Original Article

Effect of prior cancer history on survival of patients with esophageal carcinoma: a propensity score matching, population-based study

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Background: When conducting esophageal cancer clinical trials, prior cancer history is frequently considered an exclusion criterion due to the assumption that prior malignancy may exert significant interference with the prognosis in patients with esophageal carcinoma. This study aimed to evaluate the impact of prior cancer on survival of patients with esophageal cancer and provide valuable assistance for trial design.

Methods: Data regarding patients diagnosed with esophageal cancer between 2011 and 2016 were extracted from the Surveillance, Epidemiology, and End Results (SEER) database and divided into two groups depending on the presence or absence of prior cancer history. Propensity score matching (PSM) was performed to minimize the confounding bias caused by covariates. Subsequently, Kaplan-Meier analysis and multivariate Cox proportional hazards models were used to compare all-cause and esophageal cancer-specific survival between patients with and without prior cancer.

Results: Among 17,123 patients with esophageal carcinoma included in this study, 2,224 (13%) patients had prior cancer history. Before PSM, Kaplan-Meier curves between the two groups classified by prior cancer history showed no significant differences in all-cause (HR =1.047, 95% CI: 0.995–1.102, P=0.077) and esophageal cancer-specific survival (HR =0.986, 95% CI: 0.928–1.048, P=0.65). Similar results were obtained after PSM. In multivariate Cox analysis, prior malignancy was not significantly associated with all-cause (HR =1.002, 95% CI: 0.936–1.072, P=0.965) and esophageal cancer-specific survival (HR =0.964, 95% CI: 0.890–1.045, P=0.374). Subgroup analysis stratified by timing of prior cancer demonstrated that prior cancer had no significant effect on prognosis in the recent latency period subgroups (P>0.05). Furthermore, patients with a prior cancer of lung and bronchus (P=0.013) or head and neck (P=0.012) displayed significantly worse survival than patients without prior cancer, while other types of prior cancer showed no significant effect.

Conclusions: The findings suggest that prior cancer is likely not a definite factor that has an impact on all-cause and esophageal cancer-specific survival. Therefore, exclusion criteria of prior cancer history in esophageal cancer clinical trials should be seriously reconsidered.

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Introduction

Esophageal cancer is the ninth most common type of tumor in both sexes worldwide (1). Squamous cell carcinoma and adenocarcinoma are two typical histological subtypes. While squamous cell carcinoma accounts for approximately 87% of cases worldwide, a recent study has found that the incidence rate of esophageal adenocarcinoma is rapidly increasing or even exceeding that of squamous cell carcinoma in some developed countries (2). With a high mortality, which ranks seventh among all cancer types (3), esophageal carcinoma carries a relatively poor prognosis, considering that the 5-year survival rate is approximately 20% in Europe and the United States and less than 5% in low- and middle-income countries (4).

Given that prior malignancy is commonly believed to affect the prognosis of cancer patients, prior cancer history is regularly regarded as a common exclusion criterion in many clinical trials (5-7). A previous study employing pan-cancer analysis has suggested that prior cancer has varying impact on overall survival depending on the type of previous cancer (8). For instance, several studies on nasopharyngeal carcinoma, advanced breast cancer, and lung cancer have shown no significant impact of prior malignancy on survival (9-11). However, for laryngeal cancer and ovarian cancer, prior cancer history adversely interferes with prognosis (12,13). Except for one small-scale study that has merely shown no adverse effect for patients with stage IV esophageal cancer (14), there is no other study to confirm the influence of prior cancer diagnosis on survival across all stages of esophageal carcinoma. Therefore, the common understanding may lead to excessive exclusion criteria, eventually weakening the efficacy of clinical trials. To address this issue, this study used the Surveillance, Epidemiology, and End Results (SEER) database to precisely evaluate the impact of prior cancer on survival of patients with esophageal cancer across all stages and guide the formulation of eligibility criteria for clinical trials. We present the following article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-21-1707/rc).

Methods

Study design and patients

Clinical data of patients with esophageal carcinoma were obtained from the SEER database using the SEER*Stat software version 8.3.9 (https://seer.cancer.gov/, accession number 12569-Nov2020) (15). The SEER database sponsored by the National Cancer Institute provides population-based cancer incidence data that cover approximately 34.6% of the U. S. population. Individuals with a histologically confirmed esophageal carcinoma between 2011 and 2016 were identified to ensure at least a 5-year follow-up period in this study. The exclusion criteria were as follows: (I) age at diagnosis <18 years; (II) incomplete survival data and follow-up survival information; (III) diagnosis made at autopsy or via death certificates only. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Demographic and clinicopathological data, including age at diagnosis, sex, race, marital status, primary site, grade, histology recode-broad groupings, American Joint Committee on Cancer (AJCC) Stage Group (6^{th}), surgical information, radiotherapy and chemotherapy records, cause of death, and follow-up information, were extracted from the SEER database. Age at diagnosis (a continuous variable) was converted to a categorical variable (<65 and ≥65 years). The race was categorized into White, Black, and others (American Indian/AK Native, Asian/Pacific Islander). Marital status was classified as married, single, separated/widowed/divorced (sep/wid/div), and unknown. The histological type was described as adenoma and adenocarcinoma, squamous cell carcinoma, and others.

Prior cancer history was determined from the SEER sequence number, as described in a previous study (8). The sequence number represents the order of all malignancies diagnosed over the lifetime. The interval time between the diagnosis of esophageal carcinoma and the most recent

prior cancer was calculated by SEER*Stat Program and was subsequently divided into 6–12 months, 1–5 years, 5–10 years, and >10 years for further analysis.

Study outcomes

The primary outcome was all-cause survival, which referred to the interval time from the date of diagnosis to the date of death caused by all reasons, including esophageal cancer and other diseases, or last follow-up calculated by the SEER*Stat Program. The secondary outcome was esophageal cancer-specific survival, and patients were censored if they died from causes other than esophageal cancer. We evaluated the impact of prior cancer on prognosis of patients with esophageal carcinoma by analyzing all-cause survival and esophageal cancer-specific survival.

Statistical analysis

According to prior cancer history, patients in this study were divided into two groups, including the group with prior cancer and the group without prior cancer. The Pearson chi-square test was applied to analyze the differences between the two groups. We employed the propensity score matching (PSM) method to balance the confounding bias caused by covariates, including age, sex, race, marital status, primary site, grade, histological type, stage, surgical information, and radiotherapy and chemotherapy records (16). A one-to-one nearest PSM between patients with prior cancer and without prior cancer was performed with a caliper of 0.2. An adjusted cohort was built for subsequent analysis. The Kaplan-Meier analysis was utilized to compare survival function via log-rank tests in all-cause and esophageal cancer-specific survival. Multivariate propensity score-adjusted Cox proportional hazards models were also constructed incorporating covariates such as age, sex, race, marital status, primary site, grade, histological type, AJCC stage, surgical information, radiotherapy, and chemotherapy records to identify independent predictors of survival. Furthermore, subgroup analysis stratified by age, sex, race, grade, histological type, and AJCC stage of esophageal carcinoma, as well as timing, type, and stage of prior cancer was conducted to investigate the impact of prior malignancy on prognosis more deeply. Two-tailed P values <0.05 were considered statistically significant. Statistical analysis was performed using R software (version 4.0.1).

Results

Patients characteristics

In this study, 17,123 eligible patients with esophageal carcinoma were identified from the SEER database, including 2,224 (13%) patients with prior cancer and 14,899 (87%) patients without prior cancer. Esophageal carcinoma most often occurred in male White individuals aged ≥65 years. The most frequent primary site at diagnosis was the lower third of the esophagus (54.5% for the group with prior cancer; 61.5% for the group without prior cancer). In terms of histological types, adenoma and adenocarcinoma had a slightly higher incidence rate than squamous cell carcinoma (53.7% *vs.* 37.8%, respectively, for the group with prior cancer; 61.9% *vs.* 29.6%, respectively, for the group without prior cancer). Compared with cases without prior malignancy, patients with prior cancer were more often older than 65 years (77.9% *vs.* 55.1%, P<0.001), White (86.1% *vs.* 84.6%, P=0.003), and married (56.9% *vs.* 52.7%, P<0.001), and they were also more likely to have squamous cell carcinoma (37.8% *vs.* 29.6%, P<0.001). Patients with prior cancer less often received surgical treatments (21.5% *vs.* 25.0%, P<0.001), radiotherapy (51.2% *vs.* 56.6%, P<0.001), and chemotherapy (54.2% *vs.* 63.2%, P<0.001). After adjustment for the propensity scores, all variables were well-balanced between patients with and without prior cancer (P>0.05). *Table 1* summarizes the baseline characteristics of patients with esophageal carcinoma who died of all causes and esophageal carcinoma grouped by prior cancer history both before PSM and after PSM. *Figure 1* depicts the types, diagnostic time, and stage of prior cancer. Prostate cancer (31.79%), gastrointestinal tumor (17.36%), head and neck tumor (14.52%), and genitourinary tumor (11.74%) were the most common types of prior cancer. The median time between the diagnostic time of the recent prior cancer and the esophageal cancer was 69 months. As shown in *Figure 1B*, 1–5 years occupied most of the timing of prior cancer. Almost 35.43% esophageal cancer patients with prior cancer did not have a record of prior cancer stage (*Figure 1C*).

Table 1 Baseline characteristics of patients with esophageal carcinoma in original dataset and matched dataset

Characteristics	Death from all-cause						Death from esophageal cancer					
	Before PSM			After PSM			Before PSM			After PSM		
	No prior cancer, N=14,899 (87.0%)	With prior cancer, N=2,224 (13.0%)	P	No prior cancer, N=2,224 (50%)	With prior cancer, N=2,224 (50%)	P	No prior cancer, N=12,804 (88.1%)	With prior cancer, N=1,728 (11.9%)	P	No prior cancer, N=1,728 (50.0%)	With prior cancer, N=1,728 (50.0%)	P
Age (years)			<0.001			0.402			<0.001			1.000
<65	6,685 (44.9)	491 (22.1)		467 (21.0)	491 (22.1)		5,865 (45.8)	385 (22.3)		384 (22.2)	385 (22.3)	
≥65	8,214 (55.1)	1,733 (77.9)		1,757 (79.0)	1,733 (77.9)		6,939 (54.2)	1,343 (77.7)		1,344 (77.8)	1,343 (77.7)	
Gender			0.184			0.080			0.356			0.546
Female	3,052 (20.5)	428 (19.2)		382 (17.2)	428 (19.2)		2,646 (20.7)	340 (19.7)		325 (18.8)	340 (19.7)	
Male	11,847 (79.5)	1,796 (80.8)		1,842 (82.8)	1,796 (80.8)		10,158 (79.3)	1,388 (80.3)		1,403 (81.2)	1,388 (80.3)	
Race			0.003			0.293			0.017			0.282
Black	1,444 (9.7)	221 (9.9)		194 (8.7)	221 (9.9)		1,199 (9.4)	166 (9.6)		153 (8.9)	166 (9.6)	
White	12,600 (84.6)	1,915 (86.1)		1,950 (87.7)	1,915 (86.1)		10,856 (84.8)	1,490 (86.2)		1,518 (87.8)	1,490 (86.2)	
Others/unknown	855 (5.7)	88 (4.0)		80 (3.6)	88 (4.0)		749 (5.8)	72 (4.2)		57 (3.3)	72 (4.2)	
Marital status			<0.001			0.779			<0.001			0.916
Married	7,845 (52.7)	1,266 (56.9)		1,265 (56.9)	1,266 (56.9)		6,802 (53.1)	985 (57.0)		1,005 (58.2)	985 (57.0)	
Single	2,755 (18.5)	239 (10.7)		243 (10.9)	239 (10.7)		2,352 (18.4)	186 (10.8)		178 (10.3)	186 (10.8)	
Sep/wid/div	3,357 (22.5)	550 (24.7)		531 (23.9)	550 (24.7)		2,840 (22.2)	426 (24.7)		416 (24.1)	426 (24.7)	
Unknown	942 (6.3)	169 (7.6)		185 (8.3)	169 (7.6)		810 (6.3)	131 (7.6)		129 (7.5)	131 (7.6)	
Primary site			<0.001			0.895			<0.001			0.803
Cervical esophagus	239 (1.6)	78 (3.5)		69 (3.1)	78 (3.5)		201 (1.6)	55 (3.2)		46 (2.7)	55 (3.2)	
Thoracic esophagus	528 (3.5)	91 (4.1)		92 (4.1)	91 (4.1)		463 (3.6)	70 (4.1)		55 (3.2)	70 (4.1)	
Abdominal esophagus	84 (0.6)	13 (0.6)		9 (0.4)	13 (0.6)		68 (0.5)	10 (0.6)		9 (0.5)	10 (0.6)	
Upper third of esophagus	704 (4.7)	161 (7.2)		158 (7.1)	161 (7.2)		602 (4.7)	114 (6.6)		103 (6.0)	114 (6.6)	
Middle third of esophagus	2,135 (14.3)	383 (17.2)		375 (16.9)	383 (17.2)		1,863 (14.6)	293 (17.0)		301 (17.4)	293 (17.0)	
Lower third of esophagus	9,165 (61.5)	1,211 (54.5)		1,244 (55.9)	1,211 (54.5)		7,848 (61.3)	972 (56.2)		988 (57.2)	972 (56.2)	
Overlapping lesion of esophagus	680 (4.6)	75 (3.4)		63 (2.8)	75 (3.4)		603 (4.7)	59 (3.4)		61 (3.5)	59 (3.4)	
Esophagus, NOS	1,364 (9.2)	212 (9.5)		214 (9.6)	212 (9.5)		1,156 (9.0)	155 (9.0)		165 (9.5)	155 (9.0)	

Table 1 (*continued*)

Table 1 (*continued*)

Characteristics	Death from all-cause						Death from esophageal cancer					
	Before PSM			After PSM			Before PSM			After PSM		
	No prior cancer, N=14,899 (87.0%)	With prior cancer, N=2,224 (13.0%)	P	No prior cancer, N=2,224 (50%)	With prior cancer, N=2,224 (50%)	P	No prior cancer, N=12,804 (88.1%)	With prior cancer, N=1,728 (11.9%)	P	No prior cancer, N=1,728 (50.0%)	With prior cancer, N=1,728 (50.0%)	P
Grade			0.230			0.775			0.470			0.892
Well differentiated	732 (4.9)	99 (4.5)		91 (4.1)	99 (4.5)		639 (5.0)	74 (4.3)		74 (4.3)	74 (4.3)	
Moderately differentiated	4,956 (33.3)	738 (33.2)		712 (32.0)	738 (33.2)		4,248 (33.2)	584 (33.8)		561 (32.5)	584 (33.8)	
Poorly differentiated	6,122 (41.1)	882 (39.7)		888 (39.9)	882 (39.7)		5,282 (41.3)	694 (40.2)		699 (40.5)	694 (40.2)	
Undifferentiated	180 (1.2)	27 (1.2)		32 (1.4)	27 (1.2)		155 (1.2)	25 (1.4)		23 (1.3)	25 (1.4)	
Unknown	2,909 (19.5)	478 (21.5)		501 (22.5)	478 (21.5)		2,480 (19.4)	351 (20.3)		371 (21.5)	351 (20.3)	
Histology type			<0.001			0.683			<0.001			0.793
Squamous cell carcinoma	4,416 (29.6)	841 (37.8)		817 (36.7)	841 (37.8)		3,831 (29.9)	646 (37.4)		656 (38.0)	646 (37.4)	
Adenoma and adenocarcinoma	9,222 (61.9)	1,194 (53.7)		1,223 (55.0)	1,194 (53.7)		7,916 (61.8)	948 (54.9)		948 (54.9)	948 (54.9)	
Other types	1,261 (8.5)	189 (8.5)		184 (8.3)	189 (8.5)		1,057 (8.3)	134 (7.8)		124 (7.2)	134 (7.8)	
AJCC stage (6th)			<0.001			0.562			<0.001			0.626
I	1,992 (13.4)	420 (18.9)		383 (17.2)	420 (18.9)		1,691 (13.2)	303 (17.5)		287 (16.6)	303 (17.5)	
II	2,685 (18.0)	447 (20.1)		447 (20.1)	447 (20.1)		2,332 (18.2)	360 (20.8)		332 (19.2)	360 (20.8)	
III	3,138 (21.1)	363 (16.3)		391 (17.6)	363 (16.3)		2,755 (21.5)	311 (18.0)		326 (18.9)	311 (18.0)	
IV	5,265 (35.3)	606 (27.2)		621 (27.9)	606 (27.2)		4,516 (35.3)	497 (28.8)		509 (29.5)	497 (28.8)	
Unknown	1,819 (12.2)	388 (17.4)		382 (17.2)	388 (17.4)		1,510 (11.8)	257 (14.9)		274 (15.9)	257 (14.9)	
Surgery			<0.001			0.826			0.006			0.416
No/unknown	11,167 (75.0)	1,745 (78.5)		1,752 (78.8)	1,745 (78.5)		9,431 (73.7)	1,327 (76.8)		1,348 (78.0)	1,327 (76.8)	
Yes	3,732 (25.0)	479 (21.5)		472 (21.2)	479 (21.5)		3,373 (26.3)	401 (23.2)		380 (22.0)	401 (23.2)	
Radiotherapy			<0.001			0.118			0.010			0.811
No/unknown	6,472 (43.4)	1,086 (48.8)		1,033 (46.4)	1,086 (48.8)		5,460 (42.6)	794 (45.9)		786 (45.5)	794 (45.9)	
Yes	8,427 (56.6)	1,138 (51.2)		1,191 (53.6)	1,138 (51.2)		7,344 (57.4)	934 (54.1)		942 (54.5)	934 (54.1)	
Chemotherapy			<0.001			0.416			<0.001			0.428
No/unknown	5,481 (36.8)	1,018 (45.8)		990 (44.5)	1,018 (45.8)		4,575 (35.7)	742 (42.9)		718 (41.6)	742 (42.9)	
Yes	9,418 (63.2)	1,206 (54.2)		1,234 (55.5)	1,206 (54.2)		8,229 (64.3)	986 (57.1)		1,010 (58.4)	986 (57.1)	

PSM, propensity score matching; Sep/wid/div, separated/widowed/divorced; NOS, not otherwise specified; AJCC, American Joint Committee on Cancer.

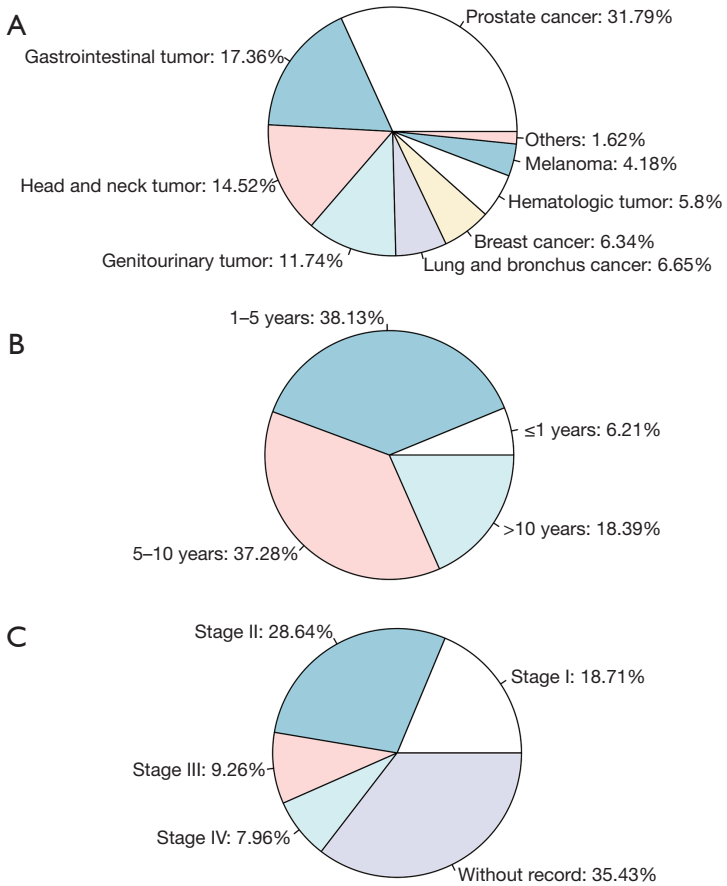

Figure 1 Distribution of type (A), diagnostic time (B), and stage (C) of prior cancer for patients with esophageal carcinoma.

Effect of prior cancer on all-cause and esophageal cancer-specific survival

To evaluate the impact of prior malignancy on survival, Kaplan-Meier survival curves before PSM did not demonstrate significant difference between patients with prior cancer and those without prior cancer in terms of all-cause survival (HR =1.047, 95% CI: 0.995–1.102, P=0.077) (*Figure 2A*) and esophageal cancer-specific survival (HR =0.986, 95% CI: 0.928–1.048, P=0.65) (*Figure 2B*), which implied that prior cancer probably had no adverse effect on prognosis of patients with esophageal cancer. For patients with prior cancer history, the 1-, 3-, and 5-year all-cause survival rates were 45.2%, 22.2%, and 15.6%, respectively. For patients with no prior malignancy, the 1-, 3-, and 5-year all-cause survival rates were 46.5%, 24.3%, and 17.5%, respectively.

After PSM, the survival curves also showed no significant difference between the two groups in terms of all-cause (HR =1.025, 95% CI: 0.958–1.097, P=0.45) (*Figure 2C*) and esophageal cancer-specific survival (HR =0.967, 95% CI: 0.893–1.047, P=0.41) (*Figure 2D*). Multivariate covariate-adjusted Cox regression models revealed that prior malignancy history was not significantly associated with inferior all-cause (HR =1.002, 95% CI: 0.936–1.072, P=0.965) and esophageal cancer-specific survival (HR =0.964, 95% CI: 0.890–1.045, P=0.374) (*Table 2*).

Figure 3A shows the results of subgroup analysis stratified by age, sex, race, grade, histological type, and AJCC stage of esophageal cancer. Except for subgroups of undifferentiated pathological grade, stage I, and stage II, other groups indicated that prior cancer history was not significantly related to the overall survival. For esophageal cancer-specific survival, subgroup analysis stratified by age, sex, race, grade, histological type, and stage of the index cancer showed similar tendency to that of all-cause survival (*Figure 3B*).

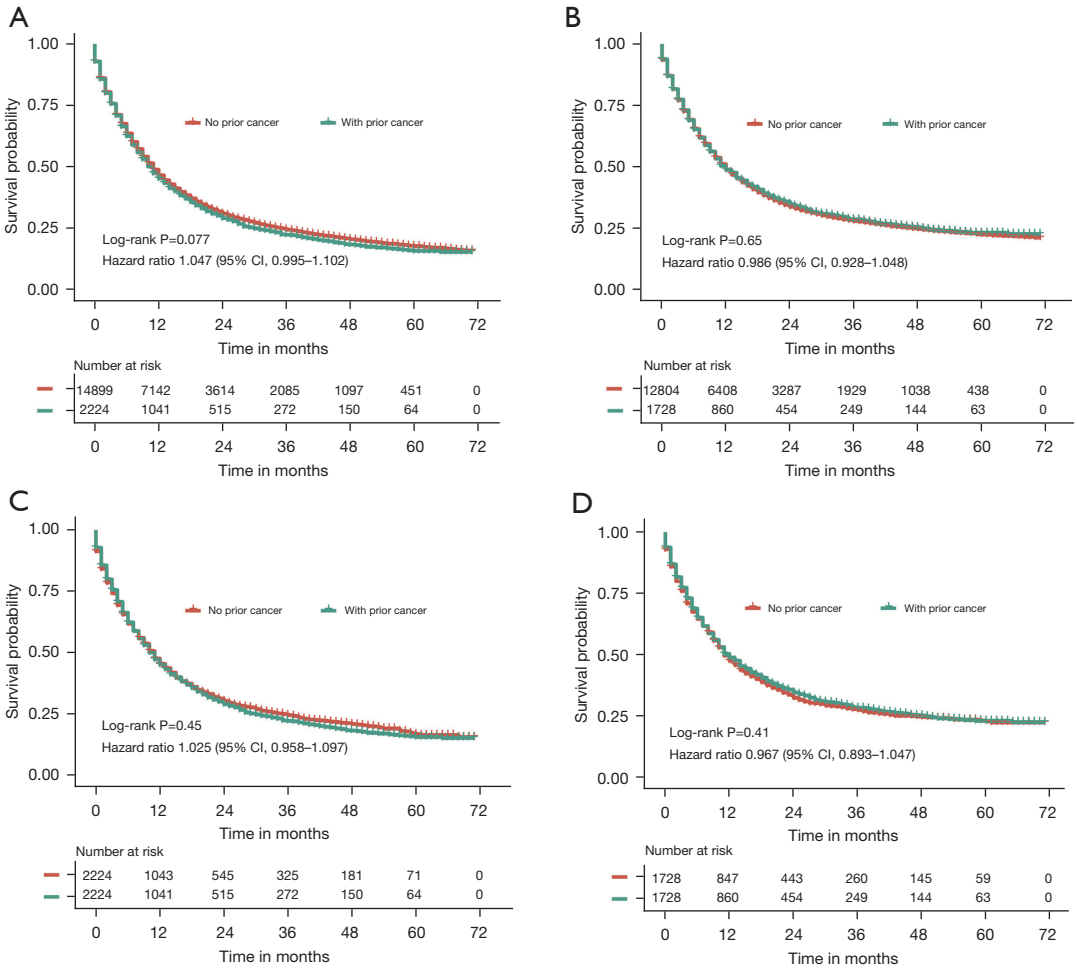

Figure 2 Evaluation of prior cancer impact on all-cause and esophageal cancer-specific survival. (A) Kaplan-Meier curves of prior cancer impact on all-cause survival before PSM; (B) Kaplan-Meier curves of prior cancer impact on esophageal cancer-specific survival before PSM; (C) Kaplan-Meier curves of prior cancer impact on all-cause survival after PSM; (D) Kaplan-Meier curves of prior cancer impact on esophageal cancer-specific survival after PSM. PSM, propensity score matching.

Effect of the diagnostic time, type, and stage of prior cancer on overall survival

Figure 4 illustrates the subgroup analysis stratified by the latency period between prior cancer and esophageal cancer diagnosis, which further investigated the effect of prior cancer on survival. In subgroups of 6–12 months, 1–5 years, and 5–10 years, prior cancer displayed no significant effect on prognosis (P>0.05). For the subgroup of >10 years, patients without prior cancer showed a slightly better survival than patients with previous malignancy (P=0.0096). Multivariate covariate-adjusted Cox regression models for the subgroup analyses stratified by latency period are shown in *Table 3*, and they confirmed that prior cancer history was not an independent risk factor for overall survival in any of the subgroups.

Figure 5 shows overall survival stratified according to the type and stage of prior cancer. Among all of the recorded types of prior cancer, patients with lung and bronchus cancer (P=0.013) or head and neck cancer (P=0.012) had significantly inferior survival compared with patients without prior cancer, while patients with other types of prior cancer showed similar overall survival to those without prior cancer. In subgroup analysis stratified by stage of prior cancer, the survival function of patients with stage I, II, III, and IV prior cancer did not display significant difference compared with patients without prior cancer history.

Table 2 Multivariable Cox regression analysis for all-cause and esophageal cancer-specific survival

Variables	All-cause adjusted HR (95% CI)	P value	Esophageal cancer-specific adjusted HR (95% CI)	P value
Prior cancer				
No prior cancer	Reference		Reference	
With prior cancer	1.002 (0.936, 1.072)	0.965	0.964 (0.890, 1.045)	0.374
Age (years)				
<65	Reference		Reference	
≥65	1.121 (1.028, 1.222)	0.010	1.122 (1.0133, 1.242)	0.027
Gender				
Female	Reference		Reference	
Male	1.151 (1.049, 1.262)	0.003	1.159 (1.041, 1.291)	0.007
Race				
Black	Reference		Reference	
White	1.022 (0.906, 1.154)	0.721	0.943 (0.817, 1.088)	0.421
Others/unknown	0.858 (0.695, 1.060)	0.157	1.009 (0.793, 1.284)	0.943
Marital status				
Married	Reference			
Single	1.062 (0.948, 1.191)	0.300	1.161 (1.015, 1.329)	0.030
Sep/wid/div	1.206 (1.109, 1.312)	<0.001	1.193 (1.080, 1.318)	<0.001
Unknown	0.894 (0.782, 1.021)	0.099	0.869 (0.739, 1.022)	0.090
Primary site				
Abdominal esophagus	Reference		Reference	
Cervical esophagus	0.542 (0.334, 0.878)	0.013	0.781 (0.452, 1.349)	0.376
Thoracic esophagus	0.634 (0.395, 1.018)	0.059	0.856 (0.501, 1.464)	0.570
Upper third of esophagus	0.594 (0.374, 0.944)	0.027	0.724 (0.430, 1.219)	0.224
Middle third of esophagus	0.590 (0.376, 0.927)	0.022	0.842 (0.509, 1.393)	0.504
Lower third of esophagus	0.602 (0.386, 0.938)	0.025	0.857 (0.522, 1.406)	0.541
Overlapping lesion of esophagus	0.704 (0.437, 1.136)	0.150	0.943 (0.553, 1.608)	0.829
Esophagus, NOS	0.591 (0.375, 0.934)	0.024	0.831 (0.499, 1.383)	0.475
Grade				
Well differentiated	Reference		Reference	
Moderately differentiated	1.648 (1.349, 2.013)	<0.001	1.606 (1.245, 2.072)	<0.001
Poorly differentiated	2.017 (1.654, 2.461)	<0.001	1.968 (1.529, 2.534)	<0.001
Undifferentiated	2.593 (1.838, 3.658)	<0.001	2.657 (1.789, 3.948)	<0.001
Unknown	1.401 (1.141, 1.719)	0.001	1.421 (1.095, 1.845)	0.008

Table 2 (*continued*)

Table 2 (*continued*)

Variables	All-cause adjusted HR (95% CI)	P value	Esophageal cancer-specific adjusted HR (95% CI)	P value
Histology type				
Adenoma and adenocarcinoma	Reference		Reference	
Squamous cell carcinoma	1.113 (1.012, 1.224)	0.028	1.087 (0.971, 1.218)	0.903
Other types	1.046 (0.920, 1.190)	0.492	0.990 (0.846, 1.159)	0.149
AJCC stage (6th)				
I	Reference		Reference	
II	1.506 (1.317, 1.723)	<0.001	1.616 (1.366, 1.911)	<0.001
III	2.112 (1.835, 2.430)	<0.001	2.498 (2.109, 2.958)	<0.001
IV	3.229 (2.844, 3.665)	<0.001	3.752 (3.209, 4.387)	<0.001
Unknown	1.649 (1.448, 1.877)	<0.001	1.862 (1.581, 2.194)	<0.001
Surgery				
No/unknown	Reference		Reference	
Yes	0.310 (0.276, 0.348)	<0.001	0.273 (0.237, 0.315)	<0.001
Radiotherapy				
No/unknown	Reference		Reference	
Yes	0.803 (0.741, 0.871)	<0.001	0.832 (0.756, 0.915)	<0.001
Chemotherapy				
No/unknown	Reference		Reference	
Yes	0.412 (0.378, 0.449)	<0.001	0.385 (0.348, 0.426)	<0.001

HR, hazard ratio; CI, confidence interval; Sep/wid/div, separated/widowed/divorced; NOS, not otherwise specified; AJCC, American Joint Committee on Cancer.

Discussion

Assuming that prior cancer history may influence the prognosis of cancer patients, prior malignancy is regularly considered an exclusion criterion in cancer clinical trials. However, little evidence has confirmed this hypothesis in different types of cancer. This study focused on the impact of prior cancer on prognosis of patients with esophageal carcinoma. The Kaplan-Meier analysis in this study revealed that for all patients diagnosed with esophageal cancer, prior cancer did not convey any adverse impact on all-cause and esophageal cancer-specific survival before PSM and after PSM. The subgroup analysis stratified by age, sex, race, grade, histological type, and stage of the index cancer confirmed these conclusions. The multivariate Cox regression analysis showed that prior malignancy was not associated with inferior all-cause and esophageal cancer-specific survival. The subgroup analysis stratified by timing of prior cancer showed no significant difference in subgroups of 6–12 months, 1–5 years, and 5–10 years; however, for the subgroup >10 years, prior cancer appeared to be associated with poor prognosis. Long-term malignancy could lead to serious decline in body function and complications, and early diagnosis of indolent prior cancer with long-term healthcare effect might increase the survival. Accordingly, we inferred that prior cancer mainly affected the survival from other causes, including prior cancer, disease progression of prior and index cancer, complications of cancer, and health condition of individuals.

In this study, approximately 13% of patients had a history of prior malignancy, which is a large proportion of the study population. Excessive exclusion criteria would limit trial accrual and low rates of participation would result in prolonged study duration, decreased generalization, and poor accuracy. Therefore, it is essential to analyze the

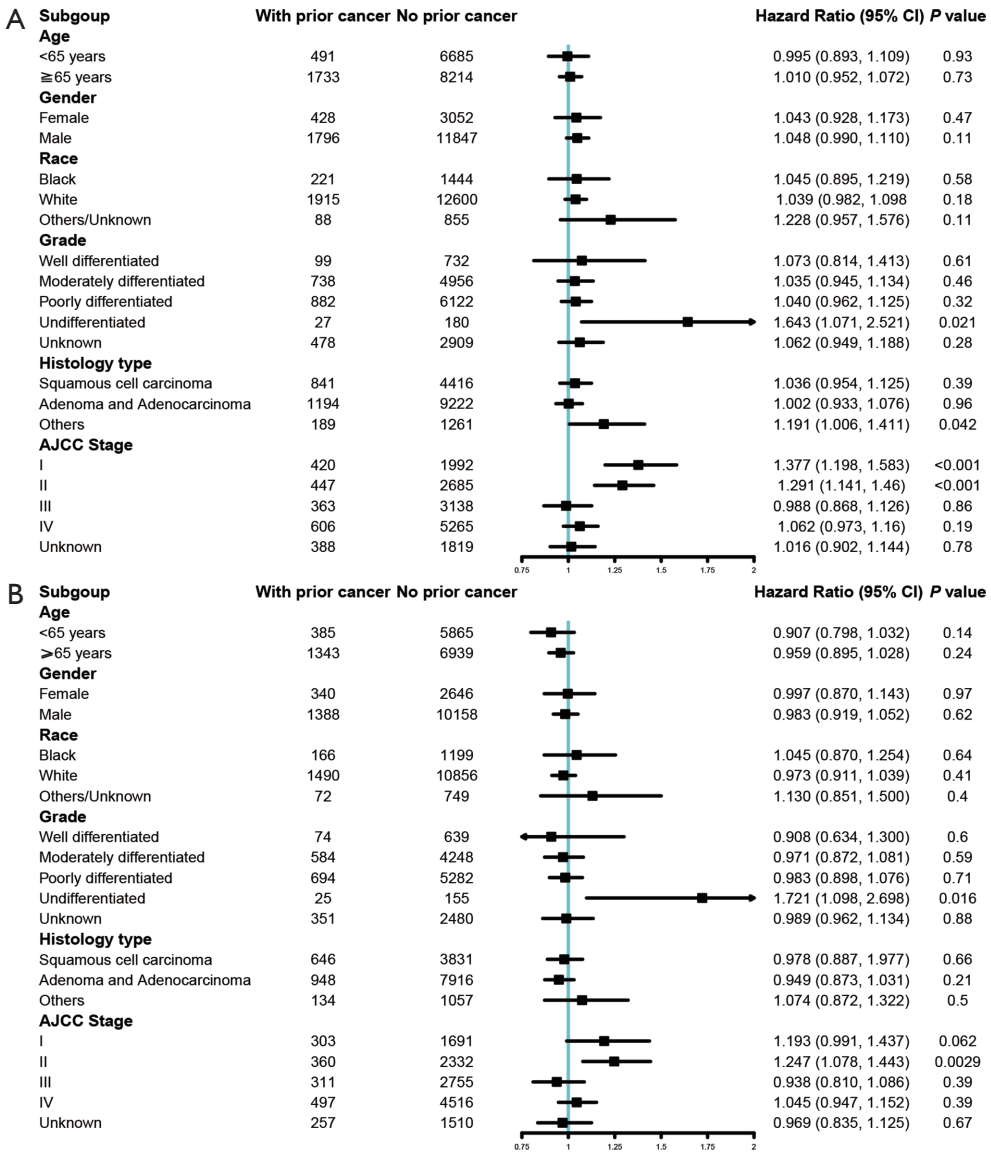

Figure 3 Subgroup analysis of prior cancer impact on all-cause (A) and esophageal cancer-specific survival (B) stratified by age, sex, race, grade, histological type, and AJCC stage of esophageal cancer. AJCC, American Joint Committee on Cancer.

correlation between prior cancer diagnosis and survival outcomes to broaden the inclusion criteria.

To our knowledge, lung cancer, liver cancer, pancreatic adenocarcinoma, breast cancer, and nasopharyngeal cancer have more aggressive tumor biological behavior (17). Previous studies have shown that prior cancer history has no significant effect on the prognosis of the aforementioned types of tumors (10,18-20). However, the malignant behavior of laryngeal cancer is relatively low, and prior cancer history has a significant adverse effect on its prognosis (12). Based on this, we could infer that the degree of the index tumor invasion might be one reason for the different effects of prior cancer history on survival in different types of cancer. This hypothesis was also verified from the subgroup analysis results that prior cancer showed a significant effect on survival for patients with stage I and II esophageal cancer, but not for those in stage III and IV. In this study, the subgroup analysis stratified by prior cancer type revealed that a higher degree of malignancy of a prior cancer, such as lung and bronchus cancer, or head

Table 3 Multivariable Cox regression analysis for overall survival in subgroups of latency period

Variables	6–12 months		1–5 years		5–10 years		>10 years	
	HR (95% CI)	P value	HR (95% CI)	P values	HR (95% CI)	P values	HR (95% CI)	P values
Prior cancer								
No prior cancer	Reference		Reference		Reference		Reference	
With prior cancer	1.064 (0.871, 1.299)	0.546	0.968 (0.883, 1.062)	0.494	0.985 (0.898, 1.080)	0.741	1.106 (0.979, 1.249)	0.105
Age (years)								
<65	Reference		Reference		Reference		Reference	
≥65	1.109 (0.983, 1.251)	0.093	1.118 (1.008, 1.240)	0.035	1.122 (1.010, 1.247)	0.031	1.112 (0.989, 1.249)	0.075
Gender								
Female	Reference		Reference		Reference		Reference	
Male	1.196 (1.049, 1.364)	0.008	1.138 (1.015, 1.276)	0.026	1.143 (1.018, 1.282)	0.023	1.175 (1.041, 1.326)	0.009
Race								
Black	Reference		Reference		Reference		Reference	
White	1.081 (0.911, 1.284)	0.372	1.000 (0.859, 1.163)	0.996	0.987 (0.849, 1.147)	0.862	1.092 (0.930, 1.281)	0.283
Others/unknown	0.714 (0.525, 0.970)	0.031	0.707 (0.543, 0.920)	0.010	0.776 (0.598, 1.007)	0.056	0.752 (0.560, 1.009)	0.058
Marital status								
Married	Reference		Reference		Reference		Reference	
Single	1.180 (1.007, 1.381)	0.040	1.101 (0.958, 1.264)	0.176	1.114 (0.971, 1.279)	0.122	1.073 (0.923, 1.248)	0.360
Sep/wid/div	1.203 (1.070, 1.353)	0.002	1.174 (1.059, 1.302)	0.002	1.203 (1.087, 1.332)	<0.001	1.166 (1.044, 1.302)	0.006
Unknown	0.988 (0.823, 1.185)	0.893	0.892 (0.762, 1.044)	0.153	1.007 (0.854, 1.188)	0.932	0.902 (0.756, 1.076)	0.253
Primary site								
Abdominal esophagus	Reference		Reference		Reference		Reference	
Cervical esophagus	0.546 (0.266, 1.119)	0.098	0.554 (0.298, 1.031)	0.062	0.626 (0.330, 1.187)	0.151	0.579 (0.309, 1.085)	0.088
Thoracic esophagus	0.585 (0.289, 1.184)	0.136	0.627 (0.341, 1.152)	0.133	0.640 (0.340, 1.205)	0.167	0.744 (0.403, 1.374)	0.344
Upper third of esophagus	0.584 (0.293, 1.166)	0.127	0.584 (0.322, 1.059)	0.077	0.650 (0.349, 1.208)	0.173	0.645 (0.353, 1.178)	0.154
Middle third of esophagus	0.575 (0.292, 1.130)	0.108	0.626 (0.350, 1.120)	0.115	0.610 (0.332, 1.121)	0.111	0.640 (0.356, 1.151)	0.136
Lower third of esophagus	0.587 (0.301, 1.144)	0.118	0.655 (0.369, 1.162)	0.148	0.632 (0.347, 1.154)	0.135	0.665 (0.374, 1.183)	0.165
Overlapping lesion of esophagus	0.780 (0.381, 1.598)	0.497	0.929 (0.503, 1.716)	0.813	0.695 (0.367, 1.316)	0.263	0.808 (0.432, 1.511)	0.504
Esophagus, NOS	0.606 (0.306, 1.201)	0.152	0.645 (0.358, 1.162)	0.144	0.668 (0.361, 1.234)	0.197	0.640 (0.354, 1.158)	0.141

Table 3 (*continued*)

Table 3 (*continued*)

Variables	6–12 months		1–5 years		5–10 years		>10 years	
	HR (95% CI)	P value	HR (95% CI)	P values	HR (95% CI)	P values	HR (95% CI)	P values
Grade								
Well differentiated	Reference		Reference		Reference		Reference	
Moderately differentiated	1.631 (1.228, 2.166)	<0.001	1.790 (1.378, 2.326)	<0.001	1.670 (1.313, 2.124)	<0.001	1.624 (1.251, 2.109)	<0.001
Poorly differentiated	1.995 (1.505, 2.645)	<0.001	2.186 (1.685, 2.835)	<0.001	2.019 (1.590, 2.563)	<0.001	1.957 (1.510, 2.537)	<0.001
Undifferentiated	2.149 (1.358, 3.401)	0.001	2.458 (1.587, 3.806)	<0.001	2.448 (1.601, 3.742)	<0.001	2.256 (1.418, 3.589)	<0.001
Unknown	1.317 (0.986, 1.760)	0.062	1.478 (1.132, 1.930)	0.004	1.361 (1.065, 1.741)	0.014	1.355 (1.037, 1.771)	0.026
Histology type								
Adenoma and adenocarcinoma	Reference		Reference		Reference		Reference	
Squamous cell carcinoma	1.095 (0.960, 1.249)	0.176	1.100 (0.978, 1.236)	0.111	1.072 (0.955, 1.203)	0.241	1.101 (0.972, 1.246)	0.131
Other types	0.990 (0.826, 1.186)	0.909	1.016 (0.866, 1.191)	0.850	0.945 (0.807, 1.107)	0.483	0.965 (0.813, 1.146)	0.686
AJCC stage (6th)								
I	Reference		Reference		Reference		Reference	
II	1.658 (1.365, 2.013)	<0.001	1.663 (1.405, 1.969)	<0.001	1.552 (1.312, 1.836)	<0.001	1.566 (1.308, 1.875)	<0.001
III	2.360 (1.934, 2.882)	<0.001	2.449 (2.058, 2.914)	<0.001	2.125 (1.784, 2.533)	<0.001	2.386 (1.982, 2.872)	<0.001
IV	3.571 (2.976, 4.285)	<0.001	3.473 (2.964, 4.068)	<0.001	3.242 (2.767, 3.797)	<0.001	3.531 (2.983, 4.179)	<0.001
Unknown	1.851 (1.537, 2.230)	<0.001	1.862 (1.583, 2.190)	<0.001	1.722 (1.465, 2.024)	<0.001	1.788 (1.503, 2.127)	<0.001
Surgery								
No/unknown	Reference		Reference		Reference		Reference	
Yes	0.300 (0.255, 0.352)	<0.001	0.305 (0.265, 0.351)	<0.001	0.299 (0.259, 0.345)	<0.001	0.292 (0.249, 0.341)	<0.001
Radiotherapy								
No/unknown	Reference		Reference		Reference		Reference	
Yes	0.847 (0.757, 0.949)	0.004	0.814 (0.738, 0.898)	<0.001	0.833 (0.755, 0.919)	<0.001	0.797 (0.717, 0.887)	<0.001
Chemotherapy								
No/unknown	Reference		Reference		Reference		Reference	
Yes	0.398 (0.353, 0.449)	<0.001	0.393 (0.354, 0.437)	<0.001	0.402 (0.362, 0.446)	<0.001	0.405 (0.362, 0.453)	<0.001

HR, hazard ratio; CI, confidence interval; Sep/wid/div, separated/widowed/divorced; NOS, not otherwise specified; AJCC, American Joint Committee on Cancer.

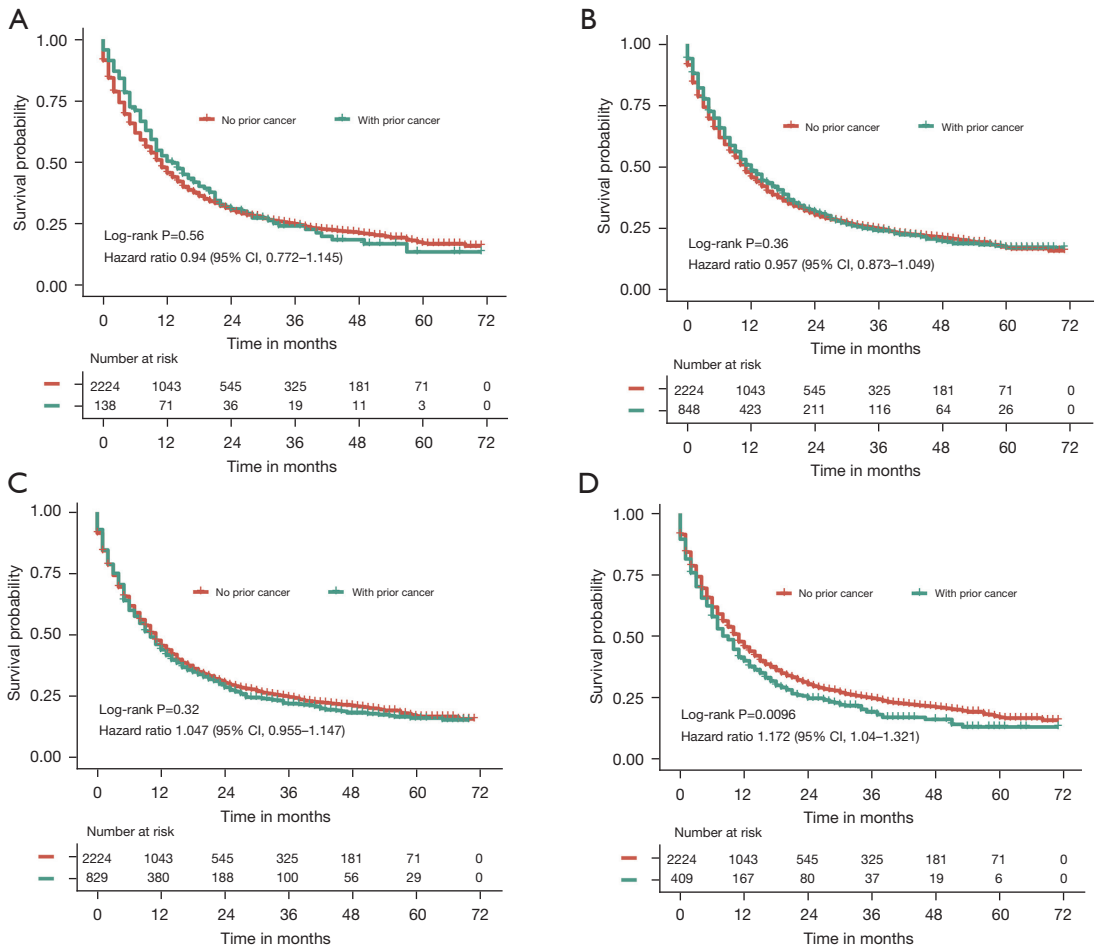

Figure 4 Subgroup analysis of prior cancer effect on overall survival stratified by diagnostic time of prior cancer in patients with esophageal carcinoma. (A) Kaplan-Meier curves of prior cancer effect on survival with latency period of 6–12 months; (B) Kaplan-Meier curves of prior cancer effect on survival with latency period of 1–5 years; (C) Kaplan-Meier curves of prior cancer effect on survival with latency period of 5–10 years; (D) Kaplan-Meier curves of prior cancer effect on survival with latency period of >10 years.

and neck cancer, might have a significant adverse effect on prognosis. In contrast, prior cancer with lower malignancy did not show significant effect on survival of patients with esophageal cancer. Accordingly, we could infer that whether prior cancer history has an impact on survival of esophageal cancer is likely determined by the characteristics of prior cancer and the degree of malignancy of esophageal cancer.

Apart from concerns about the prognostic impact, there are other potential reasons for excluding patients with a prior cancer diagnosis from clinical trials. First, patients with prior malignancy might have received chemotherapy and radiotherapy, which would lower the tolerance for current experimental treatment and interfere with the efficacy of the trial therapy (21). Second, prior cancer could trigger a series of immune responses, damage target organs, or cause complicated diseases, such as immunodeficiency, thereby greatly reducing the effectiveness in experimental patients and the reliability of results. However, alternative strategies could be applied to address this concern. For instance, a number of clinical trials excluded patients with other severe medical comorbidities or organ dysfunction and patients who had previously received prior cancer treatment (22,23).

There are several limitations to our study. First, this study is based on the SEER database, which provides retrospective data; thus, selection bias is inevitable. Although the PSM method was employed to address such bias, other hidden forms of bias caused by unobservable

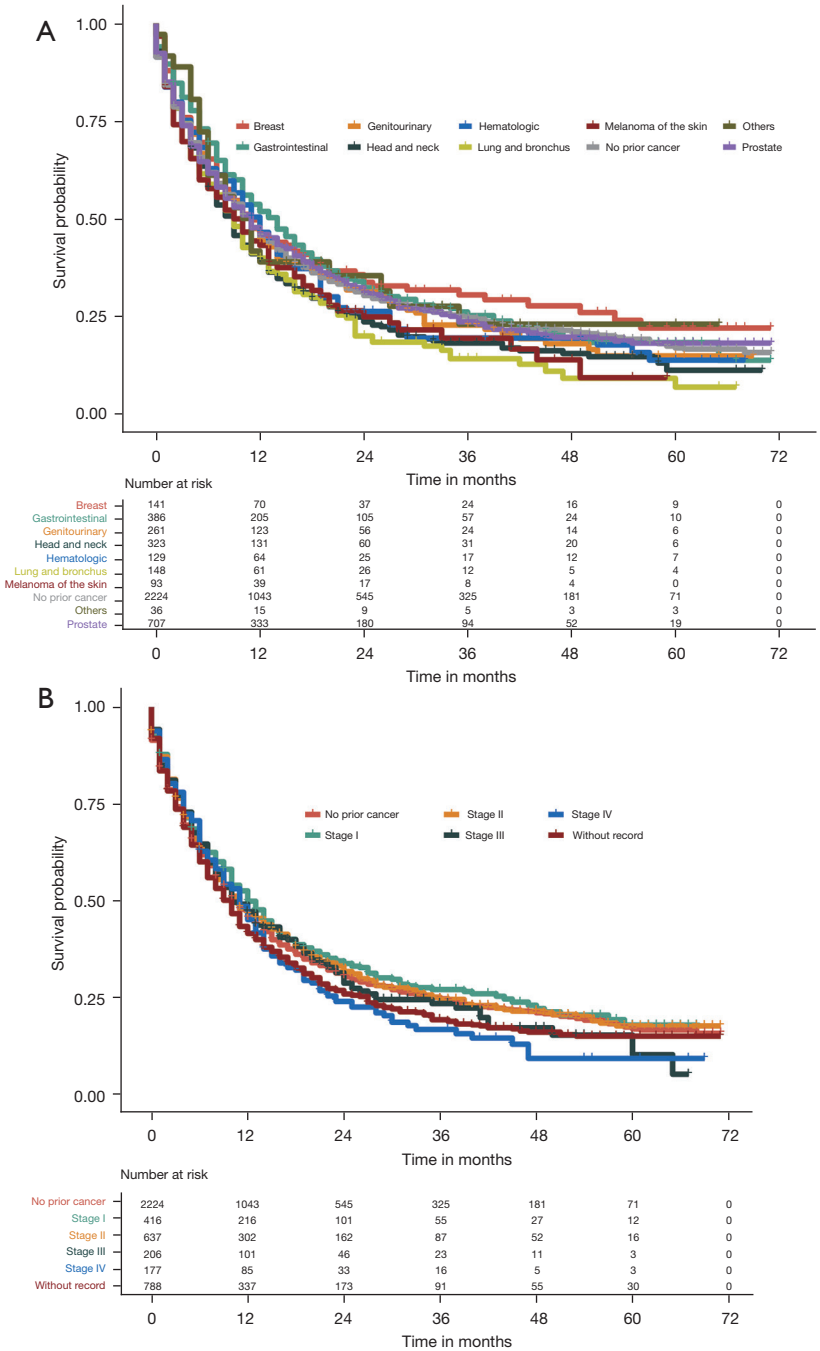

Figure 5 Subgroup analysis of prior cancer impact on overall survival in patients with esophageal carcinoma stratified by the type (A) and stage (B) of prior cancer.

confounders could not be entirely ruled out. Second, detailed information on treatment, such as the types of operation, specific radiotherapy and chemotherapy schemes, genetics, and some lifestyle factors, is not provided by the SEER database. A previous study has confirmed that cigarette smoking and alcohol drinking are two main risk factors for esophageal cancer (24); therefore, we assume that esophageal cancer patients are more likely to be heavy

smokers and alcohol abusers. It has been reported that heavy alcohol drinkers and smokers have a worse prognosis in esophageal carcinoma (25). These lifestyle factors should be included in the analysis. Moreover, data on clinical characteristics of prior cancer for many patients in the SEER database were not available and could not be further analyzed, which could have led to the limitations of the findings. Third, the database used in this study only covers approximately 9.4% of the U. S. population; therefore, the generality of our findings has to be further confirmed.

Conclusions

In summary, this study confirmed that prior cancer probably does not exert definite interference with all-cause and esophageal cancer-specific survival. Further research is still essential to explore the appropriateness of such a conclusion. Hence, these findings suggest broader inclusion criteria of clinical trials for patients with esophageal carcinoma in terms of prior malignancy history. This could assist to increase trial enrollment appropriately and reach more generalizable conclusions to guide prospective approaches for esophageal cancer treatment.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-21-1707/rc

Peer Review File: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-21-1707/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-21-1707/coif). The authors have no conflicts of interest to declare.

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).

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