Original Article

Risk of second cancer in esophageal squamous cell carcinoma and adenocarcinoma survivors: a population-based analysis in SEER dataset

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Background: Previous studies have reported increased risk of second cancer in both esophageal squamous cell cancer (ESCC) and esophageal adenocarcinoma (EAC) survivors. This study aimed to examine the risk and influential factors of second cancer in ESCC and EAC patients.

Methods: This population-based cohort study included 7,297 ESCC patients and 11,812 EAC patients who were in 1992–2019 from the Surveillance, Epidemiology, and End Results (SEER) program in the United States. These patients were followed up until diagnosis of second cancer, death, or end of the study (December 31, 2019). We calculated standard incidence ratio (SIR) and 95% confidence interval (CI) of second cancer and performed competing-risk regression to estimate the subdistribution hazard ratios (sHR) comparing categories of patients' characteristics.

Results: After a total of 49,509.38 person-years of follow-up, 431 (5.9%) ESCC patients and 636 (5.9%) EAC patients developed a second cancer. An overall increased risk of second cancer was observed in both ESCC patients (SIR: 1.66, 95% CI: 1.51–1.83) and EAC patients (SIR: 1.11, 95% CI: 1.02–1.20). ESCC patients were at increased risk of second malignancy in oral cavity and pharynx (SIR: 12.57, 95% CI: 9.87–15.79), stomach (SIR: 3.03, 95% CI: 1.77–4.85), nose and larynx (SIR: 4.79, 95% CI: 2.47–8.37), and lung and bronchus (SIR: 2.44, 95% CI: 1.96–2.99), but decreased risk of prostate cancer (SIR: 0.73, 95% CI: 0.52–0.99). EAC patients had increased risk of second malignancies in stomach (SIR: 4.41, 95% CI: 3.23–5.89), lung and bronchus (SIR: 1.26, 95% CI: 1.02–1.54), and kidney (SIR: 1.57, 95% CI: 1.05–2.25). The risk of second cancer was higher in female ESCC patients than in males (sHR: 1.34, 95% CI: 1.11–1.63) and decreased with more advanced tumor stage in both ESCC patients (sHR: 0.62, 95% CI: 0.50–0.76 for regional stage; sHR: 0.27, 95% CI: 0.20–0.36 for distant stage) and EAC patients (sHR: 0.47, 95% CI: 0.40–0.56 for regional stage; sHR: 0.10, 95% CI: 0.07–0.13 for distant stage).

Conclusions: Both ESCC and EAC patients are at considerable risk of certain types of second cancer.

Keywords: Second neoplasms; esophageal cancer; Surveillance, Epidemiology, and End Results (SEER); standardized incidence ratio; competing-risk regression

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Introduction

Esophageal cancer is the seventh most common type of malignancy globally with more than 500,000 new cases each year (1). The two most main histological subtypes of esophageal cancer are esophageal squamous cell cancer (ESCC) and esophageal adenocarcinoma (EAC) (2,3). Esophageal cancer is characterized by a poor prognosis, with an overall 5-year survival below 20–30% in most countries (4), largely due to the fact that many patients are diagnosed at an advanced stage (5). However, survival after esophageal cancer has been slightly improved in recent years. For example, the 5-year survival increased by 4–5% each year from 2000 to 2014 in the United States (4). Esophageal cancer patients are at risk of second malignancies. Previous studies reported that around 0.6–14.5% of esophageal cancer patients developed second cancer during follow-up, and the risk varied across cancer types (2,6-8). The underlying reasons for altered risk of second cancer in these patients remain unclear but may be explained by common genetic and environmental risk factors with esophageal cancer, as well as oncological treatments (9-12).

Using data from the Surveillance, Epidemiology, and End Results (SEER) program in the United States, we conducted this population-based analysis to examine the risk of second cancer in patients with esophageal squamous cell carcinoma and EAC. We further explored the risk factors for developing second cancer in these patients using competing-risk regression which takes into account competing risk from death (13). We present this article in accordance with the STROBE reporting checklist (available at https://tgh.amegroups.com/article/view/10.21037/tgh-23-29/rc).

Highlight box

Key findings

- Around 6% esophageal cancer patients developed second cancer in the United States.
- Esophageal squamous cell carcinoma patients had increased risk of second cancer in oral cavity, pharynx, nose and larynx, stomach, lung and bronchus, and decreased risk of second prostate cancer.
- Esophageal adenocarcinoma patients had increased risk of second cancer in stomach, lung and bronchus and kidney.

What is known and what is new?

- Previous studies have reported altered risk of second cancer in esophageal cancer patients.
- We assessed risk of second cancer in esophageal squamous cell carcinoma and adenocarcinoma patients using competing-risk regression.

What is the implication, and what should change now?

- Physicians treating esophageal cancer patients may need to be aware of the considerable risk of second cancer in these patients.

Methods

Data sources and study design

We obtained data from the SEER program in the United States. Data were extracted from the SEER Research Plus Data (12 registries), which included all incident cases of esophageal cancer from 12 cancer registries [San Francisco-Oakland SMSA, Connecticut, Hawaii, Iowa, New Mexico, Seattle (Puget Sound), Utah, Atlanta (Metropolitan), San Jose-Monterey, Los Angeles, Alaska Natives, Rural Georgia] between 1992–2019. The database covers approximately 12.2% of the total population of the United States. This cohort study included all incident cases of esophageal cancer during the study period and had survived for at least 2 months. These patients were followed up from their diagnosis of esophageal cancer until the occurrence of second cancer, death, loss to follow-up, or end of the study (December 31, 2019).

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The access to the SEER database was signed by the SEER Research Data Agreement (21730-Nov2021), and relevant data were collected according to approved guidelines. All used data were publicly accessible and institutional review board approval was exempted.

Statistical analysis

We calculated the standard incidence ratio (SIR) and excess risk (ER) for any second cancer (excluding esophageal cancer) to in esophageal cancer patients on relative and absolute scales, respectively, using the multiple primary standardized incidence ratios (MP-SIR) session in the SEER*Stat program (version 8.4.1). We calculated SIRs and ERs with their confidence intervals (CIs) for anatomical system, except for those with less than 10 cases of second cancer. The SIR is equal to the number of observed second cancer cases during the follow-up period by the expected number, where the overall incidence rate in the total SEER 12 1992–2019 population was used as the referent rate. The

Table 1 Characteristics of survivors of ESCC and EAC in SEER 12 registries, 1992–2019

Characteristics	ESCC (n=7,297), n (%)	EAC (n=11,812), n (%)
Gender		
Male	4,803 (65.8)	10,284 (87.1)
Female	2,494 (34.2)	1,528 (12.9)
Age at diagnosis, years		
<50	510 (7.0)	1,111 (9.4)
50–59	1,548 (21.2)	2,693 (22.8)
60–69	2,334 (32.0)	3,793 (32.1)
70–79	2,005 (27.5)	2,873 (24.3)
≥80	900 (12.3)	1,342 (11.4)
Race		
White	4,576 (62.7)	11,139 (94.3)
Black	1,533 (21.0)	232 (2.0)
American Indian/Alaska Native	33 (0.5)	66 (0.6)
Asian or Pacific Islander	1,143 (15.7)	360 (3.0)
Unknown	12 (0.2)	15 (0.1)
Year of diagnosis		
1992–1998	2,256 (30.9)	2,163 (18.3)
1999–2005	2,165 (29.7)	3,433 (29.1)
2006–2012	2,001 (27.4)	4,245 (35.9)
2013–2019	875 (12.0)	1,971 (16.7)
SEER historic stage		
Localized	1,914 (26.2)	3,095 (26.2)
Regional	3,005 (41.2)	4,238 (35.9)
Distant	2,378 (32.6)	4,479 (37.9)

ESCC, esophageal squamous cell carcinoma; EAC, esophageal adenocarcinoma; SEER, Surveillance, Epidemiology, and End Results.

ER was calculated as:

$$ER = \frac{(number\ of\ observed\ cases - number\ of\ expected\ cases) \times 10{,}000}{Person\text{-}years\ at\ risk} \quad [1]$$

We calculated SIRs and ERs of second cancer in all esophageal cancer patients by the length of follow-up (2–11, 12–59, 60–119, or ≥120 months) and separately for ESCC [histological codes according to the International Classification of Diseases for Oncology, version 3 (ICD-O-3): 8050–8078, 8083–8084)] and EAC (ICD-O-3 codes: 8140–8141, 8143–8145, 8190–8231, 8260–8265, 8310, 8401, 8480–8490, 8550–8552, 8570–8574, 8576).

We further performed competing-risks regressions to examine associations between patients' characteristics and risk of second cancer, using statistical software package SAS 9.4 (SAS Institute, Cary, NC, USA). The competing-risks regression is based on the method of Fine and Gray and estimates the subdistribution hazard ratio (sHR) of subsequent second cancer, in the presence of competing risk from death, in esophageal cancer survivors (14). Regressor variables included in the models were gender, age at diagnosis of esophageal cancer (<50, 50–59, 60–69, 70–79, or ≥80 years), race (White, Black, American Indian/Alaska Native, or Asian/Pacific Islander), period of esophageal cancer diagnosis (1992–1998, 1999–2005, 2006–2012, or 2013–2019), and tumor stage at esophageal cancer diagnosis (localized, regional, or distant). Patients with unknown race (n=27) were excluded from the competing-risk regressions. A two-sided P value below 0.05 was considered statistically significant.

Results

Patients' characteristics

The study cohort consisted of 19,109 esophageal cancer patients, including 7,297 ESCC patients and 11,812 EAC patients. Among these, 4,803 (65.8%) ESCC and 10,284 (87.1%) EAC patients were males, the majority (>90%) were diagnosed at ages 50 years or above, and 26.2% were diagnosed at localized tumor stage. The characteristics of these patients are shown in *Table 1*.

Risk of second cancer

During follow-up, 1,143 (5.6%) esophageal cancer patients developed second cancer, with an SIR of 1.29 (95% CI: 1.22–1.37; ER: 52.51). The site-specific SIRs of second cancer by the length of follow-up are shown in *Table 2*. Esophageal cancer patients were at an increased risk of second cancer in oral cavity and pharynx (SIR: 4.03, 95% CI: 3.25–4.94; ER: 13.97), stomach (SIR: 3.95, 95% CI: 3.06–5.02; ER: 10.11), pancreas (SIR: 1.43, 95% CI: 1.01–1.97; ER: 2.25), nose and larynx (SIR: 2.07, 95% CI: 1.25–3.23; ER: 1.98), lung and bronchus (SIR: 1.70, 95% CI: 1.47–1.95; ER: 16.94), and kidney (SIR: 1.48, 95% CI: 1.05–2.01; ER: 2.61), while decreased SIRs were observed

Table 2 Risk of second primary cancer after esophageal cancer by the length of follow-up and cancer type in SEER 12 registries, 1992–2019

Cancer types	Length of follow-up												Total (n=20,451)		
	2–11 months (n=20,451)			12–59 months (n=10,567)			60–119 months (n=3,183)			≥120 months (n=1,302)					
	N	SIR (95% CI)	ER	N	SIR (95% CI)	ER	N	SIR (95% CI)	ER	N	SIR (95% CI)	ER	N	SIR (95% CI)	ER
All sites	211	1.04 (0.91, 1.19)	7.22	496	1.34 (1.22, 1.46)	59.38	301	1.54 (1.37, 1.73)	101.43	135	1.17 (0.98, 1.38)	32.84	1,143	1.29 (1.22, 1.37)	52.51
All sites excluding non-melanoma skin	210	1.04 (0.91, 1.19)	7.15	495	1.34 (1.23, 1.47)	59.77	300	1.55 (1.38, 1.73)	101.56	134	1.17 (0.98, 1.38)	32.46	1,139	1.30 (1.22, 1.37)	52.64
All solid tumors	192	1.08 (0.94, 1.25)	12.57	440	1.37 (1.24, 1.50)	55.80	272	1.62 (1.44, 1.83)	99.95	126	1.29 (1.07, 1.53)	46.9	1,030	1.35 (1.27, 1.43)	53.65
Oral cavity and pharynx	21	4.06 (2.51, 6.20)	13.29	36	3.75 (2.63, 5.20)	12.46	27	5.37 (3.54, 7.82)	21.04	8	2.64 (1.14, 5.20)	8.34	92	4.03 (3.25, 4.94)	13.97
Oral cavity	12	2.82 (1.46, 4.93)	6.51	29	3.64 (2.44, 5.22)	9.92	18	4.25 (2.52, 6.72)	13.18	7	2.72 (1.09, 5.61)	7.43	66	3.47 (2.68, 4.41)	9.49
Pharynx	7	8.59 (3.45, 17.70)	5.19	5	3.52 (1.14, 8.21)	1.69	8	11.43 (4.94, 22.53)	6.99	0	0.00 (0.00, 9.08)	–0.68	20	5.99 (3.66, 9.24)	3.36
Digestive system	55	1.39 (1.05, 1.81)	12.9	164	2.29 (1.95, 2.67)	43.55	77	2.04 (1.61, 2.55)	37.62	30	1.33 (0.90, 1.90)	12.51	326	1.90 (1.70, 2.12)	31.19
Stomach	13	3.26 (1.74, 5.58)	7.57	32	4.54 (3.10, 6.40)	11.77	17	4.60 (2.68, 7.36)	12.74	5	2.25 (0.73, 5.26)	4.67	67	3.95 (3.06, 5.02)	10.11
Colon	19	1.29 (0.77, 2.01)	3.55	33	1.28 (0.88, 1.80)	3.44	17	1.31 (0.76, 2.10)	3.84	6	0.81 (0.30, 1.76)	–2.36	75	1.23 (0.97, 1.54)	2.85
Rectum and anus	2	0.32 (0.04, 1.16)	–3.57	10	0.92 (0.44, 1.69)	–0.43	3	0.56 (0.12, 1.64)	–2.24	4	1.35 (0.37, 3.46)	1.75	19	0.75 (0.45, 1.17)	–1.30
Liver	2	0.59 (0.07, 2.14)	–1.15	9	1.39 (0.64, 2.64)	1.19	4	1.12 (0.31, 2.88)	0.42	1	0.44 (0.01, 2.47)	–2.11	16	1.02 (0.58, 1.66)	0.07
Pancreas	9	1.64 (0.75, 3.11)	2.95	17	1.61 (0.94, 2.58)	3.05	6	1.00 (0.37, 2.18)	0.01	5	1.30 (0.42, 3.03)	1.93	37	1.43 (1.01, 1.97)	2.25
Respiratory system	47	1.55 (1.14, 2.06)	14.00	90	1.66 (1.33, 2.04)	16.83	59	2.08 (1.59, 2.69)	29.39	29	1.74 (1.17, 2.50)	20.73	225	1.74 (1.52, 1.98)	19.27
Nose and larynx	6	2.65 (0.97, 5.78)	3.14	6	1.53 (0.56, 3.34)	0.99	5	2.60 (0.84, 6.06)	2.95	2	1.84 (0.22, 6.64)	1.53	19	2.07 (1.25, 3.23)	1.98
Lung and bronchus	41	1.46 (1.05, 1.99)	10.91	84	1.67 (1.33, 2.07)	15.90	52	1.98 (1.48, 2.59)	24.59	27	1.74 (1.15, 2.53)	19.26	204	1.70 (1.47, 1.95)	16.94
Melanoma of the skin	2	0.24 (0.03, 0.85)	–5.46	13	0.74 (0.40, 1.27)	–2.11	7	0.68 (0.27, 1.40)	–3.18	5	0.75 (0.24, 1.75)	–2.82	27	0.63 (0.41, 0.91)	–3.23
Breast	9	0.90 (0.41, 1.72)	–0.80	14	0.75 (0.41, 1.25)	–2.26	10	1.02 (0.49, 1.88)	0.21	3	0.54 (0.11, 1.57)	–4.36	36	0.82 (0.57, 1.13)	–1.64
Male genital organs	21	0.39 (0.24, 0.60)	–27.62	72	0.77 (0.60, 0.97)	–10.18	62	1.36 (1.05, 1.75)	15.86	35	1.43 (0.99, 1.98)	17.55	190	0.87 (0.75, 1.01)	–5.55
Prostate	20	0.38 (0.23, 0.58)	–27.99	72	0.78 (0.61, 0.98)	–9.71	60	1.34 (1.02, 1.72)	14.43	35	1.44 (1.01, 2.01)	18.07	187	0.87 (0.75, 1.00)	–5.67
Urinary system	30	1.54 (1.04, 2.19)	8.80	42	1.13 (0.81, 1.52)	2.21	21	1.00 (0.62, 1.53)	0.06	11	0.84 (0.42, 1.51)	–3.48	104	1.14 (0.94, 1.39)	2.66
Urinary bladder	13	1.02 (0.54, 1.75)	0.25	25	1.04 (0.67, 1.53)	0.40	14	1.02 (0.56, 1.72)	0.32	8	0.93 (0.40, 1.84)	–0.97	60	1.02 (0.77, 1.31)	0.18
Kidney	17	2.91 (1.70, 4.67)	9.38	14	1.24 (0.68, 2.08)	1.28	6	0.97 (0.36, 2.11)	–0.18	3	0.79 (0.16, 2.31)	–1.32	40	1.48 (1.05, 2.01)	2.61
Lymphoma	7	0.80 (0.32, 1.65)	–1.46	14	0.84 (0.46, 1.42)	–1.22	10	1.09 (0.52, 2.01)	0.81	4	0.71 (0.19, 1.82)	–2.73	35	0.87 (0.61, 1.21)	–1.03
Leukemia	7	1.22 (0.49, 2.51)	1.06	17	1.55 (0.91, 2.49)	2.86	7	1.14 (0.46, 2.35)	0.84	2	0.52 (0.06, 1.89)	–3.06	33	1.24 (0.85, 1.74)	1.29

The total person-years at risk is 49,509.38. The person-years at risk for the 2–11-month group is 11,907.27, for the 12–59-month group is 21,199.53, for the 60–119-month group is 10,443.35, and for the ≥120-month group is 5,959.24. SEER, Surveillance, Epidemiology, and End Results program; N, number of second cancer cases; SIR, standardized incidence ratio; CI, confidence interval; ER, excess risk per 10,000 person-years.

Table 3 Risk for second primary cancers in survivors of ESCC and EAC in SEER 12 registries, 1992–2019

Cancer types	ESCC (n=7,285)			EAC (n=11,797)		
	N	SIR (95% CI)	ER	N	SIR (95% CI)	ER
All sites	431	1.66 (1.51, 1.83)	112.18	636	1.11 (1.02, 1.20)	19.34
All sites excluding non-melanoma skin	430	1.66 (1.51, 1.83)	112.24	633	1.11 (1.02, 1.20)	19.44
All solid tumors	389	1.72 (1.55, 1.90)	106.32	571	1.15 (1.06, 1.25)	23.79
Oral cavity and pharynx	74	12.57 (9.87, 15.79)	44.55	14	0.89 (0.49, 1.50)	–0.54
Oral cavity	50	10.55 (7.83, 13.91)	29.60	12	0.91 (0.47, 1.58)	–0.40
Pharynx	18	17.77 (10.53, 28.09)	11.11	2	0.93 (0.11, 3.36)	–0.05
Digestive system	115	2.15 (1.78, 2.58)	40.27	190	1.75 (1.51, 2.02)	25.88
Stomach	17	3.03 (1.77, 4.85)	7.45	46	4.41 (3.23, 5.89)	11.31
Colon	31	1.56 (1.06, 2.21)	7.26	41	1.09 (0.78, 1.48)	1.11
Rectum and anus	8	1.03 (0.44, 2.02)	0.13	10	0.62 (0.30, 1.13)	–1.98
Liver	6	1.29 (0.47, 2.82)	0.89	10	0.98 (0.47, 1.8)	–0.06
Pancreas	12	1.54 (0.79, 2.68)	2.74	21	1.27 (0.78, 1.93)	1.40
Respiratory system	105	2.63 (2.15, 3.19)	42.59	101	1.22 (1.00, 1.49)	5.84
Nose and larynx	12	4.79 (2.47, 8.37)	6.21	5	0.81 (0.26, 1.88)	–0.38
Lung and bronchus	91	2.44 (1.96, 2.99)	35.12	96	1.26 (1.02, 1.54)	6.27
Melanoma of the skin	5	0.57 (0.18, 1.32)	–2.51	21	0.66 (0.41, 1.01)	–3.44
Breast	16	0.67 (0.38, 1.08)	–5.22	16	0.93 (0.53, 1.51)	–0.38
Male genital organs	42	0.76 (0.55, 1.03)	–8.52	135	0.89 (0.75, 1.06)	–5.17
Prostate	40	0.73 (0.52, 0.99)	–9.50	134	0.90 (0.75, 1.06)	–4.93
Urinary system	22	0.99 (0.62, 1.49)	–0.22	76	1.19 (0.94, 1.49)	3.92
Urinary bladder	12	0.86 (0.44, 1.50)	–1.29	46	1.10 (0.80, 1.46)	1.28
Kidney	7	0.98 (0.40, 2.03)	–0.07	29	1.57 (1.05, 2.25)	3.33
Lymphoma	12	1.09 (0.56, 1.90)	0.64	20	0.74 (0.45, 1.15)	–2.18
Leukemia	13	1.85 (0.99, 3.16)	3.91	19	1.05 (0.63, 1.64)	0.27

The person-years at risk for the ESCC group is 15,288.7, and for the EAC group is 31,462.93. ESCC, esophageal squamous cell carcinoma; EAC, esophageal adenocarcinoma; SEER, Surveillance, Epidemiology, and End Results; N, number of second cancer cases; SIR, standardized incidence ratio; CI, confidence interval; ER, excess risk per 10,000 person-years.

for second prostate cancer (SIR: 0.87, 95% CI: 0.75–1.00; ER: –5.67 per 10,000 person-years) and melanoma of the skin (SIR: 0.63, 95% CI: 0.41–0.91; ER: –3.23). The SIRs varied by the length of follow-up to different degrees. Particularly, the risk of second prostate cancer decreased within 5 years of follow-up (SIR: 0.38, 95% CI: 0.23–0.58; ER: –27.99 for 2–11 months; SIR: 0.78, 95% CI: 0.61–0.98; ER: –9.71 for 12–59 months) but increased afterward (SIR: 1.34, 95% CI: 1.02–1.72; ER: 14.43 for 60–119 months; SIR: 1.44, 95% CI: 1.01–2.01; ER: 18.07 for ≥120 months).

The site-specific SIRs of second cancer by histological type are shown in *Table 3*. A total of 431 (5.9%) ESCC and 636 (5.4%) patients developed second cancer. Both ESCC and EAC patients were at increased risk of second cancer in stomach (SIR: 3.03, 95% CI: 1.77–4.85, ER: 7.45 for ESCC; SIR: 4.41, 95% CI: 3.23–5.89, ER: 11.31 for EAC) and lung and bronchus (SIR: 2.44, 95% CI: 1.96–2.99, ER: 35.12 for ESCC; SIR: 1.26, 95% CI: 1.02–1.54, ER: 6.27

Table 4 Association of selected factors with risk of second primary cancer in patients with ESCC and EAC

Factors	ESCC				EAC			
	N	Proportion (%)	sHR (95% CI)	P value	N	Proportion (%)	sHR (95% CI)	P value
Total	431	5.9			636	5.4		
Gender								
Male	252	5.2	1.00 (reference)		560	5.4	1.00 (reference)	
Female	179	7.2	1.34 (1.11, 1.63)	<0.01	76	5.0	0.94 (0.74, 1.20)	0.61
Age at diagnosis, years								
<50	33	6.5	1.00 (reference)		34	3.1	1.00 (reference)	
50–59	83	5.4	0.82 (0.55, 1.22)	0.33	133	4.9	1.41 (0.97, 2.05)	0.06
60–69	172	7.4	1.04 (0.72, 1.52)	0.82	252	6.6	1.81 (1.27, 2.58)	<0.01
70–79	105	5.2	0.66 (0.45, 0.99)	0.04	170	5.9	1.46 (1.01, 2.11)	0.04
≥80	38	4.2	0.46 (0.29, 0.74)	<0.01	47	3.5	0.77 (0.50, 1.20)	0.25
Race								
White	288	6.3	1.00 (reference)		605	5.4	1.00 (reference)	
Black	78	5.1	0.80 (0.62, 1.03)	0.08	14	6.0	1.32 (0.78, 2.23)	0.30
American Indian/ Alaska Native	1	3.0	0.62 (0.09, 4.37)	0.63	2	3.0	0.59 (0.15, 2.28)	0.45
Asian or Pacific Islander	64	5.6	0.97 (0.74, 1.28)	0.85	15	4.2	0.89 (0.54, 1.49)	0.67
Year of diagnosis								
1992–1998	132	5.9	1.00 (reference)		109	5.0	1.00 (reference)	
1999–2005	132	6.1	1.14 (0.90, 1.45)	0.28	201	5.9	1.25 (0.99, 1.60)	0.06
2006–2012	125	6.2	1.33 (1.04, 1.70)	0.02	246	5.8	1.45 (1.20, 1.82)	<0.01
2013–2019	42	4.8	1.13 (0.80, 1.60)	0.50	80	4.1	1.18 (0.88, 1.57)	0.26
SEER historic stage								
Localized	181	9.5	1.00 (reference)		348	11.2	1.00 (reference)	
Regional	185	6.2	0.62 (0.50, 0.76)	<0.01	235	5.5	0.47 (0.40, 0.56)	<0.01
Distant	65	2.7	0.27 (0.20, 0.36)	<0.01	53	1.2	0.10 (0.07, 0.13)	<0.01

ESCC, esophageal squamous cell carcinoma; EAC, esophageal adenocarcinoma; N, number of second cancer cases; sHR, subdistribution hazard ratio; CI, confidence interval; SEER, Surveillance, Epidemiology, and End Results.

for EAC). The increased risk of second cancer in oral cavity (SIR: 10.55, 95% CI: 7.83–13.91; ER: 29.60), pharynx (SIR: 17.77, 95% CI: 10.53–28.09; ER: 11.11), and nose and larynx (SIR: 4.79, 95% CI: 2.47–8.37; ER: 6.21), and the decreased risk of second prostate cancer (SIR: 0.73, 95% CI: 0.52–0.99; ER: –9.5) was restricted in ESCC patients rather than in EAC patients. EAC patients were at an increased risk of second kidney cancer (SIR: 1.57, 95% CI: 1.05–2.25; ER: 3.33).

Competing-risks regression

Associations between patients' characteristics and second cancer in ESCC and EAC patients from competing-risks regressions are shown in *Table 4*. The risk of second cancer in ESCC patients was higher in women than in men

(sHR: 1.34, 95% CI: 1.11–1.63) and decreased with more advanced tumor stage (sHR: 0.62, 95% CI: 0.50–0.76 for regional; sHR: 0.27, 95% CI: 0.20–0.36 for distant). Such risk in EAC patients increased in those who were older, except for ≥80 years (sHRs ranging from 1.41 to 1.81), diagnosed in more recent years (sHR ranging from 1.18 to 1.45) and decreased in those diagnosed at more advanced stages (sHR ranging from 0.10 to 0.47).

Discussion

This population-based study revealed an increased risk of second cancer in oral cavity and pharynx, stomach, pancreas, respiratory system and kidney, and a decreased risk of second prostate cancer and melanoma in survivors of esophageal cancer. The altered risk of second cancer varied across histological types, length of follow-up, and patients' characteristics.

Although the risk of second cancer in esophageal cancer patients has been analyzed previously (15), the present study has strengths including the population-based design, assessing outcome risk with multiple measures on both absolute and relative scales, separate analyses by histological type, and utilization of competing-risks regressions which might be suitable for the cohort of esophageal cancer patients with relatively high mortality. This study also has some limitations. First, due to the lack of relevant data, we were unable to analyze in detail how genetic background, lifestyle factors (e.g., smoking and alcohol drinking), physical conditions including obesity, comorbidities and oncological treatment influenced the risk of second cancer. Second, the number of cases remained limited for more detailed categorization of second cancer types and in some stratified analyses. Particularly, although we have noted a seemingly decreasing proportion of second lung cancer and prostate cancer and an increasing trend in stomach cancer, we were not able to evaluate in detail how second cancer types varied over calendar year of diagnosis. Third, the population-based registries included in the analysis have follow-up process according to the rules and regulations at their institutions, which vary across registries. Incomplete follow-up might have resulted in underestimated risk of second malignancies. However, only a very small proportion (~1%) was lost to follow-up in this study, and thus, its influence on our results would be minimal. Finally, this study was based on the United States population and findings may not be directly generalized to other populations.

This study found a modestly increased overall risk of second cancer in both ESCC and EAC patients, for which the reasons may vary across cancer types. Such observed increase in risk of second cancer might be, at least to some extent, due to an increased chance of detection of second cancer because of more frequent medical follow-up after esophageal cancer diagnosis. Such artificially increased risk of second cancer could be associated with the stage of esophageal cancer and other factors, e.g., length of follow-up. Therefore, the stratified analysis by the length of follow-up and inclusion of tumor stage as a regressor variable in competing-risks regression would be helpful to better interpret how frequent follow-up had possibly led to detection of a second cancer. An increased risk of second cancer was observed in oral cavity and pharynx, stomach, lung, nose and kidney, which was consistent with findings from previous studies (15-18). This might be explained by common etiology and carcinogenesis mechanisms shared by different cancer types (12,19). The two main established risk factors for ESCC are tobacco smoking and alcohol over consumption, which are also well-confirmed risk factors for these cancer types (11,12). Furthermore, ionizing radiation is a risk factor for many cancer types (20,21), and thus, radiotherapy might also explain the increase of second cancer, particularly in adjacent fields such as oral cavity, pharynx, stomach, and lung, in esophageal cancer patients (15). The increased risk of second kidney cancer might be to some extent due to oncological treatment, particularly use of chemotherapy and certain medications including analgesics (22).

Interestingly, a decreased risk of second prostate cancer was observed in survivors of esophageal cancer, particularly in ESCC patients. In stratified analysis by the length of follow-up, the risk decreased within the first 5 years of esophageal cancer diagnosis but increased thereafter. The etiology of prostate cancer has not been well understood, and the main established risk factors, i.e., inherited characteristics (23), seem not to explain such findings as the direction of altered risk changed over time. A possible explanation is that esophageal cancer patients might have paid less attention to prostate cancer and had delayed diagnosis of prostate cancer, if any, as compared to the reference population, particularly when prostate-specific antigen testing is widely available (24).

Female ESCC patients and those diagnosed at advanced stages showed higher risk (cumulative incidence as measured in competing-risks model) of second cancer, which was

consistent with previous studies (25,26). Such findings are probably due to the better survival in these groups, as a better survival after esophageal cancer, particularly ESCC, has been consistently observed in female patients (27-29), and tumor stage is the strongest prognostic factor in esophageal cancer (30). Nevertheless, further investigations with more detailed information, particularly that on treatment, would help clarify the reasons for variations in risk of second cancer in esophageal cancer patients.

Conclusions

In summary, this population-based study showed an overall increased risk of second cancer in esophageal cancer patients. The altered risk varied across histological types of esophageal cancer, types of second cancer, length of follow-up, as well as patients' characteristics. Depending on the specific type of second cancer, the altered risk may be explained by shared risk factors with esophageal cancer, oncological treatment, or cancer screening practice. Physicians treating esophageal cancer patients may need to be aware of the considerable risk of second cancer in these patients.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). SEER data are publicly available and de-identified, and thus, ethical approval was deemed unnecessary. The access of SEER database was signed by the SEER Research Data Agreement (21730-Nov2021), and relevant data were collected according to approved guidelines.

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