

Table S1 Baseline characteristics of patients with first and second primary esophagus cancers: a population-based cohort study in US, 1975–2019

Variables	Patients with first primary esophagus cancer		Patients with second primary esophagus cancer	
	N	%	N	%
Total number	74,521	–	14,820	–
Age at diagnosis, year				
20–49	5,572	7.5	367	2.5
50–64	26,957	36.2	3,164	21.3
65–69	12,067	16.2	2,388	16.1
70–74	10,486	14.1	2,651	17.9
75–79	8,500	11.4	2,560	17.3
80–84	5,949	8.0	2,036	13.7
85+	4,990	6.7	1,654	11.2
Sex				
Female	16,993	22.8	3,828	25.8
Male	57,528	77.2	10,992	74.2
Race				
White	61,256	82.2	12,636	85.3
Black	8,465	11.4	1,506	10.2
Other	4,583	6.1	676	4.6
Unknown	217	0.3	2	0
Marital status				
Married (including common law)	40,100	53.8	8,270	55.8
Divorced	7,664	10.3	1,359	9.2
Separated	1,122	1.5	185	1.2
Single (never married)	11,798	15.8	1,710	11.5
Unmarried or Domestic Partner	120	0.2	19	0.1
Widowed	9,965	13.4	2,479	16.7
Unknown	3,752	5.0	798	5.4
Median household income in the county of residence				
<\$35,000	937	1.3	159	1.1
\$35,000–\$54,999	13,762	18.5	2,679	18.1
\$55,000–\$74,999	30,748	41.3	6,300	42.5
\$75,000+	21,032	28.2	4,573	30.9
Unknown/missing/no match/not 1990–2018	8,042	10.8	1,109	7.5

Table S1 (continued)

Table S1 (continued)

Variables	Patients with first primary esophagus cancer		Patients with second primary esophagus cancer	
	N	%	N	%
Rural-urban continuum				
Counties in metropolitan areas ge 1 million pop	36,788	49.4	7,891	53.2
Counties in metropolitan areas of 250,000 to 1 million pop	13,927	18.7	2,812	19.0
Counties in metropolitan areas of lt 250 thousand pop	5,635	7.6	1,175	7.9
Nonmetropolitan counties adjacent to a metropolitan area	5,697	7.6	1,048	7.1
Nonmetropolitan counties not adjacent to a metropolitan area	3,943	5.3	722	4.9
Unknown/missing/no match/not	8,531	11.4	1,172	7.9
Calendar period of diagnosis				
1975–1989	8,027	10.8	1,107	7.5
1990–1993	3,225	4.3	549	3.7
1994–1997	4,015	5.4	728	4.9
1998–2001	7,392	9.9	1,425	9.6
2002–2006	13,467	18.1	2,650	17.9
2007–2011	14,148	19	2,988	20.2
2012–2016	14,799	19.9	3,201	21.6
2017–2020	9,448	12.7	2,172	14.7
Tumor site				
C15.0-Cervical esophagus	1,564	2.1	527	3.6
C15.1-Thoracic esophagus	2,326	3.1	534	3.6
C15.2-Abdominal esophagus	629	0.8	110	0.7
C15.3-Upper third of esophagus	4,089	5.5	1,132	7.6
C15.4-Middle third of esophagus	13,246	17.8	2,799	18.9
C15.5-Lower third of esophagus	41,080	55.1	7,399	49.9
C15.8-Overlapping lesion of esophagus	3,501	4.7	632	4.3
C15.9-Esophagus, NOS	8,086	10.9	1,687	11.4
Tumor stage*				
Distant	25,823	34.7	4,169	28.1
Localized	15,620	21.0	3,890	26.2
Regional	22,224	29.8	4,038	27.2
Unknown	10,854	14.6	2,723	18.4

Table S1 (continued)

Table S1 (continued)

Variables	Patients with first primary esophagus cancer		Patients with second primary esophagus cancer	
	N	%	N	%
Histology				
Adenocarcinoma	39,613	53.2	7,181	48.5
Squamous cell carcinoma	27,992	37.6	6,347	42.8
Others	6,916	9.3	1,292	8.7
Grade				
Well differentiated	3,435	4.6	664	4.5
Moderately differentiated	21,681	29.1	4,347	29.3
Poorly differentiated	27,596	37.0	5,198	35.1
Undifferentiated; anaplastic	1,414	1.9	271	1.8
Unknown	20,395	27.4	4,340	29.3
Surgery				
Yes	19,297	25.9	3,136	21.2
No/Unknown	55,224	74.1	11,684	78.8
Chemotherapy				
Yes	39,798	53.4	7,188	48.5
No/unknown	34,723	46.6	7,632	51.5
Radiation therapy				
Yes	40,540	54.4	7,632	51.5
No/unknown	33,981	45.6	7,188	48.5

*, tumor staging was based on SEER historic staging, i.e., localized, regional, and distant to ensure the consistency across the long range of the study period. N, number; IR, incidence rate, per 100 person-years; NOS, not otherwise specified.

Table S2 Associations of second primary esophagus cancer with tumor and clinical characteristics, compared to patients with first primary esophagus cancer: a population-based cohort study in US

Variables	First primary esophagus cancer, OR/RRR	Second primary esophagus cancer, OR/RRR (95% CI)*
Tumor characteristics		
Tumor stage		
Localized tumor	1.00	1.27 (1.21–1.32)
Histology		
Adenocarcinoma	1.00	0.75 (0.72–0.78)
Squamous cell carcinoma	1.00	1.45 (1.39–1.51)
Tumor grade		
Well differentiated	1.00	1.01 (0.93–1.10)
Moderately differentiated	1.00	1.05 (1.01–1.10)
Poorly differentiated	1.00	0.94 (0.90–0.97)
Undifferentiated; anaplastic	1.00	1.02 (0.89–1.17)
Well/moderately differentiated	1.00	1.05 (1.01–1.09)
Poorly differentiated/undifferentiated	1.00	0.94 (0.90–0.98)
Tumor site		
Lower third of esophagus	1.00	0.79 (0.76–0.82)
Treatment modalities		
Surgery	1.00	0.90 (0.85–0.94)
Chemotherapy	1.00	0.95 (0.91–0.99)
Radiation therapy	1.00	0.94 (0.90–0.97)

*, the models were adjusted for age and calendar period at diagnosis, sex, race, marital status, median household income in the county of residence and rural-urban continuum. For treatment modalities analysis, the models were additionally adjusted for tumor characteristics. Tumor characteristics were presented by relative risk ratio while treatment modalities were presented with odds ratio. OR, odds ratio; RRR, relative risk ratio; CI, confidence interval.

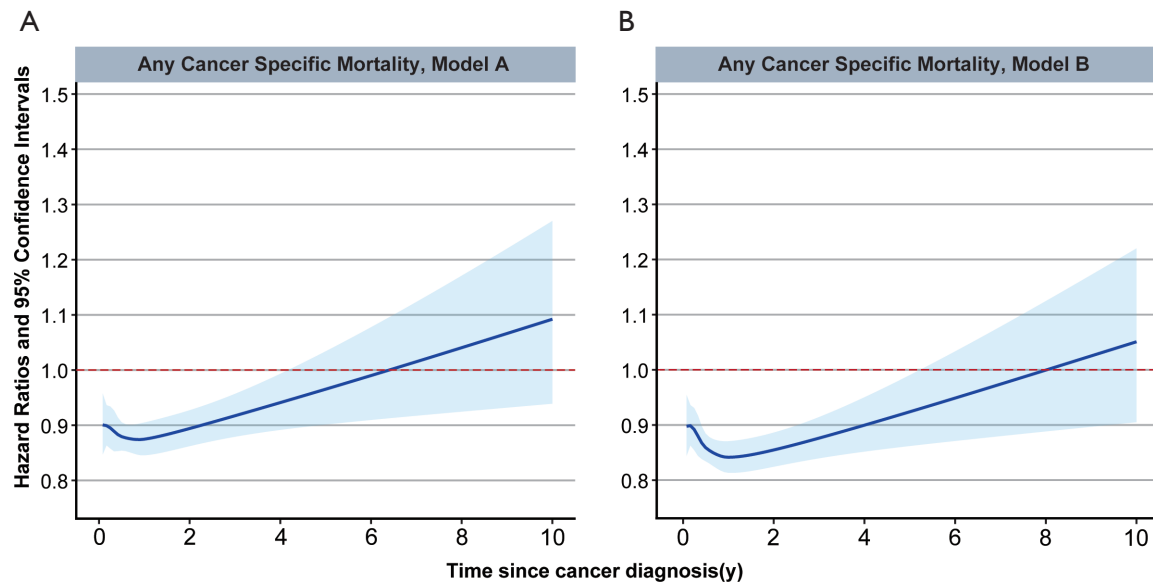


Figure S1 Hazards ratios (HRs) of any cancer-specific mortality among patients with second primary esophageal cancer from cancer diagnosis to 10 years afterwards, compared to patients with first primary esophageal cancer in the United States, 1975-2019. HRs were estimated from flexible parametric survival models, and allowing the effects of second primary esophageal cancer to vary over time. The baseline rate is using a straight line of 5 degree of freedom (4 intermediate knots, two knots on each boundary, placed at one-fifth of the events distribution), while 3 degree of freedom is used for the time-varying effect. HRs in model A (A) were adjusted for age and calendar period at diagnosis, sex, race, cohabitation status, median household income in the county of residence and rural-urban continuum. HRs in model B (B) were additionally adjusted for tumor stage, histology, tumor grade and treatment modalities.

Table S3 Associations of second primary esophagus cancer with esophagus cancer specific mortality or non-cancer related mortality, compared to patients with first primary esophagus cancer, using competing risk model: a population-based cohort study in US

Variables	No. (%) of patients	From 0 to <1 year after diagnosis		From 1 to <5 years after diagnosis		From 5 to 10 years of follow-up after diagnosis	
		N (IR)	HR (95% CI)*	N (IR)	HR (95% CI)*	N (IR)	HR (95% CI)*
Esophagus cancer specific mortality							
First primary esophagus cancer	74,521	34,008 (74.0)	1.00	14,524 (16.9)	1.00	928 (1.4)	1.00
Second primary esophagus cancer	14,820	6,018 (67.0)	0.78 (0.76–0.80)	2,500 (15.6)	0.82 (0.79–0.86)	151 (1.5)	0.85 (0.71–1.01)
Non-cancer related mortality							
First primary esophagus cancer	74,521	4,295 (9.3)	1.00	2,866 (3.3)	1.00	1,351 (2.1)	1.00
Second primary esophagus cancer	14,820	1,804 (20.1)	1.99 (1.89–2.11)	1,006 (6.3)	1.59 (1.47–1.71)	372 (3.7)	1.33 (1.18–1.50)

*, HRs were adjusted for age and calendar period at diagnosis, sex, race, marital status, median household income in the county of residence, rural-urban continuum, tumor stage, histology, tumor grade, surgery, radiation therapy, and chemotherapy. N, number of deaths; IR, incidence rate per 100 person-years; CI, confidence interval; HR, hazard ratio.

Table S4 HRs of cancer specific mortality among patients with second primary esophagus cancer (esophagus-2), stratified by demographic, tumor, and clinical characteristics, compared to patients with first primary esophagus cancer (esophagus-1): a population-based cohort study in US, 1975–2019

Variables	From 0 to <1 year after diagnosis			From 1 to <5 years after diagnosis			From 5 to 10 years after diagnosis		
	Esophagus-1, N (IR)	Esophagus-2, N (IR)	HR (95% CI)	Esophagus-1, N (IR)	Esophagus-2, N (IR)	HR (95% CI)	Esophagus-1, N (IR)	Esophagus-2, N (IR)	HR (95% CI)
Age at diagnosis, year									
20–64	13,848 (64.3)	1,260 (54.2)	0.81 (0.76–0.86)	6,997 (16.3)	639 (14.6)	0.83 (0.77–0.90)	457 (1.3)	33 (1.0)	0.73 (0.51–1.04)
≥65	20,160 (82.6)	4,758 (71.5)	0.86 (0.84–0.89)	7,527 (17.5)	1,861 (16.0)	0.89 (0.85–0.94)	471 (1.6)	118 (1.7)	0.94 (0.76–1.15)
Sex									
Male	25,995 (72.6)	4,406 (66.0)	0.84 (0.82–0.87)	11,410 (17.1)	1,843 (15.6)	0.86 (0.82–0.91)	709 (1.4)	106 (1.4)	0.89 (0.72–1.10)
Female	8,013 (79.0)	1,612 (70.0)	0.85 (0.81–0.90)	3,114 (16.1)	5,040 (14.4)	0.92 (0.85–1.00)	219 (1.4)	45 (1.6)	0.90 (0.64–1.26)
Race									
White	27,326 (71.3)	5,116 (66.3)	0.86 (0.84–0.89)	12,210 (16.6)	2,154 (15.3)	0.87 (0.83–0.91)	805 (1.4)	133 (1.5)	0.88 (0.73–1.07)
Black	4,455 (94.0)	633 (73.8)	0.79 (0.73–0.86)	1,483 (20.2)	230 (17.8)	0.83 (0.72–0.96)	84 (1.7)	15 (2.2)	1.03 (0.57–1.85)
Other/unknown	2,227 (76.7)	269 (66.6)	0.73 (0.64–0.83)	831 (16.0)	116 (18.0)	1.23 (1.01–1.51)	39 (1.0)	3 (0.7)	0.62 (0.17–2.26)
Cohabitation status									
No	15,530 (90.1)	2,560 (79.2)	0.83 (0.80–0.87)	5,277 (18.2)	891 (17.2)	0.88 (0.82–0.95)	331 (1.7)	42 (1.5)	0.70 (0.50–0.97)
Yes	16,893 (63.9)	3,159 (59.9)	0.87 (0.83–0.90)	8,580 (16.3)	1,491 (14.9)	0.88 (0.83–0.93)	563 (1.4)	103 (1.5)	1.01 (0.81–1.25)
Unknown	1,585 (69.9)	299 (63.6)	0.79 (0.70–0.90)	667 (15.0)	118 (14.3)	0.90 (0.73–1.10)	34 (1.0)	6 (1.3)	0.81 (0.31–2.12)
Median household income in the county of residence									
<\$55,000	6,676 (75.0)	1,126 (66.9)	0.80 (0.75–0.85)	2,777 (17.0)	473 (16.6)	0.92 (0.84–1.02)	170 (1.5)	22 (1.4)	0.79 (0.50–1.26)
\$55,000+	22,678 (69.3)	4,320 (64.4)	0.86 (0.83–0.89)	10,378 (16.3)	1,864 (15.0)	0.87 (0.83–0.92)	673 (1.4)	122 (1.5)	0.89 (0.73–1.09)
Unknown/missing/no match/not 1990–2018	4,654 (107.6)	572 (98.1)	0.88 (0.81–0.96)	1,369 (23.1)	163 (22.3)	0.84 (0.71–0.99)	85 (2.1)	7 (2.0)	1.38 (0.60–3.19)
Rural-urban continuum									
Metropolitan counties	24,793 (70.1)	4,682 (64.1)	0.85 (0.82–0.88)	11,149 (16.3)	2,039 (15.2)	0.89 (0.85–0.93)	718 (1.4)	130 (1.5)	0.87 (0.72–1.05)
Nonmetropolitan counties	4,284 (71.7)	737 (70.1)	0.82 (0.75–0.88)	1,922 (16.9)	285 (16.1)	0.84 (0.74–0.96)	123 (1.4)	14 (1.3)	0.97 (0.54–1.74)
Unknown/missing/no match/not 1990–2018	4,931 (106.9)	599 (96.5)	0.87 (0.80–0.95)	1,453 (22.8)	176 (22.2)	0.85 (0.72–0.99)	87 (1.9)	7 (1.8)	1.35 (0.59–3.11)
Calendar period at diagnosis									
1975–1989	4,652 (107.7)	571 (98.1)	0.88 (0.81–0.96)	1,368 (23.1)	162 (22.3)	0.84 (0.71–0.99)	85 (2.1)	7 (2.0)	1.39 (0.60–3.20)
1990–2006	13,654 (78.4)	2,344 (73.2)	0.86 (0.82–0.89)	5,993 (17.7)	991 (16.9)	0.89 (0.83–0.95)	484 (1.5)	78 (1.6)	0.88 (0.69–1.12)
2007–2020	15,702 (64.8)	3,103 (59.7)	0.85 (0.81–0.88)	7,163 (15.5)	1,347 (14.3)	0.92 (0.86–0.97)	359 (1.3)	66 (1.3)	0.90 (0.69–1.19)
Tumor stage									
Localized	4,429 (37.8)	1,036 (37.1)	0.82 (0.77–0.88)	3,008 (9.6)	649 (9.7)	0.87 (0.80–0.95)	359 (1.2)	70 (1.3)	0.88 (0.68–1.15)
Regional	8,024 (49.7)	1,367 (47.6)	0.84 (0.79–0.89)	5,726 (17.5)	920 (16.9)	0.89 (0.83–0.95)	384 (1.7)	54 (1.7)	0.94 (0.70–1.26)
Distant	15,779 (126.8)	2,382 (123.1)	0.90 (0.86–0.94)	4,059 (31.2)	559 (29.0)	0.90 (0.82–0.99)	83 (1.7)	6 (1.1)	0.52 (0.22–1.22)
Unknown	5,776 (102.1)	1,233 (89.4)	0.79 (0.74–0.84)	1,731 (19.3)	372 (18.9)	0.84 (0.75–0.85)	102 (1.6)	21 (2.0)	1.16 (0.70–1.92)

Table S4 (continued)

Table S4 (continued)

Variables	From 0 to <1 year after diagnosis			From 1 to <5 years after diagnosis			From 5 to 10 years after diagnosis		
	Esophagus-1, N (IR)	Esophagus-2, N (IR)	HR (95% CI)	Esophagus-1, N (IR)	Esophagus-2, N (IR)	HR (95% CI)	Esophagus-1, N (IR)	Esophagus-2, N (IR)	HR (95% CI)
Histology									
Adenocarcinoma	15,924 (60.1)	2,738 (59.0)	0.88 (0.85–0.92)	8,436 (16.1)	1,287 (14.9)	0.91 (0.86–0.97)	528 (1.3)	78 (1.3)	0.91 (0.71–1.16)
Squamous cell carcinoma	14,299 (86.2)	2,684 (70.4)	0.80 (0.77–0.84)	5,193 (18.2)	1,069 (16.6)	0.86 (0.80–0.92)	340 (1.6)	67 (1.7)	0.89 (0.68–1.17)
Other	3,785 (131.0)	596 (114.5)	0.83 (0.76–0.91)	895 (17.0)	144 (15.4)	0.74 (0.62–0.89)	60 (1.4)	6 (1.1)	0.64 (0.26–1.57)
Tumor grade (differentiation)									
Well	1,176 (48.1)	215 (47.6)	0.76 (0.65–0.89)	676 (10.8)	90 (8.3)	0.75 (0.60–0.95)	71 (1.2)	10 (1.1)	0.71 (0.35–1.42)
Moderate	9,127 (62.5)	1,670 (58.1)	0.87 (0.83–0.92)	5,000 (16.4)	861 (15.1)	0.84 (0.78–0.90)	376 (1.6)	58 (1.5)	0.84 (0.63–1.11)
Poor	14,060 (84.2)	2,418 (79.9)	0.88 (0.84–0.92)	5,895 (20.5)	3,981 (27.4)	0.92 (0.86–0.98)	287 (1.4)	51 (1.8)	1.12 (0.82–1.52)
Undifferentiated	753 (94.4)	129 (81.9)	0.77 (0.63–0.93)	271 (20.2)	47 (17.2)	0.75 (0.54–1.04)	15 (1.4)	3 (1.5)	0.49 (0.12–2.04)
Unknown	8,892 (78.0)	1,586 (64.3)	0.79 (0.75–0.83)	2,682 (14.0)	521 (13.1)	0.90 (0.82–0.99)	179 (1.3)	29 (1.2)	0.67 (0.44–1.02)
Surgery									
No/unknown	30,085 (101.6)	5,432 (85.2)	0.85 (0.82–0.87)	9,691 (23.7)	1,857 (22.4)	0.83 (0.77–0.91)	525 (1.8)	59 (1.3)	0.82 (0.63–1.09)
Yes	3,923 (24.0)	586 (22.5)	0.87 (0.79–0.95)	4,833 (10.7)	643 (9.3)	0.90 (0.85–0.94)	403 (1.1)	92 (1.6)	0.94 (0.75–1.19)
Radiation therapy									
No/unknown	17,464 (102.5)	3,227 (90.5)	0.84 (0.81–0.88)	4,515 (13.6)	808 (12.2)	0.84 (0.78–0.90)	346 (1.2)	51 (1.0)	0.71 (0.53–0.97)
Yes	16,544 (57.2)	2,791 (51.6)	0.86 (0.82–0.89)	10,009 (19.0)	1,692 (18.0)	0.90 (0.85–0.95)	582 (1.7)	100 (1.9)	0.99 (0.80–1.23)
Chemotherapy									
No/unknown	19,118 (116.0)	3,596 (97.8)	0.83 (0.80–0.86)	4,032 (12.8)	808 (12.4)	0.85 (0.79–0.82)	342 (1.2)	58 (1.2)	0.82 (0.61–1.09)
Yes	14,890 (50.5)	2,422 (45.7)	0.87 (0.83–0.91)	10,492 (19.2)	1692 (17.8)	0.89 (0.84–0.93)	586 (1.6)	93 (1.8)	0.94 (0.75–1.17)

HRs were adjusted for age and calendar period at diagnosis, sex, race, cohabitation status, Median household income in the county of residence, Rural-urban continuum, tumor stage, histology, tumor grade, surgery, radiation therapy, and chemotherapy, if applicable. N, number of deaths; IR, incidence rate per 100 person-years; HR, hazard ratio; CI, confidence interval.

Table S5 HRs of overall mortality among patients with second primary esophagus cancer (esophagus-2), stratified by demographic, tumor, and clinical characteristics, compared to patients with first primary esophagus cancer (esophagus-1): a population-based cohort study in US, 1975–2019

Variables	From 0 to <1 year after diagnosis			From 1 to <5 years after diagnosis			From 5 to 10 years after diagnosis		
	Esophagus-1, N (IR)	Esophagus-2, N (IR)	HR (95% CI)	Esophagus-1, N (IR)	Esophagus-2, N (IR)	HR (95% CI)	Esophagus-1, N (IR)	Esophagus-2, N (IR)	HR (95% CI)
Age at diagnosis, year									
20–64	16,734 (77.7)	1,853 (79.7)	1.01 (0.96–1.06)	8695 (20.3)	966 (22.0)	1.00 (0.94–1.07)	1,066 (2.9)	118 (3.6)	1.09 (0.90–1.32)
≥65	24,956 (102.3)	6,589 (99.1)	0.98 (0.95–1.00)	10,175 (23.6)	2,841 (24.5)	1.01 (0.97–1.05)	1,454 (5.0)	450 (6.4)	1.17 (1.05–1.30)
Sex									
Male	31,909 (89.1)	6,260 (93.8)	0.98 (0.96–1.01)	14,800 (22.2)	2,831 (24.0)	0.99 (0.95–1.04)	1,919 (3.9)	410 (5.6)	1.12 (1.01–1.25)
Female	9,781 (96.4)	2,182 (94.7)	0.96 (0.92–1.01)	4,070 (21.0)	976 (22.3)	1.04 (0.97–1.12)	601 (4.0)	158 (5.6)	1.20 (0.99–1.44)
Race									
White	33,520 (87.5)	7,100 (92.0)	0.99 (0.96–1.01)	15,853 (21.6)	3,276 (23.3)	0.99 (0.96–1.03)	2,153 (3.8)	501 (5.5)	1.13 (1.02–1.25)
Black	5,512 (116.3)	943 (109.9)	0.95 (0.89–1.02)	1,935 (26.4)	375 (29.0)	1.04 (0.92–1.16)	241 (4.9)	49 (7.3)	1.11 (0.80–1.54)
Other/unknown	2,658 (91.6)	399 (98.8)	0.91 (0.82–1.02)	1,082 (20.9)	156 (24.2)	1.25 (1.05–1.49)	126 (3.4)	18 (4.1)	1.20 (0.69–2.10)
Cohabitation status									
No	19,049 (110.5)	3,559 (110.2)	0.95 (0.92–0.99)	6,984 (24.1)	1,392 (26.8)	1.01 (0.96–1.08)	873 (4.5)	174 (6.0)	1.00 (0.84–1.18)
Yes	20,663 (78.1)	4,432 (84.0)	1.00 (0.97–1.03)	10,988 (20.9)	2,220 (22.2)	1.00 (0.95–1.04)	1,542 (3.7)	370 (5.4)	1.20 (1.06–1.34)
Unknown	1,978 (87.2)	451 (95.9)	0.96 (0.87–1.07)	898 (20.2)	195 (23.6)	1.07 (0.91–1.26)	105 (3.2)	24 (5.1)	1.08 (0.65–1.77)
Median household income in the county of residence									
<\$55,000	8,291 (93.2)	1,651 (98.1)	0.94 (0.89–0.99)	3,608 (22.0)	706 (24.8)	1.04 (0.95–1.13)	438 (3.8)	102 (6.5)	1.23 (0.98–1.55)
\$55,000+	27,695 (84.6)	5,992 (89.3)	0.98 (0.95–1.01)	13,427 (21.1)	2,836 (22.8)	1.00 (0.96–1.04)	1,841 (3.8)	441 (5.3)	1.07 (0.96–1.19)
Unknown/missing/no match/not 1990–2018	5,704 (131.8)	799 (137.0)	1.03 (0.95–1.11)	1,835 (30.9)	265 (36.3)	1.02 (0.90–1.17)	241 (5.8)	25 (7.0)	1.90 (1.21–3.00)
Rural-urban continuum									
Metropolitan counties	30,376 (85.9)	6,562 (89.8)	0.98 (0.95–1.00)	14,471 (21.2)	3,076 (22.9)	1.00 (0.96–1.04)	1,921 (3.7)	485 (5.6)	1.10 (1.00–1.22)
Nonmetropolitan counties	5,287 (88.5)	1,043 (99.2)	0.94 (0.88–1.01)	2,451 (21.5)	447 (25.3)	1.01 (0.91–1.12)	340 (3.9)	56 (5.4)	1.27 (0.94–1.71)
Unknown/missing/no match/not 1990–2018	6,027 (130.7)	837 (134.8)	1.02 (0.95–1.10)	1,948 (30.6)	284 (35.9)	1.03 (0.91–1.17)	259 (5.8)	27 (6.8)	1.86 (1.20–2.88)
Calendar period at diagnosis									
1975–1989	5,698 (132.0)	798 (137.2)	1.03 (0.95–1.11)	1,829 (30.9)	264 (36.3)	1.03 (0.90–1.17)	240 (5.8)	25 (7.0)	1.90 (1.20–2.99)
1990–2006	16,639 (95.6)	3,285 (102.6)	0.99 (0.95–1.03)	7,737 (22.9)	1,494 (25.5)	1.01 (0.95–1.07)	1,360 (4.2)	290 (6.1)	1.07 (0.93–1.22)
2007–2020	19,353 (79.9)	4,359 (83.9)	0.97 (0.94–1.00)	9,304 (20.1)	2,049 (21.8)	1.04 (0.99–1.09)	920 (3.2)	253 (4.9)	1.22 (1.05–1.41)
Tumor stage									
Localized	5,773 (49.3)	1,594 (57.1)	1.00 (0.94–1.05)	4,372 (13.9)	1,134 (17.0)	1.04 (0.97–1.11)	1,105 (3.6)	282 (5.1)	1.11 (0.97–1.27)
Regional	9,781 (60.6)	1,861 (64.9)	0.94 (0.89–0.99)	7,279 (22.3)	1,304 (24.0)	0.98 (0.92–1.04)	908 (4.1)	174 (5.5)	1.15 (0.97–1.36)
Distant	18,893 (151.8)	3,097 (160.0)	0.98 (0.94–1.02)	4,891 (37.6)	768 (39.8)	1.02 (0.94–1.10)	194 (3.9)	32 (5.8)	1.19 (0.79–1.79)
Unknown	7,243 (128.0)	1,890 (137.1)	0.99 (0.94–1.04)	2,328 (25.9)	601 (30.5)	1.02 (0.93–1.11)	313 (4.9)	80 (7.7)	1.35 (1.04–1.76)

Table S5 (continued)

Table S5 (continued)

Variables	From 0 to <1 year after diagnosis			From 1 to <5 years after diagnosis			From 5 to 10 years after diagnosis		
	Esophagus-1, N (IR)	Esophagus-2, N (IR)	HR (95% CI)	Esophagus-1, N (IR)	Esophagus-2, N (IR)	HR (95% CI)	Esophagus-1, N (IR)	Esophagus-2, N (IR)	HR (95% CI)
Histology									
Adenocarcinoma	19,884 (75.1)	3,782 (81.5)	0.98 (0.95–1.02)	10,865 (20.8)	1,909 (22.1)	1.01 (0.96–1.06)	1,315 (3.3)	275 (4.8)	1.10 (0.96–1.26)
Squamous cell carcinoma	17,043 (102.8)	3,760 (98.6)	0.95 (0.92–0.99)	6,745 (23.7)	1,644 (25.5)	1.01 (0.96–1.07)	1,016 (4.9)	258 (6.5)	1.18 (1.02–1.36)
Other	4,763 (164.9)	900 (172.8)	1.03 (0.96–1.11)	1,260 (24.0)	254 (27.2)	0.92 (0.80–1.06)	189 (4.4)	35 (6.3)	0.94 (0.62–1.42)
Tumor grade (differentiation)									
Well	1,503 (61.4)	328 (72.7)	0.92 (0.81–1.03)	943 (15.1)	159 (14.7)	0.93 (0.78–1.11)	219 (3.7)	47 (5.1)	1.01 (0.72–1.42)
Moderate	11,178 (76.5)	2,316 (80.6)	1.00 (0.96–1.05)	6,455 (21.2)	1,328 (23.2)	0.98 (0.92–1.04)	924 (3.9)	196 (5.2)	1.13 (0.96–1.33)
Poor	16,885 (101.1)	3,270 (108.0)	1.00 (0.97–1.04)	7,387 (25.7)	1,385 (9.5)	1.02 (0.96–1.08)	786 (3.9)	170 (6.1)	1.15 (0.97–1.36)
Undifferentiated	927 (116.2)	174 (110.5)	0.84 (0.70–0.99)	339 (25.3)	69 (25.3)	0.83 (0.63–1.09)	42 (3.9)	10 (5.0)	0.30 (0.09–0.94)
Unknown	11,197 (98.2)	2,354 (95.4)	0.94 (0.90–0.98)	3,746 (19.5)	866 (21.8)	1.05 (0.97–1.13)	549 (3.9)	145 (5.9)	1.13 (0.92–1.37)
Surgery									
No/unknown	36,593 (123.5)	7,564 (118.7)	0.98 (0.95–1.00)	12,460 (30.5)	2,778 (33.5)	1.03 (0.98–1.07)	1,135 (3.9)	320 (7.3)	1.12 (0.98–1.27)
Yes	5,097 (31.2)	878 (33.7)	0.99 (0.92–1.07)	6,410 (14.2)	1,029 (14.9)	0.95 (0.89–1.02)	1,385 (3.9)	248 (4.3)	1.14 (0.99–1.32)
Radiation therapy									
No/unknown	21,941 (128.8)	4,704 (131.9)	0.99 (0.96–1.03)	6,159 (18.5)	1,378 (20.8)	1.03 (0.97–1.10)	985 (3.3)	229 (4.5)	1.04 (0.89–1.21)
Yes	19,749 (68.3)	3,738 (69.1)	0.96 (0.93–1.00)	12,711 (24.1)	2,429 (25.9)	0.99 (0.95–1.04)	1,535 (4.4)	339 (6.6)	1.18 (1.05–1.33)
Chemotherapy									
No/unknown	23,806 (144.5)	5,224 (142.1)	0.98 (0.95–1.01)	5,666 (18.0)	1,393 (21.4)	1.04 (0.98–1.11)	1,030 (3.5)	250 (5.0)	1.06 (0.92–1.22)
Yes	17,884 (60.7)	3,218 (60.7)	0.96 (0.93–1.00)	13,204 (24.2)	2,414 (25.5)	0.98 (0.94–1.03)	1,490 (4.2)	318 (6.0)	1.17 (1.03–1.32)

HRs were adjusted for age and calendar period at diagnosis, sex, race, cohabitation status, Median household income in the county of residence, Rural-urban continuum, tumor stage, histology, tumor grade, surgery, radiation therapy, and chemotherapy, if applicable. N, number of deaths; IR, incidence rate per 100 person-years; HR, hazard ratio; CI, confidence interval.

Table S6 HRs of non-cancer related mortality among patients with second primary esophagus cancer (esophagus-2), stratified by demographic, tumor, and clinical characteristics, compared to patients with first primary esophagus cancer (esophagus-1): a population-based cohort study in US, 1975–2019

Variables	From 0 to <1 year after diagnosis			From 1 to <5 years after diagnosis			From 5 to 10 years after diagnosis		
	Esophagus-1, N (IR)	Esophagus-2, N (IR)	HR (95% CI)	Esophagus-1, N (IR)	Esophagus-2, N (IR)	HR (95% CI)	Esophagus-1, N (IR)	Esophagus-2, N (IR)	HR (95% CI)
Age at diagnosis, year									
20–64	1,356 (6.3)	429 (18.4)	2.53 (2.26–2.82)	957 (2.2)	226 (5.2)	1.96 (1.69–2.27)	486 (1.3)	75 (2.3)	1.47 (1.14–1.89)
≥65	2,939 (12.0)	1,375 (20.7)	1.71 (1.60–1.82)	1,909 (4.4)	780 (6.7)	1.43 (1.32–1.56)	865 (3.0)	297 (4.2)	1.29 (1.13–1.47)
Sex									
Male	3,281 (9.2)	1,372 (20.6)	1.89 (1.78–2.02)	2,189 (3.3)	751 (6.4)	1.53 (1.41–1.67)	1,029 (2.1)	271 (3.7)	1.25 (1.08–1.43)
Female	1,014 (10.0)	432 (18.8)	1.83 (1.63–2.05)	677 (3.5)	255 (4.7)	1.50 (1.30–1.74)	322 (2.1)	101 (3.6)	1.49 (1.18–1.89)
Race									
White	3,430 (9.0)	1,485 (19.2)	1.85 (1.74–1.97)	2,395 (3.3)	864 (6.1)	1.48 (1.37–1.61)	1,149 (2.0)	331 (3.6)	1.30 (1.14–1.47)
Black	589 (12.4)	234 (27.3)	2.08 (1.77–2.43)	301 (4.1)	109 (8.4)	1.85 (1.47–2.33)	132 (2.7)	29 (4.3)	1.15 (0.74–1.80)
Other/unknown	276 (9.5)	85 (21.1)	1.80 (1.40–2.31)	170 (3.3)	33 (5.1)	1.62 (1.09–2.41)	70 (1.9)	12 (2.7)	1.44 (0.71–2.90)
Cohabitation status									
No	2,006 (11.6)	775 (24.0)	1.86 (1.71–2.02)	1,176 (4.1)	390 (7.5)	1.49 (1.33–1.68)	455 (2.3)	116 (4.0)	1.17 (0.94–1.46)
Yes	2,060 (7.8)	914 (17.3)	1.88 (1.73–2.03)	1,527 (2.9)	557 (5.6)	1.53 (1.38–1.69)	837 (2.0)	239 (3.5)	1.33 (1.15–1.55)
Unknown	229 (10.1)	115 (24.4)	1.94 (1.54–2.46)	163 (3.7)	59 (7.1)	1.62 (1.17–2.22)	59 (1.8)	17 (3.6)	1.23 (0.67–2.28)
Median household income in the county of residence									
<\$55,000	830 (9.3)	373 (22.2)	1.94 (1.71–2.20)	523 (3.2)	174 (6.1)	1.54 (1.29–1.84)	235 (2.1)	73 (4.7)	1.49 (1.11–1.99)
\$55,000+	2845 (8.7)	1,239 (18.5)	1.81 (1.69–1.94)	2,030 (3.2)	750 (6.0)	1.50 (1.37–1.63)	989 (2.0)	283 (3.4)	1.19 (1.04–1.37)
Unknown/missing/no match/not 1990–2018	620 (14.3)	192 (32.9)	2.12 (1.80–2.50)	313 (5.3)	82 (11.2)	1.76 (1.37–2.27)	127 (3.1)	16 (4.5)	2.53 (1.40–4.57)
Rural-urban continuum									
Metropolitan counties	3,129 (8.8)	1,392 (19.1)	1.84 (1.72–1.96)	2,197 (3.2)	797 (5.9)	1.46 (1.34–1.58)	1,019 (2.0)	315 (3.6)	1.25 (1.09–1.42)
Nonmetropolitan counties	514 (8.6)	214 (20.4)	1.87 (1.59–2.20)	342 (3.0)	122 (6.9)	1.71 (1.38–2.13)	190 (2.2)	39 (3.8)	1.55 (1.07–2.24)
Unknown/missing/no match/not 1990–2018	652 (14.1)	198 (31.9)	2.09 (1.77–2.45)	327 (5.1)	87 (11.0)	1.80 (1.41–2.31)	142 (3.2)	18 (4.6)	2.48 (1.42–4.32)
Calendar period at diagnosis									
1975–1989	618 (14.3)	192 (33.0)	2.12 (1.80–2.50)	308 (5.2)	82 (11.3)	1.80 (1.40–2.32)	127 (3.1)	16 (4.5)	2.54 (1.40–4.58)
1990–2006	1,708 (9.8)	703 (22.0)	1.85 (1.69–2.02)	1,154 (3.4)	393 (6.7)	1.52 (1.35–1.72)	742 (2.3)	188 (3.9)	1.18 (1.00–1.40)
2007–2020	1,969 (8.1)	909 (17.5)	1.83 (1.69–1.98)	1,404 (3.0)	531 (5.6)	1.50 (1.36–1.66)	482 (1.7)	168 (3.3)	1.44 (1.20–1.73)
Tumor stage									
Localized	1,010 (8.6)	453 (16.2)	1.64 (1.46–1.83)	1,094 (3.5)	405 (6.1)	1.41 (1.26–1.59)	654 (2.1)	191 (3.5)	1.21 (1.02–1.43)
Regional	1,123 (7.0)	365 (12.7)	1.57 (1.40–1.78)	976 (3.0)	295 (5.4)	1.48 (1.29–1.69)	430 (1.9)	103 (3.3)	1.37 (1.09–1.71)
Distant	1,170 (9.4)	461 (23.8)	2.27 (2.03–2.53)	357 (2.7)	130 (6.7)	2.05 (1.66–2.54)	89 (1.8)	24 (4.4)	1.92 (1.14–3.23)
Unknown	992 (17.5)	525 (38.1)	2.03 (1.82–2.26)	439 (4.9)	176 (8.9)	1.53 (1.28–1.83)	178 (2.8)	54 (5.2)	1.50 (1.08–2.08)

Table S6 (continued)

Table S6 (continued)

Variables	From 0 to <1 year after diagnosis			From 1 to <5 years after diagnosis			From 5 to 10 years after diagnosis		
	Esophagus-1, N (IR)	Esophagus-2, N (IR)	HR (95% CI)	Esophagus-1, N (IR)	Esophagus-2, N (IR)	HR (95% CI)	Esophagus-1, N (IR)	Esophagus-2, N (IR)	HR (95% CI)
Histology									
Adenocarcinoma	2,027 (7.7)	714 (15.4)	1.59 (1.46–1.74)	1,468 (2.8)	450 (5.2)	1.43 (1.28–1.59)	673 (1.7)	171 (3.0)	1.17 (0.98–1.39)
Squamous cell carcinoma	1,809 (10.9)	857 (22.5)	1.96 (1.80–2.13)	1,170 (4.1)	471 (7.3)	1.58 (1.42–1.76)	571 (2.7)	174 (4.4)	1.43 (1.20–1.71)
Other	459 (15.9)	233 (44.7)	2.74 (2.33–3.22)	228 (4.3)	85 (9.1)	1.67 (1.29–2.17)	107 (2.5)	27 (4.9)	1.29 (0.78–2.14)
Tumor grade (differentiation)									
Well	208 (8.5)	86 (19.1)	1.70 (1.31–2.20)	196 (3.1)	54 (5.0)	1.40 (1.02–1.93)	128 (2.2)	37 (4.0)	1.28 (0.85–1.93)
Moderate	1,304 (8.9)	482 (16.8)	1.65 (1.48–1.83)	968 (3.2)	350 (6.1)	1.49 (1.31–1.69)	463 (2.0)	119 (3.1)	1.33 (1.08–1.63)
Poor	1,461 (8.7)	611 (20.2)	1.98 (1.79–2.18)	932 (3.2)	310 (2.1)	1.60 (1.40–1.82)	427 (2.1)	104 (3.8)	1.18 (0.94–1.47)
Undifferentiated	73 (9.1)	34 (21.6)	2.37 (1.52–3.70)	37 (2.8)	19 (7.0)	1.99 (1.08–3.65)	24 (2.2)	6 (3.0)	0.12 (0.02–0.78)
Unknown	1,249 (11.0)	591 (23.9)	2.01 (1.82–2.22)	733 (3.8)	273 (6.9)	1.50 (1.30–1.73)	309 (2.2)	106 (4.3)	1.42 (1.12–1.81)
Surgery									
No/unknown	3,480 (11.7)	1,568 (24.6)	1.97 (1.86–2.10)	1,828 (4.5)	709 (8.5)	1.59 (1.45–1.74)	623 (2.1)	209 (4.7)	1.27 (1.08–1.49)
Yes	815 (5.0)	236 (9.1)	1.49 (1.29–1.73)	1,038 (2.3)	297 (4.3)	1.35 (1.18–1.54)	728 (2.1)	163 (2.8)	1.29 (1.08–1.54)
Radiation therapy									
No/unknown	2,352 (13.8)	1,087 (30.5)	1.99 (1.85–2.14)	1,042 (3.1)	426 (6.4)	1.64 (1.46–1.85)	540 (1.8)	160 (3.1)	1.24 (1.02–1.49)
Yes	1,943 (6.7)	717 (13.3)	1.74 (1.59–1.89)	1,824 (3.5)	580 (6.2)	1.44 (1.31–1.59)	811 (2.3)	212 (4.1)	1.31 (1.12–1.53)
Chemotherapy									
No/unknown	2,651 (16.1)	1,258 (34.2)	2.04 (1.90–2.18)	1,199 (3.8)	469 (7.2)	1.56 (1.40–1.75)	587 (2.0)	176 (3.5)	1.21 (1.02–1.45)
Yes	1,644 (5.6)	546 (10.3)	1.59 (1.44–1.75)	1,667 (3.1)	537 (5.7)	1.48 (1.34–1.64)	764 (2.2)	196 (3.7)	1.31 (1.11–1.54)

HRs were adjusted for age and calendar period at diagnosis, sex, race, cohabitation status, Median household income in the county of residence, Rural-urban continuum, tumor stage, histology, tumor grade, surgery, radiation therapy, and chemotherapy, if applicable. N, number of deaths; IR, incidence rate per 100 person-years; HR, hazard ratio; CI, confidence interval.

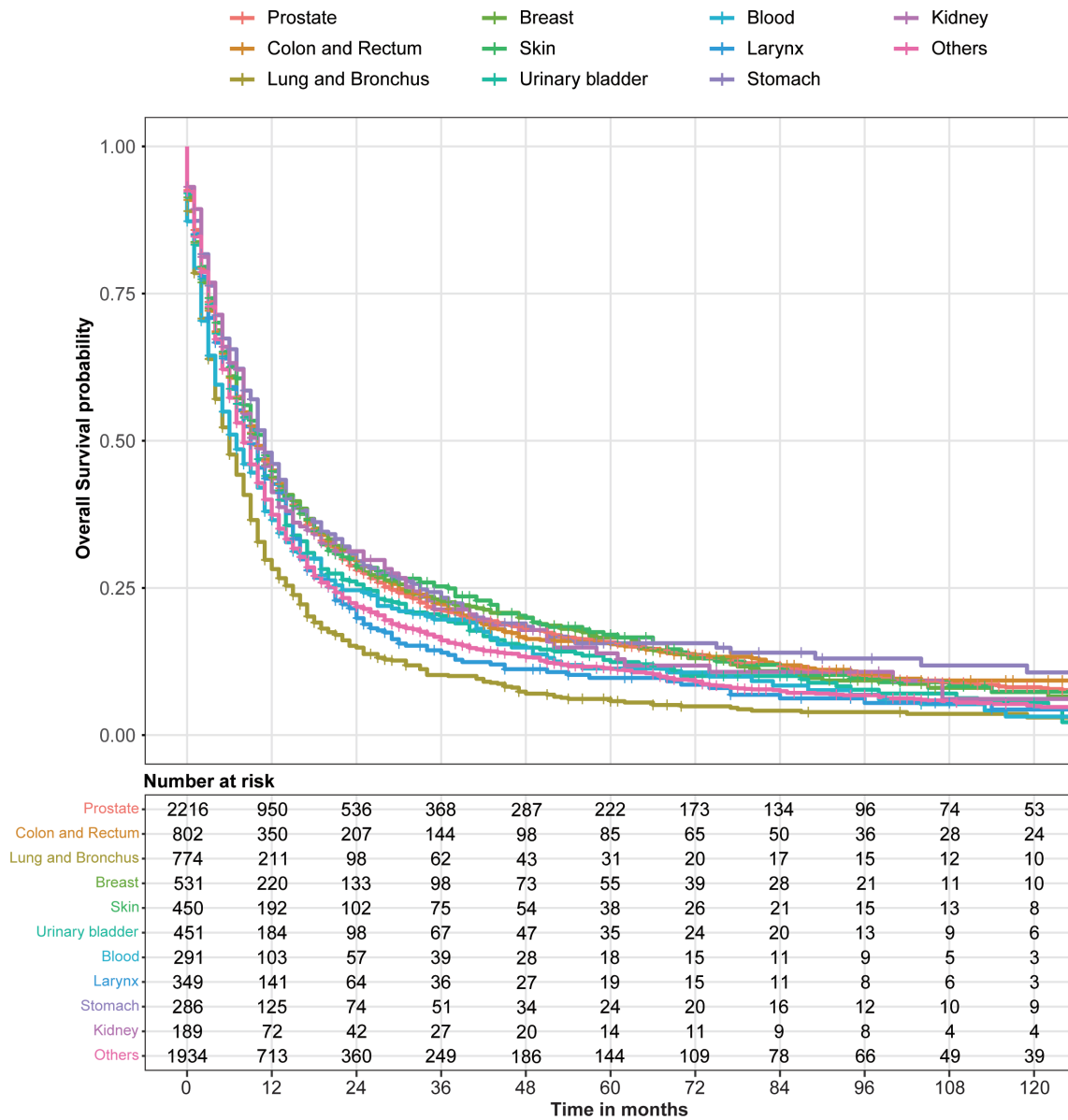


Figure S2 The comparisons of overall survival among second primary esophagus cancer patients with different sites of first malignancy.