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ORIGINAL RESEARCH

Risk of Second Primary Cancer Among Patients with Cardio-Esophageal Cancer in Finland: A Nationwide Population-Based Study

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Purpose: The occurrence of a second primary cancer (SPC) after primary esophageal carcinoma (EC) or gastric cardia carcinoma (GCC) is well acknowledged. However, previous research on the risk of SPC among these patients has been predominantly conducted in Asian countries. Yet, notable population-dependent variation in histological types and risk profiles exists. This register-based study assesses the histology-specific risk of SPC among individuals initially diagnosed with a first primary EC or GCC.

Patients and Methods: We obtained data on 7197 patients diagnosed with EC/GCC in Finland between 1980 and 2022 from the Finnish Cancer Registry. Standardized incidence ratios (SIR) of SPC were subsequently calculated relatively to the cancer risk of the general population.

Results: The average and median follow-up times were 2.8 years and 10.5 months. Adenocarcinomas and squamous cell carcinomas comprised 57.8% (n = 4165) and 36.6% (n = 2631) of all cases, respectively. An increased SIR was noted among EC/GCC patients after 15–20 years of follow-up (SIR 1.49, 95% CI: 1.01–2.11). Among adenocarcinoma patients, an increased SIR for SPCs of the digestive organs was seen in the 40–54-year-old group (SIR 9.86, 95% CI: 3.62–21.45). Squamous cell carcinoma patients displayed increased SIRs for cancer of the mouth/pharynx (SIR 3.20, 95% CI: 1.17–6.95) and respiratory organs (1.77, 1.07–2.76).

Conclusion: Healthcare professionals should be aware of the increased risk of SPCs occurring in the mouth/pharynx, respiratory and digestive organs in survivors of EC/GCC. Patients should be advised about this risk and remain alert for symptoms, even beyond the standard 5-year follow-up period.

Keywords: esophageal squamous cell carcinoma, adenocarcinoma, gastric cardia carcinoma, tumor, second primary cancer

Introduction

According to the Global Cancer Observatory database (www.gco.iarc.fr), esophageal carcinoma (EC) ranks as the eighth most common cancer worldwide with well over half a million new cases diagnosed annually worldwide. Moreover, the number of new cases is anticipated to increase by approximately 40% in the next decade. However, incidence rates vary significantly worldwide. Namely, around 80% of new EC cases occur in Asia, with China and Bangladesh having the highest country-specific age-standardized rates (ASR World) of 13.8 and 14.8 per 100,000, respectively, in the Asian continent. In contrast, Europe accounts for only 9% of new cases, with the United Kingdom and the Netherlands showing the highest rates (6.4 and 6.8 ASR World, respectively). Furthermore, notable population-dependent variation in histological types and risk profiles exists. Indeed, while esophageal squamous cell carcinoma (SCC) persists as the

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predominant subtype of EC, particularly in low- and middle-income countries, esophageal adenocarcinoma (AC) is currently more prevalent in high-income countries.[1] Esophageal AC originates from glandular cells located in the lower third of the esophagus, often in areas where they have undergone transformation into an intestinal cell type – a condition known as Barrett's esophagus. It has been mainly associated with smoking tobacco, obesity, and acid reflux. In contrast, esophageal SCC is linked to risk factors such as tobacco, alcohol, high-temperature beverages and foods, and betel nut chewing.[1]

The 5-year relative-survival for EC remains low, hovering around 20% in the Nordic countries.[2] Additionally, the occurrence of a second primary cancer (SPC) after primary EC is acknowledged.[3] SPCs are considered to arise independently, not as a recurrence or metastasis of the initial cancer, and can occur at any time after the diagnosis and treatment of the first primary cancer. The carcinogenic impacts of tobacco and alcohol can affect multiple areas of the aerodigestive tract simultaneously, leading to field cancerization, where genetically altered, pre-cancerous cells in the tissue surrounding a primary tumor may give rise to an SPC.[4,5] Indeed, SPCs can share genetic markers with the primary tumor, suggesting a common cell origin. Investigating the long-term follow-up of cancer patients, as well as the genetic mutations and molecular pathways that contribute to the development of SPCs in cancer survivors, is a key focus in current research.[6]

Existing research on the risk of SPC among EC survivors has predominantly centered on participants from Japan, China, and the United States.[7–11] Assessing the risk of SPC among EC patients presents challenges not only due to the low survival ratio and the difficulty in gathering sufficiently large cohorts of patients but also because of how tumors at the gastroesophageal junction are classified. Given that the gastroesophageal junction can be associated with both the esophagus and the gastric cardia, we included also patients diagnosed with gastric cardia carcinoma (GCC) in our study. Our retrospective register study seeks to assess the histology-specific risk of SPC among individuals initially diagnosed with a first primary EC including GCC in Finland from 1980 to 2022.

Materials and Methods

Population

We obtained data on patients diagnosed with EC or GCC in Finland between 1980 and 2022 from the Finnish Cancer Registry. The Finnish Cancer Registry has been recording all new primary cancer cases diagnosed in Finland since 1953, providing comprehensive information on the primary site, histology, and complete follow-up until death or emigration. We used ICD-O-3 topographical and morphological codes (available at http://www.iacr.com.fr/index.php?Itemid=577) to select patients diagnosed with EC (ICD10-codes: C15.3, C15.4, C15.5, C15.8, C15.9) or GCC (ICD10-code: C16.0) of any histology except hematological malignancies. Patients with any previous cancer, except for basal-cell carcinoma of the skin, as well as those whose first primary cancer diagnosis and death were simultaneously recorded, were excluded. Hematological neoplasms, such as lymphomas, were not included in the material.

Second Primary Cancer Data

We retrieved data on subsequent SPCs among individuals diagnosed with EC or GCC. The Finnish Cancer Registry does not record cases of SPCs occurring at the same site as the index tumor, unless of different histological type. However, we acknowledge a risk for misclassification, where regional or distant recurrences might be erroneously categorized as SPCs, and vice versa. To mitigate this, we included only metachronous SPCs, ie, malignant tumors diagnosed at six months or later after the initial primary EC/GCC diagnosis. We excluded all synchronous SPCs, ie, malignant tumors diagnosed within six months after the primary EC/GCC diagnosis (n = 144). Follow-up started at six months after the diagnosis of primary EC/GCC and ended at the time of death, diagnosis of an SPC, or December 31st, 2022; whichever event occurred first. No patients emigrated during the follow-up.

Statistical Analyses

We evaluated the risk of SPC among EC/GCC patients by using standardized incidence ratios (SIRs) and their associated 95% confidence intervals. This involved comparing the observed number of SPC cases among EC/GCC patients with the

expected numbers derived from age, sex, and calendar-specific rates of the Finnish general population, employing person-years (PYs) of observations (initiated six months after the primary EC/GCC diagnosis for patients and up to first primary in the general population) and assuming a Poisson distribution for the observed SPC cases. We stratified patients by histology (AC and SCC), age at diagnosis, sex, extent of the primary disease, time elapsed since primary cancer diagnosis, and calendar period of EC/GCC diagnosis (1980–1994, 1995–2009, 2010–2022) to explore variations in SPC risk over the follow-up period. In addition, we assessed the additional burden of SPCs among EC/GCC patients by calculating the excess absolute risk (EAR), which measures the difference in absolute risk between the EC/GCC patient population and the general population per 1000 person-years at risk. A *P*-value over 0.05 was considered non-significant (n.s.). We conducted all statistical analyses using R software (The R Project for Statistical Computing) version 4.2.2 with the utilization of the *popEpi* and *forestplot* packages.

Ethical Considerations

All results are presented anonymously, making it impossible to identify individual study subjects. Moreover, for data privacy reasons, observed numbers and risk estimates are omitted, whenever less than five cancer cases were reported to the Finnish Cancer Registry.

Results

A total of 7197 EC/GCC patients – 2692 GCCs (37.4%) and 4505 ECs (62.6%) – were identified from 1980 to 2022 adding to 19,301 person-years (PY) of follow-up. Men and women represented 65.4% (n = 4708) and 34.6% (n = 2489) of cases, respectively. The average and median age were 69.2 and 69.6 for men and 74.8 and 76.2 for women. The average and median follow-up times were 2.8 years and 10.5 months, respectively (interquartile range 0.3–2.49 years). Of all EC/GCC cancer cases, 57.8% (n = 4165) were ACs and 36.6% (n = 2631) were SCCs. A total of 401 cases (5.6%) were of other histological types, such as neuroendocrine tumors, sarcomas, and carcinoma NOS (not otherwise specified) cases.

Figure 1 provides a summary of the SIRs and EARs for SPCs among all EC/GCC patients categorically stratified. A metachronous SPC was diagnosed in 328 patients (4.6% of all patients) over the entire follow-up: in 4.8% of men (n = 226) and 4.1% of women (n = 102). Out of all SPCs, 63.8% were diagnosed within 0.5 to 5 years and 11% after 10 years from the initial EC/GCC diagnosis. Overall, the SPC risk when compared to the cancer risk of the general population was not elevated among men or women: SIRs 0.95 (95% CI: 0.83–1.09) and 1.05 (95% CI: 0.86–1.28), respectively. Besides an increased risk of SPC observed among 40–54-year-old EC/GCC patients (SIR 3.23, 95% CI: 1.85–5.25), and after 15–20 years of follow-up (1.49, 1.01–2.11) stratification by period (1980–1994, 1995–2009, and 2012–2022), and the extent of primary disease did not reveal any elevated SIR. The increased risk of SPC observed among 40–54-year-old EC/GCC patients and after 15–20 years of follow-up equated to 7.05 (95% CI: 3.47–14.34) and 10.32 (3.53–30.17) excess SPCs per 1000 PYs, respectively.

The digestive and respiratory organs harbored most SPCs, with 20.1% (n = 67) and 18.6% (n = 61) of all diagnosed SPCs, respectively (Figure 2). EC/GCC patients displayed an increased risk for cancers of the respiratory organs (SIR 1.39, 95% CI: 1.06–1.78), which remained elevated also 15–20 years after diagnosis of primary EC/GCC (2.58, 1–04-5.31) and was specifically noticeable in the 40–54 (8.84, 2.41–22.64) and 55–64 (2.41, 1.24–4.20) age groups (data not shown). Additionally, 40–54-year-old patients displayed an elevated SIR for cancers of the digestive organs (SIR 6.63, 95% CI: 2.43–14.43) (data not shown).

Adenocarcinoma

Of all AC patients, a metachronous SPC was diagnosed in 5.6% (n = 174) and 3.7% (n = 38) of men and women, respectively, which translated to SIRs of 0.96 (95% CI: 0.83–1.12) and 0.95 (95% CI: 0.67–1.31) (Figure 3). After 15–20 years of follow-up, AC contributed to 13.85 (95% CI: 4.27–44.85) excess SPCs per 1000 PYR. The overall risk of SPC was statistically significantly increased only in the 40–54-age category (SIR 4.05, 95% CI: 2.16–6.93 and EAR 9.40), who displayed an increased risk for SPCs occurring in the digestive organs (SIR 9.86, 95% CI: 3.62–21.45) (data not shown). No increased risk was observed when stratified by SPC organ site (Figure 4).

	No.	%	PYs	Obs.	Exp.	SIR [95% CI]	P-value	EAR [95% CI]
Sex								
All	7,197	100	19,303.1	328	333.8	0.98 [0.88 , 1.10]	n.s.	-0.30 [-143.25 , 0.00]
Men	4,708	65.4	11,939.6	226	236.7	0.95 [0.83 , 1.09]	n.s.	-0.90 [-14.12 , -0.06]
Women	2,489	34.6	7,363.5	102	97.1	1.05 [0.86 , 1.28]	n.s.	0.67 [0.01 , 37.02]
Age								
< 40	46	0.6	142.9					
40-54	596	8.3	1,566.2	16	5	3.23 [1.85 , 5.25]	<.001	7.05 [3.47 , 14.34]
55-64	1,473	20.5	4,234.4	43	37.5	1.15 [0.83 , 1.54]	n.s.	1.29 [0.12 , 13.5]
65-74	2,288	31.8	6,611.2	117	115.5	1.01 [0.84 , 1.21]	n.s.	0.22 [0.00 , >1000]
> 75	2,794	38.8	6,748.5	151	175.7	0.86 [0.73 , 1.01]	n.s.	-3.65 [-9.70 , -1.38]
Period								
1980–1994	2,139	29.7	3,469.0	36	50	0.72 [0.50 , 1.00]	n.s.	-4.04 [-9.35 , -1.75]
1995–2009	2,755	38.3	7,062.9	124	123.5	1.00 [0.83 , 1.20]	n.s.	0.07 [0.00 , >1000]
2010–2022	3,244	45.1	8,771.2	168	160.2	1.05 [0.90 , 1.22]	n.s.	0.89 [0.03 , 23.04]
Follow-up time								
0.5-1 year	7,197	100	2,863.5	30	44.5	0.67 [0.45 , 0.96]	0.036	-5.06 [-10.62 , -2.42]
1-5 years	4,592	63.8	8,881.9	141	142	0.99 [0.84 , 1.17]	n.s.	-0.11 [<-1000 , 0.00]
5-10 years	1,063	14.8	3,842.1	75	69.6	1.08 [0.85 , 1.35]	n.s.	1.41 [0.06 , 32.61]
10-15 years	538	7.5	1,991.1	36	40	0.90 [0.63 , 1.25]	n.s.	-2.02 [-37.68 , -0.11]
15-20 years	276	3.8	985.8	31	20.8	1.49 [1.01 , 2.11]	0.034	10.32 [3.53 , 30.17]
> 20 years	120	1.7	738.6	15	16.8	0.89 [0.50 , 1.47]	n.s.	-2.43 [<-166.36 , -0.04]
Primary cancer								
Unknown	2,293	31.9	5,198.3	100	93.7	1.07 [0.87 , 1.30]	n.s.	1.22 [0.06 , 26.9]
Localized	1,567	21.8	8,129.3	147	145.2	1.01 [0.86 , 1.19]	n.s.	0.22 [0.00 , >1000]
Non-localized	3,337	46.4	5,975.4	81	94.9	0.85 [0.68 , 1.06]	n.s.	-2.33 [-8.27 , -0.65]

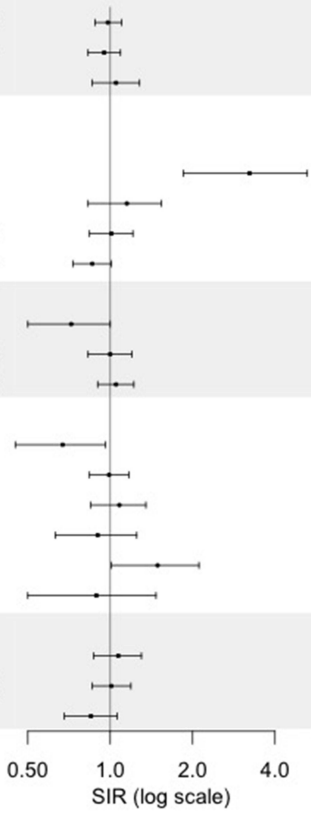

Figure 1 Standardized incidence ratios and excess absolute risk per 1000 person-years for any metachronous second primary cancer among 7197 esophageal and gastric cardia carcinoma patients diagnosed in Finland during 1980–2022 stratified by sex, age at diagnosis of primary tumor, follow-up period, follow-up time, and primary disease stage.

Abbreviations: CI, confidence interval; Exp, expected; EAR, excess absolute risk; n.s., non-significant; No., number; Obs., observed; PYs, person-years; SIR, standardized incidence ratio.

Squamous Cell Carcinoma

A metachronous SPC was diagnosed in 3.4% (n = 45) and 4.5% (n = 58) of men and women, respectively (Figure 5). The overall risk of SPC was not elevated among men (SIR 1.02, 95% CI: 0.74–1.36) or women (1.15, 0.87–1.48) (Figure 5). Besides an increased SIR in the 2010–2022 period (SIR 1.35, 95% CI: 1.01–1.77 and EAR 6.01), no increased risk was observed when stratified by age category, period, follow-up time, or extent of the primary disease. However, when stratified by SPC site, SCC patients displayed increased SIRs for cancer of the mouth/pharynx (SIR 3.20, 95% CI: 1.17–6.95) and respiratory organs (1.77, 1.07–2.76), yielding 0.64 (95% CI: 0.20–2.05) and 1.28 (0.46–3.61) excess SPCs per 1000 PYR, respectively. The risk for SPCs of the respiratory organs was elevated only among women (SIR 2.60, 95% CI: 1.19–4.93), as shown in Figure 6, and in the 40–54 and 55–64 age categories: SIRs 16.96 (95% CI: 2.05–61.25) and 4.73 (1.74–10.30), respectively (data not shown).

Discussion

While the overall SPC risk among EC/GGC was not elevated compared to the risk of primary cancer among the general Finnish population, an increased risk of SPC was noted after 15–20 years of follow-up. Additionally, stratification by age and histology revealed an increased risk of cancers in the digestive organs among AC patients and mouth/pharynx and respiratory organs among SCC patients, specifically in the 40–54-year-old group. Apart from these aerodigestive organs, there were no statistically significant findings concerning the risk of SPCs at other anatomical sites.

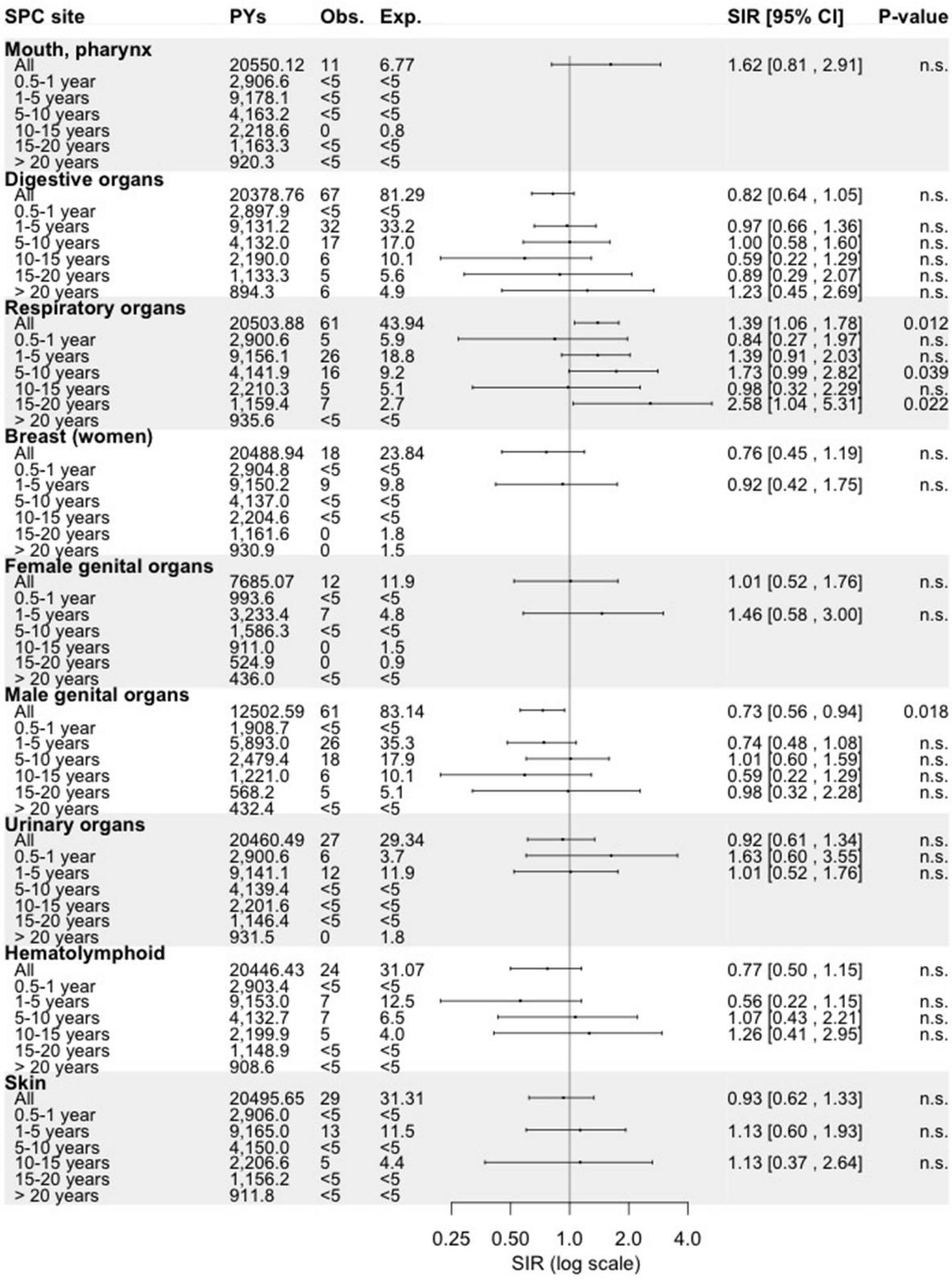

Figure 2 Standardized incidence ratios per 1000 person-years for second primary cancer by site (if more than four cases recorded) and stratified by follow-up time among patients with esophageal and gastric cardia carcinoma in Finland during 1980–2022.

Abbreviations: CI, confidence interval; Exp, expected; n.s., non-significant; No., number; Obs., observed; PYs, person-years; SIR, standardized incidence ratio.

	No.	%	PYs	Obs.	Exp.	SIR [95% CI]	P-value	EAR [95% CI]
Sex								
All	4,165	100	11,983.3	212	220.5	0.96 [0.84 , 1.10]	n.s.	-0.71 [-20.12 , -0.03]
Men	3,145	75.5	8,924.7	174	180.7	0.96 [0.83 , 1.12]	n.s.	-0.75 [-36.01 , -0.02]
Women	1,020	24.5	3,058.6	38	39.9	0.95 [0.67 , 1.31]	n.s.	-0.61 [-390.59 , 0.00]
Age								
< 40	39	0.9	94.5					
40-54	398	9.6	1,041.0	13	3.2	4.05 [2.16 , 6.93]	<.001	9.41 [4.57 , 19.36]
55-64	877	21.1	2,712.5	27	24.5	1.10 [0.73 , 1.60]	n.s.	0.91 [0.01 , 56.39]
65-74	1,326	31.8	4,109.2	73	76.8	0.95 [0.74 , 1.19]	n.s.	-0.94 [-73.1 , -0.01]
> 75	1,525	36.6	4,026.0	98	115.9	0.85 [0.69 , 1.03]	n.s.	-4.44 [-13.14 , -1.50]
Period								
1980–1994	969	23.3	1,691.6	20	26.6	0.75 [0.46 , 1.16]	n.s.	-3.92 [-14.7 , -1.05]
1995–2009	1,614	38.8	4,222.8	83	79.8	1.04 [0.83 , 1.29]	n.s.	0.75 [0.00 , 214.4]
2010–2022	2,146	51.5	6,068.8	109	114.1	0.96 [0.78 , 1.15]	n.s.	-0.84 [-47.4 , -0.01]
Follow-up time								
0.5-1 year	4,165	100	1,715.6	19	27.5	0.69 [0.42 , 1.08]	n.s.	-4.94 [-13.54 , -1.81]
1-5 years	2,831	68	5,715.4	89	96.7	0.92 [0.74 , 1.13]	n.s.	-1.35 [-14.78 , -0.12]
5-10 years	684	16.4	2,448.4	56	48.2	1.16 [0.88 , 1.51]	n.s.	3.17 [0.48 , 20.96]
10-15 years	340	8.2	1,229.9	23	26.9	0.86 [0.54 , 1.28]	n.s.	-3.14 [-35.87 , -0.27]
15-20 years	160	3.8	538.6	20	12.5	1.59 [0.97 , 2.46]	0.049	13.85 [4.27 , 44.85]
> 20 years	61	1.5	335.4	5	8.7	0.57 [0.19 , 1.34]	n.s.	-11.03 [-36.07 , -3.37]
Primary cancer								
Unknown	1,301	31.2	3,192.0	62	61	1.02 [0.78 , 1.30]	n.s.	0.31 [0.00 , >1000]
Localized	784	18.8	4,776.5	93	93.9	0.99 [0.80 , 1.21]	n.s.	-0.19 [<-1000 , 0.00]
Non-localized	2,080	49.9	4,014.8	57	65.6	0.87 [0.66 , 1.13]	n.s.	-2.15 [-11.96 , -0.39]

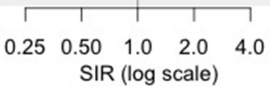

Figure 3 Standardized incidence ratios and excess absolute risk per 1000 person-years for any metachronous second primary cancer among 4165 esophageal and gastric cardia adenocarcinoma patients diagnosed in Finland during 1980–2022 stratified by sex, age at diagnosis of primary tumor, follow-up period, follow-up time, and primary disease stage.

Abbreviations: CI, confidence interval; Exp., expected; EAR, excess absolute risk; n.s., non-significant; No., number; Obs., observed; PYs, person-years; SIR, standardized incidence ratio.

Our study includes all cases of EC and those recorded as GCC, acknowledging that some cases extending the gastroesophageal junction might have been classified as GCC and vice versa depending on histology and clinical reporting. The exact etiology and definition of ACs at the cardia and gastroesophageal junction remains unclear and subject to debate. Current thinking suggests that gastric cardia AC is epidemiologically and biologically distinct from ACs found in the esophagus or the other parts of the stomach. From a histological perspective, cancers at the gastroesophageal junction are typically ACs, while those in the distal esophagus may be either SCCs or ACs.[12,13]

Though our study did not show an increased overall risk of SPC in patients with either AC or SCC, the associations of primary AC with digestive organ cancers and primary SCC with cancers of the mouth/pharynx and respiratory organs are consistent with previous reports. In the Netherlands, van de Ven et al[7] analyzed 9058 esophageal SCC patients over a median follow-up period of 9.8 months, comparable to our median of 10.5 months. They reported a 4.36 times higher risk of developing a metachronous SPC compared to the risk of primary cancer of the general population, particularly noting increased risks for head and neck (SIR 14.17) and lung cancers (3.00), which align with our findings. Chen et al[8] in Taiwan examined 18,026 EC patients, predominantly male (92.5%), over a median follow-up of 9.1 months. Without access to histological details, they excluded all SPCs diagnosed within one year of the primary tumor. They found significantly higher SIRs than we found for cancers of the head and neck (SIR 15.83), stomach (3.30), lungs (2.10), kidneys (2.24), and leukemia (2.72). A Japanese study involving 3022 EC patients – mainly males (70.7%) and primarily esophageal SCC cases (over 90%) – who survived at least 2 months following the diagnosis of primary EC reported an

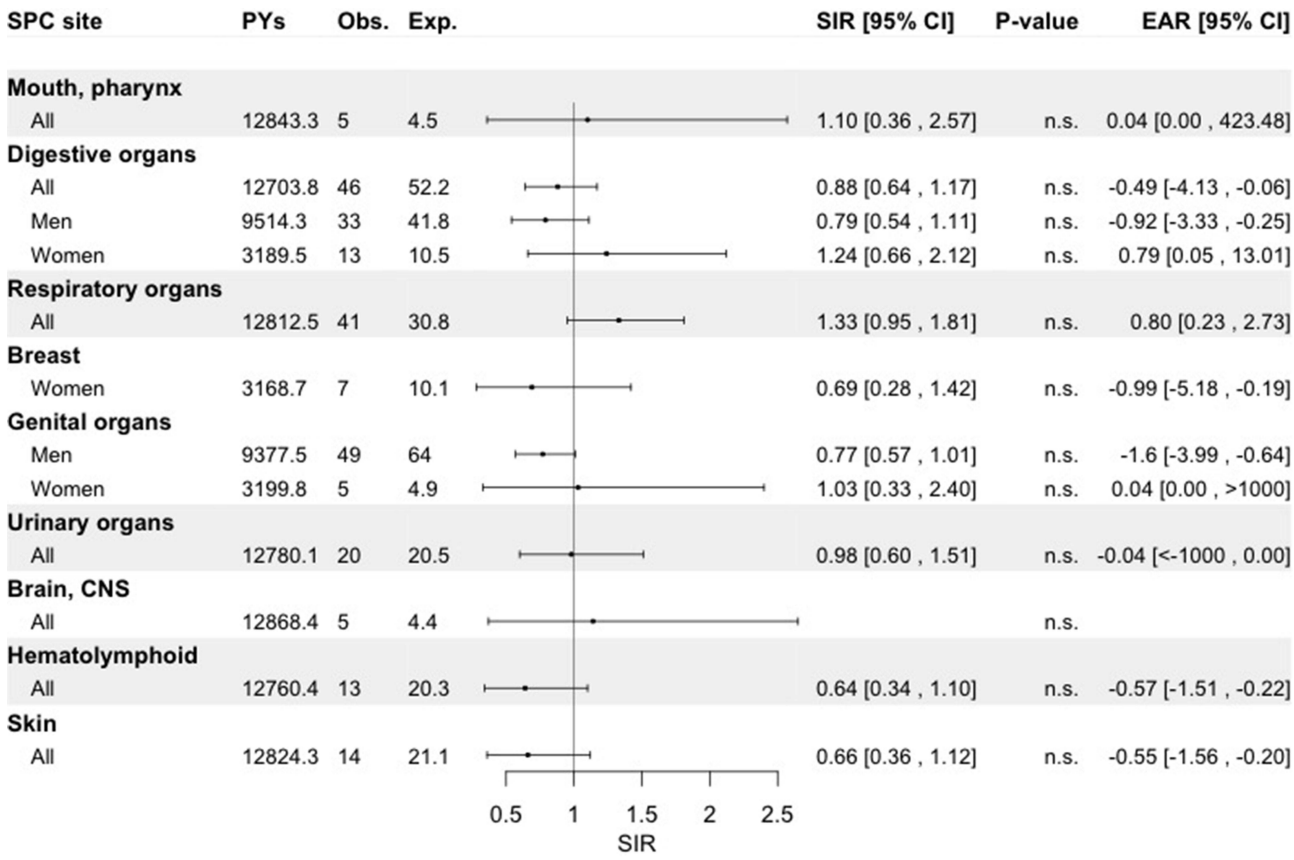

Figure 4 Standardized incidence ratios and excess absolute risk per 1000 person-years for second primary cancer by site (if more than four cases recorded) among patients with esophageal and gastric cardia adenocarcinoma in Finland during 1980–2022.

Abbreviations: CI, confidence interval; Exp., expected; EAR, excess absolute risk; n.s., non-significant; No., number; Obs., observed; PYs, person-years; SIR, standardized incidence ratio.

increased risk of SPC, particularly for the mouth/pharynx (SIR 16.16), larynx (6.44), lung (2.36), stomach (2.84), and leukemia (4.42).[11] Zhu et al[9] utilized data from the database of the National Cancer Institute's SEER – which covers approximately 26% of the US population – and analyzed 24,557 EC patients who survived at least 2 months after diagnosis of EC, with a median follow-up of 6.5 years. The authors noted an overall SIR of 1.34 for all SPCs. They identified higher risks for cancers of the mouth/pharynx (SIR 8.64), stomach (2.87), small intestine (3.80), larynx (3.19), lungs (1.68), and thyroid (2.50). Finally, a multicenter study by Chuang et al[10] of 13 population-based cancer registries from Europe, Australia, Canada, and Singapore reviewed data of 52,589 patients diagnosed with EC. The study comprised 10,049 esophageal AC patients with a mean follow-up time of 1.1 years and 28,036 esophageal SCC patients with a mean follow-up time of 1.3 years. The authors described an increased SPC risk among esophageal SCC patients (SIR 1.28), particularly for cancers of the mouth/pharynx (6.68), stomach (1.53), larynx (3.24), lung (1.55), kidney (1.88), and thyroid (2.92). Although the overall SPC risk was not elevated in esophageal AC patients, a notable risk for stomach cancer was identified (SIR 2.13). Of note, in contrast to our study, SPCs diagnosed within six months of diagnosis of primary EC were also included.

The use of tobacco and alcohol, well-established risk factors for esophageal SCC, are also known to increase the risk of cancers in the head and neck, as well as in the respiratory organs.[1,14,15] Conversely, risk factors associated with esophageal AC, such as tobacco use and obesity, are linked to cancers in other parts of the digestive system.[1,16,17] Additionally, existing research suggests that radiotherapy treatment in EC patients might increase the risk of developing secondary cancers in adjacent organs.[9] This might account for the higher incidence of thyroid cancer among EC patients observed in the studies by Zhu et al[9] and Chuang et al.[10]

	No.	%	PYs	Obs.	Exp.	SIR [95% CI]	P-value	EAR [95% CI]
Sex								
All	2,631	100	6,117.3	103	94.9	1.08 [0.89 , 1.32]	n.s.	1.32 [0.11 , 15.54]
Men	1,333	50.7	2,399.4	45	44.3	1.02 [0.74 , 1.36]	n.s.	0.29 [0.00 , >1000]
Women	1,298	49.3	3,717.9	58	50.6	1.15 [0.87 , 1.48]	n.s.	1.98 [0.26 , 15.05]
Age								
< 40	2	0.1	9.9					
40-54	163	6.2	373.1					
55-64	525	20	1,267.3	16	10.8	1.48 [0.85 , 2.41]	n.s.	4.12 [0.92 , 18.50]
65-74	842	32	2,101.0	38	32.2	1.18 [0.84 , 1.62]	n.s.	2.77 [0.35 , 22.08]
> 75	1,099	41.8	2,366.1	47	50.7	0.93 [0.68 , 1.23]	n.s.	-1.57 [-57.98 , -0.04]
Period								
1980–1994	1,006	38.2	1,489.6	14	19.8	0.71 [0.39 , 1.19]	n.s.	-3.91 [-13.77 , -1.11]
1995–2009	994	37.8	2,381.3	37	36.6	1.01 [0.71 , 1.39]	n.s.	0.16 [0.00 , >1000]
2010–2022	944	35.9	2,246.4	52	38.5	1.35 [1.01 , 1.77]	0.036	6.01 [2.11 , 17.12]
Follow-up time								
0.5-1 year	2,631	100	995.1	11	14.7	0.75 [0.37 , 1.34]	n.s.	-3.72 [-21.52 , -0.64]
1-5 years	1,526	58	2,705.0	46	38.5	1.20 [0.88 , 1.59]	n.s.	2.78 [0.47 , 16.28]
5-10 years	315	12	1,141.2	17	17.6	0.97 [0.56 , 1.55]	n.s.	-0.52 [<-1000, 0.00]
10-15 years	162	6.2	617.2	13	10.8	1.21 [0.64 , 2.07]	n.s.	3.65 [0.16 , 84.00]
15-20 years	93	3.5	355.5	7	6.7	1.04 [0.42 , 2.14]	n.s.	0.73 [0.00 , >1000]
> 20 years	46	1.7	303.3	9	6.7	1.35 [0.62 , 2.56]	n.s.	7.65 [0.61 , 96.39]
Primary cancer								
Unknown	854	32.5	1,575.6	32	26.2	1.22 [0.83 , 1.72]	n.s.	3.67 [0.54 , 24.98]
Localized	703	26.7	2,906.2	50	44.5	1.12 [0.83 , 1.48]	n.s.	1.88 [0.15 , 23.81]
Non-localized	1,074	40.8	1,635.6	21	24.2	0.87 [0.54 , 1.33]	n.s.	-1.94 [-32.81 , -0.12]

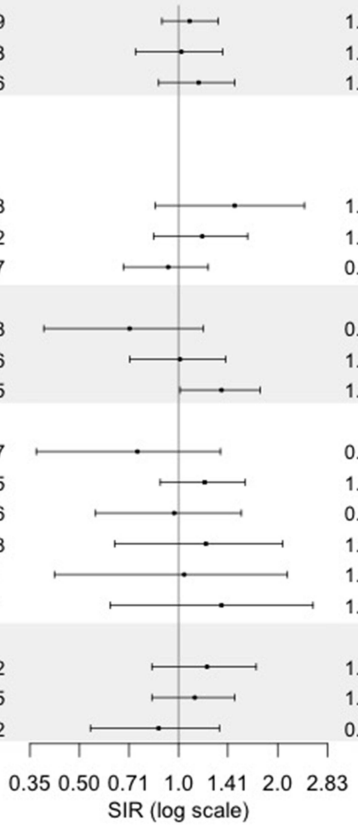

Figure 5 Standardized incidence ratios and excess absolute risk per 1000 person-years for any metachronous second primary cancer among 2631 esophagus and gastric cardia squamous cell carcinoma patients diagnosed in Finland during 1980–2022 stratified by sex, age at diagnosis of primary tumor, follow-up period, follow-up time, and primary disease stage.

Abbreviations: CI, confidence interval; Exp., expected; EAR, excess absolute risk; n.s., non-significant; No., number; Obs., observed; PYs, person-years; SIR, standardized incidence ratio.

The risk of SPC occurring in the respiratory organs among SCC patients in our study was statistically significant only among women (SIR 2.60, 95% CI: 1.19–4.93 in women versus 1.38, 0.66–2.53 in men). Factors such as smoking and alcohol consumption are known to contribute to the development of SPCs in the upper aerodigestive tract.[18,19] The observed increased risk of SPCs in women might be due to the inherent nature of SIR analysis. In SIR analysis, the actual incidence rate is compared with the expected rate, which is calculated based on age, sex, and calendar year-specific rates in the general population. Since men generally have a higher prevalence of smoking, alcohol use, and related diseases, the SIR for women may appear higher due to comparatively lower rates in the female reference population.[20,21]

Contrasting with earlier research findings, the observation in our study that patients with EC/GCC did not have an overall increased risk for SPCs, except for the specific age group of 40–54-year-olds who showed an increased risk for SPCs of the digestive (AC patients) and mouth/pharynx and respiratory organs (SCC patients), might be explained by a few potential factors. EC often has a relatively poor prognosis.[2] This reduced survival time – also reflected in the current study by the short median (10.5 months) and average follow-up times (2.84 years) – may limit the opportunity for these patients to develop SPCs. Additionally, there might be a selection bias in which patients with more robust overall health or a less aggressive EC/GCC survive longer and are less likely to develop SPCs, in contrast to those with poorer health or risky habits, such as smoking and alcohol consumption, or more aggressive cancers may not live long enough for an SPC to surface. Still, an increased risk of SPC was noticeable after 15–20 years of follow-up. Patients with EC/GCC may also be under close medical supervision with regular follow-up visits. While this could theoretically increase

SPC site	PYs	Obs.	Exp.	SIR [95% CI]	P-value	EAR [95% CI]
Mouth, pharynx						
All	6,447.3	6	1.9	3.20 [1.17 , 6.95]	0.008	0.64 [0.20 , 2.05]
Digestive organs						
All	6,422.4	17	24.7	0.69 [0.40 , 1.10]	n.s.	-1.19 [-3.43 , -0.41]
Men	2,536.2	5	10.3	0.48 [0.16 , 1.13]	n.s.	-2.10 [-4.78 , -0.92]
Women	3,886.2	12	14.3	0.84 [0.43 , 1.46]	n.s.	-0.60 [-11.13 , -0.03]
Respiratory organs						
All	6,433.7	19	10.7	1.77 [1.07 , 2.76]	0.018	1.28 [0.46 , 3.61]
Men	2,531.1	10	7.3	1.38 [0.66 , 2.53]	n.s.	1.08 [0.11 , 10.45]
Women	3,902.6	9	3.5	2.60 [1.19 , 4.93]	0.007	1.42 [0.49 , 4.10]
Breast						
Women	3,859.9	9	11.7	0.77 [0.35 , 1.46]	n.s.	-0.70 [-6.15 , -0.08]
Genital organs						
Men	2,480.2	10	15.1	0.66 [0.32 , 1.22]	n.s.	-2.06 [-6.93 , -0.61]
Women	3,884.6	7	6.2	1.13 [0.45 , 2.32]	n.s.	0.20 [0.00 , 146.39]
Urinary organs						
All	6,421.9	6	7.3	0.82 [0.30 , 1.79]	n.s.	-0.20 [-8.33 , 0.00]
Brain, CNS						
All		<5				
Hematolymphoid						
All	6,439.7	9	9.1	0.99 [0.45 , 1.88]	n.s.	-0.02 [<-1000 , 0.00]
Skin						
All	6,426.5	13	8.7	1.50 [0.80 , 2.57]	n.s.	0.68 [0.13 , 3.44]

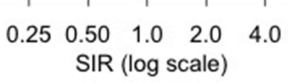

Figure 6 Standardized incidence ratios and excess absolute risk per 1,000 person-years for second primary cancer by site (if more than four cases recorded) among patients with esophageal and gastric cardia squamous cell carcinoma in Finland during 1980–2022.
Abbreviations: CI, confidence interval; Exp., expected; EAR, excess absolute risk; n.s., non-significant; No., number; Obs., observed; PYs, person-years; SIR, standardized incidence ratio.

the detection rate of SPCs, it may also lead to early intervention and treatment of pre-cancerous changes, potentially preventing the development of SPCs. Lastly, our estimates might appear low compared to some studies that had less stringent inclusion criteria, as we included only SPCs diagnosed after six months of diagnosis of primary EC. Additionally, our expected numbers were derived from age, sex, and calendar-specific rates of the Finnish general population with PYs of observations calculated six months after the primary EC/GCC diagnosis for patients and up to first primary in the general population, in contrast to studies continuing follow-up – and thus accumulation of PYs – in the general population even after diagnosis of the primary cancer, resulting in lower cancer incidences in the general population and conversely higher SIRs. As no details are given regarding the follow-up methodology for the general population in the previously referenced studies,[7–11] we cannot dismiss this possibility, which might account for the higher SIRS observed in those studies.

To the best of our knowledge, our study, encompassing over 7000 patients and spanning four decades with practically no loss to follow-up, stands as one of the largest cohorts published in Europe to date. This allowed for a detailed analysis of SPC risk relative to the time elapsed since EC/GCC diagnosis and the patient's age at diagnosis. Despite the relatively short median and average follow-up periods – a consequence of EC's typically poor survival rates – our study effectively assesses site-specific risks for SPC with considerable statistical reliability. Furthermore, the accuracy and completeness of the Finnish Cancer Registry significantly reinforce the study's validity. This is demonstrated by its high coverage – 96% of all solid tumors during 2009–2013 – and diagnostic precision – 93% of tumors morphologically verified – according to quality assessments.[22] Population-based studies also help reduce the selection bias common in hospital or clinical series.[23] A key strength of our study is the reduced risk of misclassification of an SPC as a recurrence of the

primary disease, owing to the Finnish Cancer Registry's policy of not recording new cancers occurring at the same site as the primary tumor.

It is crucial to acknowledge certain caveats in our study. The foremost limitation is the lack of information on risk factors such as smoking, alcohol use, and obesity, along with specific details of initial treatments including types of radiotherapy and chemotherapy. This gap in data hampers us from assessing their impact on the development of SPCs. Our research also faces challenges with accurately classifying the precise location of SPCs, a common issue, albeit unavoidable, in clinical settings. This could lead to errors where SPCs located near the original tumor site are mistakenly identified as either local tumor spread or recurrences of the primary disease. Similarly, there's a possibility of misclassifying metastases from the primary tumor as SPCs or the other way around. Despite these challenges, our study provides valuable insight into the SPC risk among EC/GCC patients and aims to enhance the awareness of clinicians regarding this risk. However, the results of this study should be applied cautiously to other populations, as treatment of EG/GCC and risk factors can vary considerably.

Conclusion

In conclusion, in Finland, patients with EC/GCC demonstrated an elevated risk of developing SPC of the mouth/pharynx, respiratory, and digestive organs, despite generally poor survival rates. The increased risk of SPC was also observable after 15–20 years of follow-up and was particularly evident in patients with AC who were more likely to develop SPCs in other digestive organs. Conversely, patients with SCC primarily showed an increased risk for SPCs occurring in the mouth/pharynx and respiratory organs. Notably, this elevated risk was observed in patients aged 40–54 years. It's imperative for healthcare professionals to be aware of the increased risk of SPCs in survivors of primary cancer. These patients should be advised about this risk and encouraged to adopt healthier lifestyles. Additionally, they should remain alert for symptoms, even beyond the standard 5-year follow-up period, as early diagnosis may offer an advantage in terms of survival.

Data Sharing Statement

Data sharing is not available due to privacy/ethical restrictions.

Ethics Approval

The current study was based on data from existing registries and did not include any human intervention. Study participants were not contacted during the execution of the study. All methods were carried out in accordance with relevant guidelines and regulations. Approval from any institutional review board or ethics committee was not required for this research.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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