Risk of Second Primary Cancer among Esophageal Cancer Patients: a Pooled Analysis of 13 Cancer Registries

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Abstract

Background: **The objective of this study is to assess the risk of second primary cancers following a first primary esophageal cancer as well as the risk of esophageal cancer as a second primary, following first primary cancers of other sites.**

Methods: **The present investigation is a multicenter study of 13 population-based cancer registries in Europe, Australia, Canada, and Singapore. To assess excess occurrence of second cancers after esophageal cancers, we calculated standardized incidence ratios (SIR) by dividing the observed numbers of second cancers by the expected number of cancers calculated from the accumulated person-years and the age-, sex-, calendar period-, and registry-specific first primary cancer incidence rates.**

Results: **During the study period, 959 cases of second primary cancers occurred after an initial esophageal cancer, resulting in a SIR of 1.15 (95% confidence interval, 1.08-1.22). Second primary stomach cancers were associated with first primary esophageal adenocarcinomas (SIR, 2.13; 95% confidence interval, 1.26-3.37) and second primary cancers of the oral cavity and pharynx (6.68; 5.33-8.26), stomach (1.53; 1.14-2.01), larynx (3.24; 1.88-5.18), lung (1.55; 1.28-1.87), kidney (1.88; 1.18-2.85), and thyroid (2.92; 1.18-6.02) were associated with first primary squamous cell carcinomas of the esophagus. An excess of esophageal cancer as a second primary were observed following first primary cancers of the aerodigestive tract, female breast, cervix, testis, bladder, Hodgkin's lymphoma, and non–Hodgkin lymphoma.**

Conclusion: **We observed associations of esophageal cancer with second primary head and neck cancers and lung cancer regardless of years of follow-up, which may suggest that common risk factors play a role in multiple tumor development.** (Cancer Epidemiol Biomarkers Prev 2008;17(6):1543–9)

Introduction

Patients who have cancer of the esophagus experience very poor survival. Only 16% of patients with esophageal cancer in the United States (1) and 9% in Europe (2) live for 5 years after diagnosis. The major risk factors for esophageal squamous cell carcinoma (SCC) are tobacco smoking and alcohol consumption (3). Other potential risk factors include hot beverages (4), nutritional deficiencies (5), pickled vegetables, nitrosamine-rich food (6), and some genetic factors (3, 7). Radiation therapy is also associated with esophageal cancer (3, 8). Recently, there has been an increasing trend of esophageal adenocarcinoma in the lower third of the esophagus in western countries (9). The increase is thought to be associated with obesity (10, 11) and Barrett's esophagus, a condition in which the metaplastic epithelium replaces normal esophageal mucosa that seems to arise in response to chronic inflammation from gastroesophageal reflux disease (12).

There have been limited reports in the literature regarding the incidence of a second primary cancer in patients with esophageal cancer as the index site, most likely because of poor survival. Poon et al. (13) reviewed a series of 1,055 patients with esophageal cancer between

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1982 and 1996 in Hong Kong, 47 patients had antecedent tumors, 43 had synchronous tumors diagnosed simultaneously or within 6 months of diagnosis of the first primary esophageal cancer and 10 patients developed metachronous cancers. Among 291 patients with esophageal cancer in Japan, during the period between 1974 and 1997, ~7% developed synchronous tumors and 4% developed metachronous cancers (14).

Clusters of second cancers provide a unique clue to the understanding of cancer etiology and its mechanisms. Multiple cancers could be due to common risk factors or treatment for the first cancer. If the risk increases over time, the association may be more likely to be due to treatment for the first cancer. Otherwise, if an association treating the index cancer as the second cancer is observed, then common risk factors may be suggested for the association (15, 16).

Due to low survival among patients with esophageal cancer and the difficulty of accumulating a sufficient number of patients with second primaries, the study of second primary cancers following esophageal cancer has been challenging. The present investigation is a multicenter study including cancer data from 13 population-based cancer registries in Europe, Australia, Canada, and Singapore. The data were used to assess the incidence of second cancer among 52,589 patients diagnosed with a first primary esophageal cancer between 1943 and 2000. In addition, our aim was to assess the risk of second primary esophageal cancers after first primary cancers of various types to determine whether associations were likely to be caused by common etiologic factors or treatment.

Materials and Methods

An international multicenter study was initiated to incorporate large cancer registries that have been in operation for at least 25 years, to conduct a systematic analysis of second primary cancers (17, 18). The registries included Australia (New South Wales), Canada (British Columbia, Manitoba, and Saskatchewan), Denmark,

Table 1. General characteristics of patients with first primary and second primary esophageal cancer from 13 cancer registries

	Esophageal cancer as first primary		Esophageal cancer as second primary
	Total	With second cancer	
	n (%)	*n* (SPC %)	*n* (%)
Total	52,589	959 (1.8)	3,731
Sex			
Female	19,110 (36.3)	295 (1.5)	1,395 (37.4)
Male	33,479 (63.7)	664 (2.0)	2,336 (62.6)
Age at diagnosis (y)			
<56	6,573 (12.5)	127 (1.9)	240 (6.4)
56-65	13,054 (24.8)	275 (2.1)	661 (17.7)
66-74	16,363 (31.1)	338 (2.1)	1,168 (31.3)
75+	16,599 (31.6)	219 (1.3)	1,662 (44.5)
Calendar period at diagnosis			
~1974	14,668 (27.9)	192 (1.3)	382 (10.2)
1975-1983	12,717 (24.2)	240 (1.9)	672 (18.0)
1984-1990	11,788 (22.4)	278 (2.4)	1,052 (28.2)
1991~	13,416 (25.5)	249 (1.9)	1,625 (43.6)
Time since first cancer diagnosis			
<6 mo	26,330 (50.1)	329 (1.2)	313 (8.4)
6-11 mo	12,732 (24.2)	99 (0.8)	237 (6.3)
1-4 y	11,048 (21.0)	313 (2.8)	1,358 (36.4)
5+ y	2,479 (4.7)	218 (8.8)	1,823 (48.9)
Morphologic group			
Adenocarcinoma	10,049 (19.1)	197 (2.0)	839 (22.5)
SCC	28,036 (53.3)	604 (2.2)	2,085 (55.9)
Other or unspecified	14,504 (27.6)	158 (1.1)	807 (21.6)
Registries			
Australia, New South Wales (1972-1997)	5,167 (9.8)	102 (2.0)	391 (10.5)
Canada, British Columbia (1970-1998)	2,697 (5.1)	88 (3.3)	302 (8.1)
Canada, Manitoba (1970-1998)	795 (1.5)	33 (4.2)	99 (2.7)
Canada, Saskatchewan (1967-1998)	539 (1.0)	25 (4.6)	66 (1.8)
Denmark (1943-1997)	8,026 (15.3)	132 (1.6)	710 (19.0)
Finland (1953-1998)	9,543 (18.1)	79 (0.8)	390 (10.5)
Iceland (1955-2000)	438 (0.8)	17 (3.9)	32 (0.9)
Norway (1953-1999)	5,062 (9.6)	99 (2.0)	392 (10.5)
Singapore (1968-1992)	2,579 (4.9)	24 (0.9)	49 (1.3)
Slovenia (1961-1998)	2,075 (3.9)	34 (1.6)	130 (3.5)
Spain, Zaragoza (1978-1998)	507 (1.0)	10 (2.0)	31 (0.8)
Sweden (1961-1998)	5,010 (9.5)	142 (2.8)	435 (11.7)
United Kingdom, Scotland (1975-1996)	10,151 (19.3)	174 (1.7)	704 (18.9)

Abbreviation: SPC, second primary cancer.

Table 2. Number of cases (*n*) and SIRs of selected second cancers after esophageal cancer by histologic type of esophageal cancer

Site of the second cancer (ICD-9)	Adenocarcinoma		SCC	
	n	SIR (95% CI)	*n*	SIR (95% CI)
All malignant (140-208)	197	1.14 (0.99-1.32)	604	1.28 (1.18-1.38)
Oral cavity, pharynx (140-149)	7	1.70 (0.68-3.50)	85	6.68 (5.33-8.26)
Lip (140)	3	2.52 (0.52-7.36)	6	1.68 (0.62-3.66)
Tongue (141)	1	1.63 (0.04-9.10)	18	9.98 (5.91-15.8)
Salivary gland (142)	1	3.18 (0.08-17.7)	1	1.08 (0.03-6.00)
Mouth (143-145)	2	2.19 (0.26-7.90)	24	9.49 (6.08-14.1)
Pharynx (146-149)	0	0.00 (0.00-3.40)	36	9.23 (6.47-12.8)
Oropharynx (146)	0	0.00 (0.00-8.77)	14	11.6 (6.35-19.5)
Nasopharynx (147)	0	0.00 (0.00-21.4)	2	1.47 (0.18-5.30)
Hypopharynx (148)	0	0.00 (0.00-9.52)	14	12.6 (6.87-21.1)
Pharynx, unspecified (149)	0	0.00 (0.00-34.8)	6	27.7 (10.2-60.3)
Stomach (151)	18	2.13 (1.26-3.37)	51	1.53 (1.14-2.01)
Liver (155) (−155.2)	0	0.00 (0.00-2.27)	13	1.79 (0.95-3.06)
Larynx (161)	2	0.98 (0.12-3.53)	17	3.24 (1.88-5.18)
Lung (162)	27	0.91 (0.60-1.32)	112	1.55 (1.28-1.87)
Female breast (174)	6	1.03 (0.38-2.25)	31	0.84 (0.57-1.20)
Cervix uteri (180)	0	0.00 (0.00-6.41)	5	1.21 (0.39-2.83)
Prostate (185)	42	1.36 (0.98-1.84)	55	0.92 (0.69-1.19)
Testis (186)	0	0.00 (0.00-17.0)	1	2.52 (0.06-14.0)
Bladder (188, 189.3, 189.4)	7	0.68 (0.27-1.39)	28	1.25 (0.83-1.81)
Kidney (189) (-189.3, 189.4)	6	1.46 (0.54-3.19)	22	1.88 (1.18-2.85)
Thyroid gland (193)	2	4.04 (0.49-14.6)	7	2.92 (1.18-6.02)
Non–Hodgkin lymphoma (200, 202)	8	1.82 (0.79-3.59)	6	0.50 (0.18-1.09)

Abbreviation: SCC, squamous cell carcinoma.

Finland, Iceland, Norway, Scotland, Singapore, Slovenia, Sweden, and Spain (Zaragoza). These registries had cancer data covering different time periods between 1943 and 2000. A high degree of completeness of ascertainment by the registry is suggested by an appropriate level of microscopically verified cases, a low proportion of cases registered from death certificates only, and consistent inclusion in the *Cancer incidence in five continents* monograph series (19).

Data were provided from each cancer registry on all first primary cancers, including age and sex of the subject, diagnosis and date of the first primary, follow-up for mortality, and diagnosis and date of the second primary, if any. In this study, registries used different cancer codes, which were systematically converted into International Classification of Disease, ninth revision (ICD-9). Here, we have analyzed the occurrence of second cancers in patients who survived from esophageal cancer (ICD-9: 150) at diagnosis. Coding of multiple primaries in the cancer registries has followed a common set of rules proposed by the International Association of Cancer Registries and the IARC (20). According to the rules, a primary cancer is one that originates in a primary site or tissue and is thus neither an extension, a recurrence, nor a metastasis. Only one tumor was recognized as arising in an organ or pair of organs or tissue (as defined by the three-character category of the ICD or the topography of the ICD-O). Nonmelanoma skin cancer (ICD-9: 173) was excluded from the analysis because of the inconsistency in reporting across the registries.

To assess the potential excess of second cancer occurrence after having a first primary esophageal cancer, the number of second primary cancers observed was compared with the expected number of cancers to obtain the standardized incidence ratios (SIR). SIRs adjusted for age, sex, year, and registry were calculated using indirect standardized methods (17, 18). The expected number was calculated from accumulated person-years and the age-, sex-, and calendar period-specific (depending on the registries) first primary cancer incidence rates in each of the cancer registries. All cases of first primary esophageal cancer were followed up for second primary cancer from the date of esophageal cancer diagnosis (1943-2000) to the date of second primary cancer (1943-2000), date of death, or end of follow-up (1992-2000), depending on the coverage of each registry when the study closed. The same methodology was adopted for esophageal cancer as a second primary after the other cancers as the first primaries. Cumulative incidence, i.e., the probability of developing a second cancer after the first esophageal cancer within a time point, was determined by the Kaplan-Meier method.

Results

Table 1 summarizes the characteristics for patients who had esophageal cancer as a first primary or a second primary. Among the 52,589 first primary esophageal cancer cases, 10,049 were adenocarcinoma with 11,178 person-years of follow-up (mean follow-up time, 1.1 years), 28,036 were SCCs with 37,541 person-years in total (mean follow-up time, 1.3 years), 954 had histologies other than adenocarcinoma or SCC (person-years, 993; mean follow-up time, 1.0 years), and 13,550 had unspecified histologic types of esophageal cancer (person-years, 13,665; mean follow-up time, 1.0 years).

The overall follow-up ranged from 1 day to 43.5 years (33.6 years for adenocarcinoma, 37.2 for SCC), with a median of 6 months.

Nine hundred and fifty-nine (1.8%) patients with a first primary esophageal cancer developed a second cancer. Among patients with first primary cancers other than esophageal cancer (n = 4,140,046), 3,731 patients developed esophageal cancer as a second primary. The male/female ratio was ~2:1 for both first and second primary esophageal cancer patients. Female patients tended to be diagnosed with a first primary esophageal cancer at an older age than the males.

Table 2 shows the SIRs of a second primary cancer following a first primary esophageal SCC or adenocarcinoma. Overall, the SIR for second primaries following a first primary esophageal cancer of any histology was 1.15 [95% confidence interval (CI), 1.08-1.22]. Second primary stomach cancers were the only cancers with excess risk following a first primary esophageal adenocarcinoma (n = 18; SIR, 2.13; 95% CI, 1.26-3.37). The ratio of second primary stomach cancer was increased within the first 6 months after diagnosis of the first primary esophageal adenocarcinoma (n = 12; SIR, 4.25; 95% CI, 2.19-7.42; data not shown). Following first primary SCC of the esophagus, elevated risks were seen for second primary cancers of the oral cavity and pharynx, stomach, larynx, lung, kidney, and thyroid.

Table 3 shows the SIRs for second primary cancers following a first primary SCC of the esophagus by follow-up time. During the first 6 months, increased SIRs were observed in second primary cancers of the oral cavity and pharynx, stomach, liver, and kidney. After 6 months of follow-up, only cancers of the oral cavity and pharynx, larynx, and lung were associated with a first primary esophageal SCC.

Figure 1 shows the patterns of cumulative incidence of selected cancers within the first 15 years following a diagnosis of esophageal SCC. The cumulative incidence increased over the follow-up period with a rate of ~0.3% to 0.5% per year. The 5-, 10-, and 15-year cumulative risks were 1.8%, 2.9%, and 3.6%, respectively, for head and neck cancers (including oral, pharyngeal, and laryngeal cancers) and 1.7%, 3.5%, and 5.0%, respectively, for lung cancer.

The SIRs for esophageal cancers as a second primary cancer following first primary cancers of other sites overall and by follow-up time are shown in Table 4. Second primary esophageal cancers were most frequently SCCs (56%), similar to the histologic distribution of first primary esophageal cancers. The histology of second primary esophageal cancers was 61% SCC after a primary breast cancer, 55% after cervical cancer, 47% after testicular cancer, 49% after bladder cancer, and 56% after lymphoma. Overall, the SIR of all types of esophageal cancer was increased after cancers of the oral cavity and pharynx (percentage of SCC: 74%), larynx (72%), lung (58%), female breast, cervix uteri, testis, bladder, Hodgkin's lymphoma, and non–Hodgkin lymphoma. SIRs for second primary esophageal cancers increased with follow-up time following first primary breast cancer in women, and Hodgkin's and non–Hodgkin lymphomas.

Discussion

In our study, 1.8% of patients with primary esophageal cancer developed a second primary cancer, resulting in a 15% excess risk of second primary cancers. Approximately one third of the second primary cancers following

Table 3. Number of cases (n) and SIRs for selected second cancers in SCC of the esophagus patients by follow-up duration

Site of the second cancer (ICD-9)	<6 mo		6-11 mo		1-4 y		≥5 y	
	n	SIR (95%CI)	n	SIR (95%CI)	n	SIR (95%CI)	n	SIR (95%CI)
All malignant (140-208)	199	1.53 (1.33-1.76)	59	0.91 (0.69-1.17)	208	1.44 (1.25-1.65)	138	1.03 (0.87-1.22)
Oral cavity, pharynx (140-149)	23	6.35 (4.02-9.52)	9	5.02 (2.30-9.53)	39	10.1 (7.17-13.8)	14	4.06 (2.22-6.82)
Lip (140)	3	2.76 (0.57-8.07)	0		1	0.94 (0.02-5.24)	2	2.24 (0.27-8.08)
Tongue (141)	5	10.1 (3.28-23.6)	2	7.79 (0.94-28.1)	8	14.3 (6.16-28.1)	3	6.10 (1.26-17.8)
Salivary gland (142)	1	3.83 (0.10-21.3)	0		0		0	
Mouth (143-145)	7	9.89 (3.97-20.4)	3	8.47 (1.75-24.8)	9	11.4 (5.21-21.6)	5	7.38 (2.40-17.2)
Pharynx (146-149)	7	6.52 (2.62-13.4)	4	7.59 (2.07-19.4)	21	17.8 (11.0-27.2)	4	3.58 (0.98-9.16)
Oropharynx (146)	1	2.82 (0.07-15.7)	1	5.90 (0.15-32.9)	11	29.0 (14.5-51.8)	1	3.30 (0.08-18.4)
Nasopharynx (147)	1	2.93 (0.07-16.3)	0		1	2.49 (0.06-13.9)	0	
Hypopharynx (148)	4	12.6 (3.42-32.1)	3	18.5 (3.82-54.1)	5	15.1 (4.90-35.2)	2	6.60 (0.80-23.8)
Pharynx, unspecified (149)	1	17.0 (0.42-94.5)	0		4	57.5 (15.7-0147)	1	17.3 (0.43-96.2)
Stomach (151)	28	2.82 (1.87-4.07)	3	0.62 (0.13-1.81)	13	1.35 (0.72-2.31)	7	0.79 (0.32-1.62)
Liver (155) (-155.2)	6	3.37 (1.24-7.33)	2	2.25 (0.27-8.12)	4	1.90 (0.52-4.87)	1	0.40 (0.01-2.23)
Larynx (161)	2	1.34 (0.16-4.85)	1	1.36 (0.03-7.56)	8	5.02 (2.17-9.88)	6	4.19 (1.54-9.11)
Lung (162)	30	1.47 (0.99-2.10)	6	0.60 (0.22-1.31)	43	1.98 (1.43-2.67)	33	1.64 (1.13-2.31)
Female breast (174)	4	0.46 (0.12-1.17)	6	1.21 (0.44-2.63)	11	0.87 (0.43-1.56)	10	0.96 (0.46-1.76)
Cervix uteri (180)	0		1	1.66 (0.04-9.25)	2	1.40 (0.17-5.07)	2	1.96 (0.24-7.10)
Prostate (185)	21	1.24 (0.77-1.89)	7	0.85 (0.34-1.75)	17	0.99 (0.58-1.58)	10	0.57 (0.27-1.04)
Testis (186)	0		0		1	8.48 (0.21-47.2)	0	
Bladder (188,189.3,189.4)	9	1.39 (0.64-2.65)	2	0.64 (0.08-2.32)	9	1.34 (0.61-2.55)	8	1.30 (0.56-2.56)
Kidney (189) (-189.3,189.4)	10	3.09 (1.48-5.68)	3	1.82 (0.38-5.31)	8	2.22 (0.96-4.36)	1	0.31 (0.01-1.75)
Thyroid gland (193)	3	4.71 (0.97-13.8)	0		3	3.99 (0.82-11.7)	1	1.50 (0.04-8.37)
Non–Hodgkin lymphoma (200, 202)	3	0.96 (0.20-2.81)	0		2	0.54 (0.06-1.94)	1	0.29 (0.01-1.60)

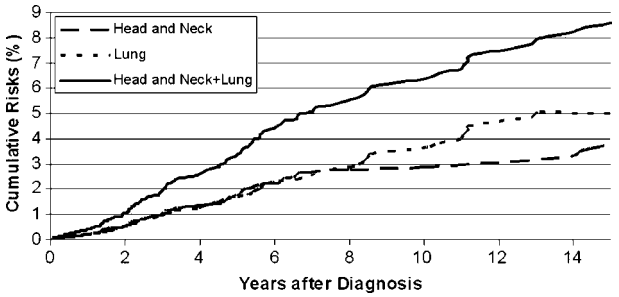

Figure 1. Cumulative risks of selected second cancers after primary esophagael SCC.

esophageal SCC developed within the first 6 months after the diagnosis, probably due to the increased surveillance and high mortality rate. In Europe, the 5-year survival rates for esophageal cancer were 5% for 1978 to 1980, 7% for 1981 to 1983, 8% for 1984 to 1986, 9% for 1987 to 1989 (21), and 8.5% for 1990 to 1994 (2). Patients who survive longer have a longer risk period in which a second primary cancer may develop. Thus, as esophageal cancer survival and diagnostic tools are improved, second primary cancers will become an important issue for esophageal cancer survivors.

It is well known that the most common sites for second primary cancers associated with esophageal cancer are the aerodigestive tract organs, which include the oral cavity, pharynx, larynx, and lung (13, 14, 22, 23). In our study, first primary esophageal tumors were associated with second primaries of the aerodigestive tract. The opposite association, between first primary aerodigestive tract tumors and second primary esophageal tumors was also observed. This association, particularly with head and neck cancers, has been described within the context of a ''field cancerization'' effect (24), in which carcinogenic effects from tobacco and alcohol that promote tumors on the aerodigestive tract may simultaneously act on other parts of the aerodigestive tract mucosa, thus triggering the development of multiple primary cancers that are independent of each other. Family history of upper aerodigestive tract cancers was also found to be associated with multiple occurrence of upper aerodigestive tract cancer in patients with esophageal cancer (25). In contrast to esophageal SCC, we did not observe significant associations between tobacco-related cancers with primary esophageal adenocarcinomas. This is consistent with the observation that the association of tobacco with esophageal adenocarcinoma is thought to be weaker than its association with esophageal SCC (26, 27).

The excess or marginal excess risk of second primaries in the stomach, liver, kidney, and thyroid glands after diagnosis of a first primary SCC of the esophagus were only observed within the first 6 months. The anatomic proximity of these cancer sites might have led to increased examination during follow-up examinations (surveillance bias), or a misdiagnosis of local spread of the primary esophageal cancer to other sites as a new primary. Surveillance bias to a distant organ, such as the

Table 4. Number of cases (*n*) and SIRs of esophageal cancer after selected first primary cancers, by follow-up duration

Site of the primary cancer (ICD-9)	<12 mo		1-4 y		5-9 y		≥10 y		Overall	
	n	SIR (95%CI)	*n*	SIR (95%CI)	*n*	SIR (95%CI)	*n*	SIR (95%CI)	*n*	SIR (95%CI)
Oral cavity, pharynx (140-149)	107	6.09 (4.99-7.36)	215	5.06 (4.41-5.79)	111	3.44 (2.83-4.15)	84	2.15 (1.72-2.66)	517	3.94 (3.60-4.29)
Lip (140)	11	1.66 (0.83-2.97)	31	1.43 (0.97-2.03)	22	1.18 (0.74-1.78)	43	1.72 (1.24-2.31)	107	1.48 (1.22-1.79)
Tongue (141)	22	9.90 (6.21-15.0)	46	11.2 (8.17-14.9)	21	7.78 (4.82-11.9)	9	3.55 (1.63-6.75)	98	8.47 (6.87-10.3)
Salivary gland (142)	3	2.37 (0.49-6.93)	5	1.57 (0.51-3.67)	3	1.21 (0.25-3.53)	6	1.46 (0.53-3.17)	17	1.54 (0.90-2.46)
Mouth (143-145)	29	8.67 (5.80-12.4)	75	10.9 (8.53-13.6)	40	8.94 (6.38-12.2)	15	3.93 (2.20-6.48)	159	8.57 (7.29-10.0)
Pharynx (146-149)	42	10.2 (7.37-13.8)	58	8.82 (6.70-11.4)	25	6.47 (4.19-9.55)	11	3.13 (1.56-5.60)	136	7.53 (6.32-8.91)
Oropharynx (146)	20	13.9 (8.50-21.5)	36	14.9 (10.4-20.6)	15	10.5 (5.86-17.3)	5	4.11 (1.34-9.60)	76	11.7 (9.21-14.6)
Nasopharynx (147)	0		2	0.84 (0.10-3.02)	0		1	0.58 (0.01-3.24)	3	0.43 (0.09-1.27)
Hypopharynx (148)	17	14.0 (8.18-22.5)	18	12.1 (7.20-19.2)	9	12.7 (5.83-24.2)	4	8.46 (2.31-21.7)	48	12.4 (9.14-16.4)
Pharynx, unspecified (149)	5	21.1 (6.85-49.2)	2	7.08 (0.86-25.6)	1	6.59 (0.16-36.7)	1	9.19 (0.23-51.2)	9	11.5 (5.28-21.9)
Stomach (151)	28	1.00 (0.66-1.44)	27	0.86 (0.57-1.25)	19	1.01 (0.61-1.58)	26	1.30 (0.85-1.91)	100	1.02 (0.83-1.24)
Liver (155) (-155.2)	4	1.95 (0.53-5.00)	2	1.34 (0.16-4.85)	0				6	1.10 (0.40-2.39)
Larynx (161)	22	2.95 (1.85-4.46)	65	3.34 (2.58-4.26)	49	3.36 (2.49-4.45)	46	3.24 (2.37-4.33)	182	3.27 (2.81-3.78)
Lung (162)	62	1.17 (0.90-1.50)	83	1.87 (1.49-2.32)	48	2.21 (1.63-2.92)	33	1.80 (1.24-2.53)	226	1.64 (1.44-1.87)
Female breast (174)	28	0.76 (0.50-1.09)	118	1.10 (0.91-1.32)	116	1.49 (1.23-1.79)	185	2.09 (1.80-2.42)	447	1.44 (1.31-1.58)
Cervix uteri (180)	5	1.09 (0.35-2.55)	28	2.33 (1.55-3.37)	21	1.82 (1.13-2.79)	47	1.37 (1.01-1.82)	101	1.62 (1.32-1.97)
Prostate (185)	79	0.91 (0.72-1.13)	175	0.87 (0.75-1.01)	90	1.02 (0.82-1.25)	33	0.93 (0.64-1.30)	377	0.92 (0.83-1.01)
Testis (186)	2	2.82 (0.34-10.2)	3	1.22 (0.25-3.56)	4	1.28 (0.35-3.27)	21	1.95 (1.21-2.98)	30	1.76 (1.19-2.51)
Bladder (188, 189.3, 189.4)	33	1.00 (0.69-1.41)	90	1.10 (0.89-1.36)	64	1.17 (0.90-1.49)	57	1.24 (0.94-1.60)	244	1.13 (1.00-1.29)
Kidney (189) (-189.3, 189.4)	11	1.01 (0.50-1.81)	23	0.99 (0.63-1.49)	14	0.92 (0.50-1.55)	13	0.92 (0.49-1.57)	61	0.96 (0.74-1.24)
Thyroid gland (193)	3	1.45 (0.30-4.24)	6	1.07 (0.39-2.33)	9	1.84 (0.84-3.50)	11	1.38 (0.69-2.47)	29	1.41 (0.95-2.03)
Hodgkin's lymphoma (201)	0		1	0.33 (0.01-1.83)	3	1.24 (0.25-3.61)	20	5.22 (3.19-8.05)	24	2.24 (1.44-3.34)
Non–Hodgkin lymphoma (200, 202)	9	0.80 (0.37-1.52)	33	1.42 (0.98-2.00)	20	1.47 (0.90-2.27)	21	1.98 (1.23-3.03)	107	1.41 (1.13-1.75)

kidney, would be possible because of the awareness of the first diagnosis. Diagnosis of a first cancer may persuade the patient to seek a more detailed examination; hence, the patient might find another coexisting cancer. Regular review after a cancer diagnosis may well increase the likelihood of a subsequent cancer at any anatomic site being detected and diagnosed. Advanced imaging techniques have improved the capability of diagnosing coexisting cancers in patients during follow-up examinations.

An excess of esophageal cancers as a second primary was also observed after first primary breast cancer in women, cervical cancer, testicular cancer, and lymphoma (Hodgkin's and non–Hodgkin's lymphoma). The association between these cancer sites and second primary esophageal cancer have also been observed in other studies (28-33). Possible explanations for this association are that radiotherapy and chemotherapy act directly or interact with other factors, such as hormonal status, cigarette smoking, and genetic susceptibility (34).

Although we observed various associations between esophageal cancer and other primary sites, our study has several limitations. First, because multiple comparisons were made, it is possible that some associations were due to chance, especially for those cancers with small numbers. On the other hand, the small sample size may also contribute to a lack of association. For example, with no cases of liver cancer and six cases of kidney cancer following esophageal adenocarcinoma, we were unable to detect their associations. Second, we are unable to explore whether therapy or shared risk factors such as smoking habits were responsible for some of the observed associations because we had no information on therapy or lifestyle factors. Third, surveillance bias may have affected our results. However, we estimated SIRs for follow-up periods after 1 year and observed relevant associations. Finally, we were unable to calculate the SIRs for second primary esophageal cancer by histology because reference rates were only calculated by cancer site. Nonetheless, the long follow-up and large sample size of the present study gave us a better opportunity than other studies to evaluate the risk for rare second cancers and conduct stratified analysis which may be a compromise with our limitations.

In conclusion, the results from our study suggest that as survival from esophageal cancer improves, second primary cancers will become a special concern for patients with esophageal cancer. We observed strong associations of first primary esophageal cancer with second primary head and neck cancers and lung cancer, suggesting that common risk factors play a role in multiple tumor development. Second primary cancers of the stomach, liver, and kidney occurred most frequently within 6 months after the diagnosis of first primary esophageal cancer. An excess of second primary esophageal cancer was observed after breast cancer in women, Hodgkin's lymphoma and non–Hodgkin lymphoma increased with longer follow-up times after diagnosis, suggesting a potential treatment effect.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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