	8.3
10 - 20 years			158	77.2	7,029	2.05	1.60 - 2.38	< .001	11.5
More than 20 years			58	35.1	2,738	1.65	1.60 - 2.12	0.004	8.4
Extent of the primary OSCC									
Localized	3,122	47	414	229.1	21,817	1.81	1.64 - 1.99	< .001	8.5
Locoregionally advanced/metastasized	1,513	23	89	47.9	4,982	1.86	1.50 - 2.27	< .001	8.3
Unknown	1,967	30	137	69.9	6,596	1.96	1.65 - 2.31	< .001	10.2
Location of OSCC									
Tongue	3,201	48	315	174.3	17,290	1.81	1.61 - 2.01	< .001	8.1
Floor of mouth	1,438	22	165	69.2	6,576	2.38	2.04 - 2.77	< .001	14.6
Hard palate	24	0.4	0	0.8	55				
Gum	333	5	19	8.6	683	2.22	1.36 - 3.37	0.015	15.3
Others	1,606	24	141	94.0	8791	1.50	1.27 - 1.76	< .001	5.3

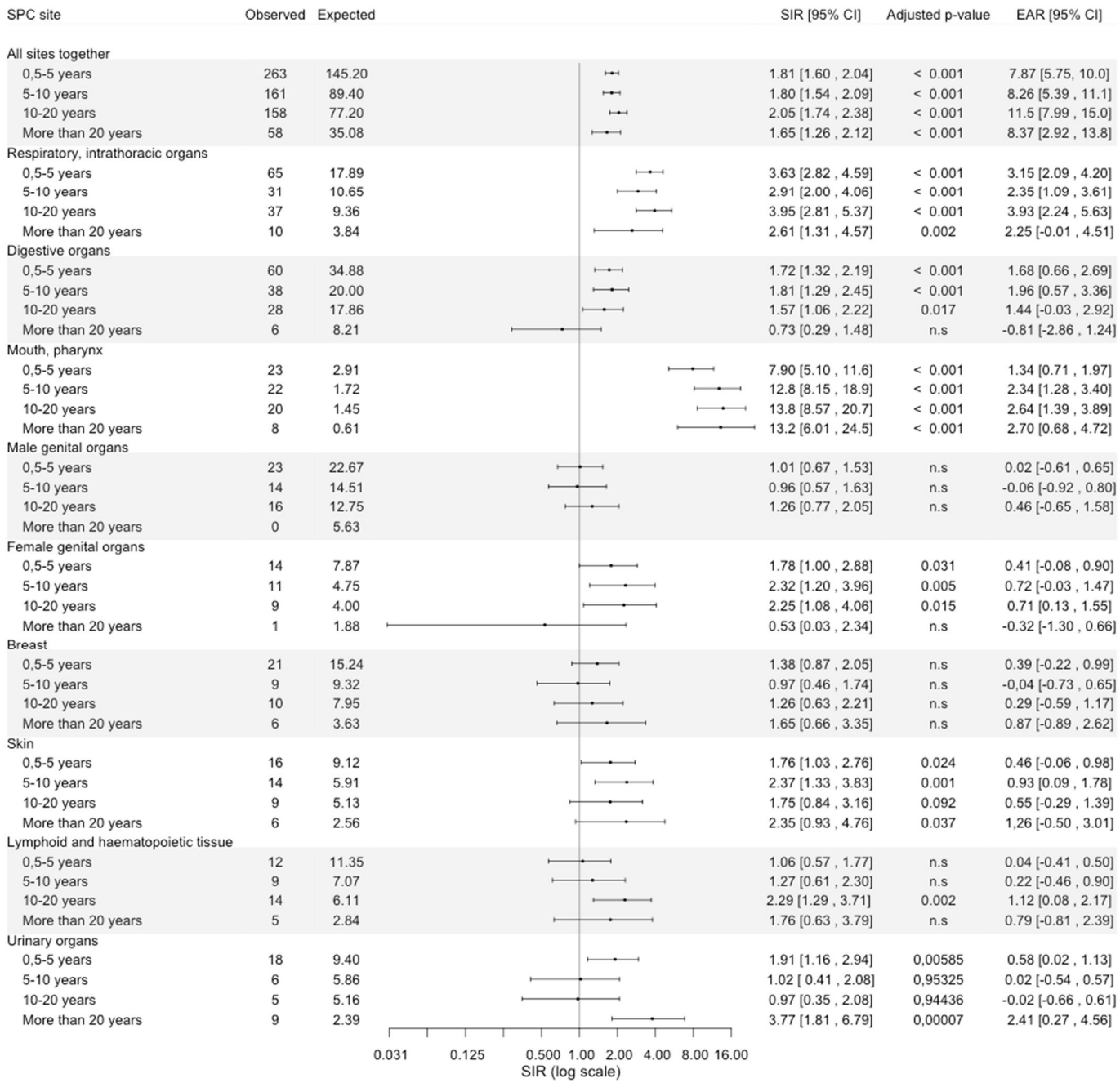
Abbreviations: CI, confidence interval; EAR, excess absolute risk; PYR, person-years at risk; SIR, standardized incidence ratio.

Figure 3. Standardized incidence ratios for second primary cancer by site and stratified by gender among patients with oral squamous cell carcinoma (OSCC) in Finland during 1953-2015.



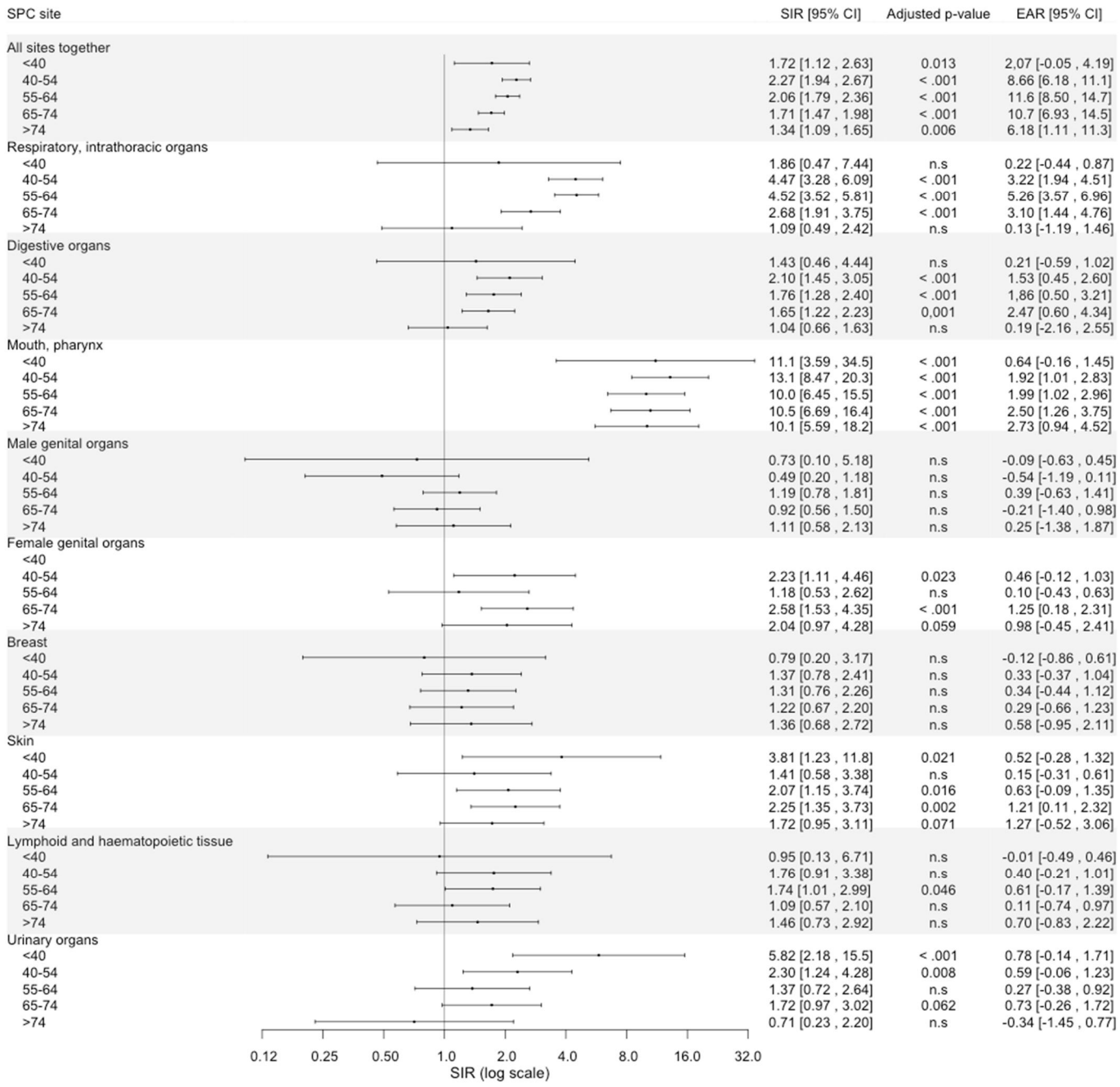
Abbreviations: CI, confidence interval; EAR, excess absolute risk per 1000 PYR; n.s., non-significant; SIR, standardized incidence ratio.

Figure 4. Standardized incidence ratios for second primary cancer by site and stratified by time of diagnosis (time elapsed from diagnosis of primary tumour) among patients with oral squamous cell carcinoma (OSCC) in Finland during 1953-2015.



Abbreviations: CI, confidence interval; EAR, excess absolute risk per 1000 PYR; n.s., non-significant; SIR, standardized incidence ratio.
Only sites with more than 10 observed cases are reported.

Figure 5. Standardized incidence ratios for second primary cancer by site and stratified by age among patients with oral squamous cell carcinoma (OSCC) in Finland during 1953-2015.



Abbreviations: CI, confidence interval; EAR, excess absolute risk per 1000 PYR; n.s., non-significant; SIR, standardized incidence ratio.
Only sites with more than 10 observed cases are reported.
For data privacy reasons, observed and expected values are not reported