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Do cancer survivors have an increased risk of developing subsequent cancer? A population-based study

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Abstract

Background The number of cancer survivors has steadily increased due to earlier detection and more effective therapies. Do all types of cancer survivors have an increased risk of developing subsequent cancers compared with the general population?

Methods Patients diagnosed with malignant cancer between January 2000 and December 2021 were included from the SEER 17 Registries (excl AK) database. Events were defined as subsequent cancer at any site according to ICD-O-3/WHO 2008. The observed and expected numbers of subsequent cancers were retrieved, and observed/expected (O/E) ratios and excess risks were calculated to assess the risk of developing subsequent cancers in cancer survivors compared with the United States general population within the same period. We obtained standard incidence ratios for the entire cohort and stratified the data by demographics, treatment, and cancer type.

Results Our findings indicate that compared with the general population, cancer survivors have a 16% greater risk of developing subsequent cancers ($p < 0.05$). All the subgroups also presented a significantly greater risk of developing subsequent cancers, even after stratification by demographics, treatment, and historic stage. Male patients with prostate cancer had a 31% lower risk of developing subsequent cancers, whereas female patients with lung and bronchus cancer presented a 93% increased risk.

Conclusion Our findings suggest that nearly all groups of cancer survivors experienced a significantly increased risk of developing subsequent cancers, whereas men with prostate cancer presented a 31% lower risk. These differential risks provide clinicians with evidence-based suggestions for tailored surveillance and prevention strategies.

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Keywords Cancer survivor, Subsequent cancer, Standard incidence ratios, Epidemiology, SEER Program

Introduction

Cancer is one of the leading causes of morbidity and mortality worldwide [1]. Moreover, the number of cancer survivors has steadily increased due to improvements in screening, diagnosis, treatment, and supportive care [2–4]. Most cancer survivors in the United States are long-term and very long-term survivors, and the number of cancer survivors in the United States is projected to grow to 26.0 million by 2040 [4]. As the population of cancer survivors grows, so does our knowledge of the

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challenges faced by those cancer survivors, including the risk of developing another cancer. Murphy et al. studied the prevalence of previous cancer in newly diagnosed cancer patients. They reported that approximately one-fourth (25.2%) of older (≥65 years) and 11% of younger adults newly diagnosed with cancer had a history of prior cancer [5]. Do all cancer survivors have an increased risk of developing subsequent cancers compared with the general population? Are there differences in subsequent cancer risk across various demographic and clinical characteristics? Can we quantify this risk to provide clinicians and researchers with evidence for tailoring follow-up care for cancer survivors?

The Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute (NCI) is an authoritative source of information on cancer incidence and survival in the United States. SEER currently collects and publishes cancer incidence and survival data from population-based cancer registries covering approximately 48.0 percent of the United States (U.S.) population [6]. The multiple primary-standardized incidence ratio (MP-SIR) approach is a valuable tool for conducting analyses of multiple primary cancers and examining hypotheses that delve into the potential etiological connections between two cancers. This method involves tracking a specified group of individuals who have previously been diagnosed with cancer over time. By comparing the observed number with the number of cancers that would be expected, the rate ratio between the specif ic group and the general population can be obtained [7]. In this study, we conducted population-based research to evaluate the risk of developing subsequent cancer among cancer survivors in the United States based on the SEER program dataset.

Method

Database and software

This retrospective, population-based study was exempt from requiring research ethics board approval and informed consent by our institution, as the study participants were identified through a deidentified and publicly accessible database. Our study conforms to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines [8]. All information on the cancer survivors and subsequent cancer events analyzed in this study were sourced exclusively from the Incidence—SEER Research Data, 17 Registries (excluding AK) database [9]. All the data were retrieved and computed via SEER*Stat software version 8.4.4.

Population and analysis

The inclusion criteria: (1) patients diagnosed with malignant cancer between January 2000 and December 2021, (2) patients diagnosed with subsequent cancer between January 2000 and Decemvber 2021. The exclusion criteria: (1) patients with unknown age records, (2) death certificated only and autopsy only cases, (3) patients with unknown race and origin, (4) latency period less than 2 months. We used the default multiple primary selection to include only the first primary. Events were defined as cancer of any site according to International Classification of Disease-Oncology-3 (ICD-O-3)/World Health Organization (WHO) 2008. Latency is the running count of time since the subject's exposure date. The latency exclusion period is 2 months to avoid potential events being ignored at the exposure date. Standardized incidence ratios (SIRs) were extracted through multiple outcome analyses. The observed and expected numbers of subsequent cancers were retrieved. The observed/expected (O/E) ratio represents the risk of developing events for cancer survivors compared with the US general population within the same period. The 95% confidence intervals (CIs) were calculated via the exact method. The excess risk refers to the number of excess cancer cases (beyond the expected number) per 10,000 persons per year. The excess risk and persons included in the cohort were also retrieved. We obtained information for the whole cohort and subsequently stratified by sex, race and origin, age at diagnosis, marital status at diagnosis, latency, treatment, historic stage, primary cancer type, and subsequent cancer type.

Variables

Marital status at diagnosis was defined according to the variable "Marital status at diagnosis" and categorized into married, unmarried, and unknown. The unmarried group included single (never married), separated, divorced, widowed and unmarried or domestic partner. The historic stage was defined based on the variables of "Combined Summary Stage (2004+)" and "Summary stage 2000 (1998–2017)". The records of treatment for the primary cancer were categorized according to the variables "Reason no cancer-directed surgery", "Radiation recode" and "Chemotherapy recode". The primary cancer type was classified based on the variable of " Site rec ICD-O-3/WHO 2008 (individual sites only)".

Results

We included 6,381,804 cancer survivors in this study, 706,658 of whom subsequently developed cancer. Among male patients, lung and bronchus cancer was the most common subsequent cancer, accounting for 16.4% (66,392/405,825) of all cases. Breast cancer was the most common secondary cancer in female patients, accounting for 25.3% (76,157/300,833) of all cases. The mean ages at which male and female cancer survivors developed

subsequent cancers were 72.23 and 69.53 years old, respectively (Table 1 and Supplementary Table 1). Table 1 shows the top 20 subsequent cancers observed for the entire cohort, while Supplementary Table 1 provides a comprehensive list of all subsequent cancers.

For the entire cohort, the O/E ratio was 1.16, representing a 16% increased risk, and the excess risk was 25.44 per 10,000 individuals. Subgroup analyses stratified by sex, race/ethnicity, age at diagnosis, marital status at diagnosis, latency period, treatment received, and historical stage consistently revealed a significantly greater risk of subsequent cancers across all subgroups. Specifically, female cancer survivors presented a greater excess risk (35.88 per 10,000) than males did (14.91 per 10,000). Furthermore, cancer survivors diagnosed before the age of 60 presented the highest excess risk (32.89 per 10,000) among all age groups. Regarding the latency period, the highest excess risk (38.50 per 10,000) was observed in the 2–11 months following the diagnosis of the primary cancer (Table 2).

Male and female patients were analyzed separately for primary tumor sites, focusing on the top 20 most common cancer types. The figures visually present these findings, while the full results are available in the supplementary materials for reference. We found that almost all cancer types presented a significantly increased risk. Male patients diagnosed with urinary bladder cancer presented the highest O/E ratio (1.65), indicating a 65% increased risk of developing subsequent cancers. Conversely, patients with prostate cancer presented a significantly lower O/E ratio (0.69), corresponding to a 31% lower risk of developing subsequent cancers compared to the general population (Fig. 1 and Supplementary Table 2). Among female patients, those with lung and bronchus cancer presented the highest O/E ratio (1.93), indicating a 93% increased risk (Fig. 2 and Supplementary Table 3).

Discussion

With the aging of the national population and advancements in early detection and treatment, a growing proportion of individuals diagnosed with cancer are expected to live long-term [10]. Consequently, the number of cancer survivors is projected to increase significantly in the coming decades. This vulnerable population of cancer survivors presents significant challenges for

Table 1 Top 20 subsequent cancers observed in the entire cohort

Subgroups	Male and female		Male		Female	
	Observed	Mean age at event (years)	Observed	Mean age at event (years)	Observed	Mean age at event (years)
All sites	7,06,658	71.08	4,05,825	72.23	3,00,833	69.53
Lung and bronchus	1,14,293	72.81	66,392	73.32	47,901	72.12
Breast	77,210	67.69	1,053	73.33	76,157	67.61
Prostate	55,640	70.92	55,640	70.92	0	
Melanoma of the skin	48,628	70.59	33,480	72.29	15,148	66.83
Urinary bladder	48,126	75.32	39,162	75.47	8,964	74.64
Kidney and renal pelvis	30,939	69.07	21,471	69.34	9,468	68.47
Miscellaneous	28,761	74.11	17,523	74.8	11,238	73.04
Kidney	28,447	68.54	19,789	68.9	8,658	67.72
NHL—Nodal	22,397	71.68	13,840	71.81	8,557	71.46
Pancreas	20,814	73.65	12,083	73.8	8,731	73.44
Rectum, rectosig junct, anus, anal canal and anorectum	19,609	69.72	11,904	70.54	7,705	68.46
Thyroid	15,082	61.61	5,520	64.63	9,562	59.87
Acute non-lymphocytic leukemia (ANLL)	14,529	69.62	8,432	70.59	6,097	68.27
Acute myeloid leukemia	13,548	69.52	7,855	70.5	5,693	68.18
Corpus Uteri	13,532	67.23	0		13,532	67.23
Rectum	12,925	69.91	8,254	70.93	4,671	68.12
Stomach	12,357	72.71	8,095	73.65	4,262	70.93
NHL—extranodal	11,117	72.31	6,753	72.53	4,364	71.98
Myeloma	10,753	72.8	7,147	73.14	3,606	72.12
Sigmoid colon	10,152	71.35	6,154	72.04	3,998	70.29
Liver	9,726	70.49	7,293	70.43	2,433	70.65

Table 2 Standard incidence ratios of subsequent cancers in cancer survivors stratified by demographic characteristics, treatment, and historical stage

Subgroups	Observed	Expected	O/E	CI Lower	CI Upper	Excess risk	Persons
All	7,06,658	6,06,865.56	1.16#	1.16	1.17	25.44	63,81,804
Sex							
Male	4,05,825	3,76,699.37	1.08#	1.07	1.08	14.91	32,50,764
Female	3,00,833	2,30,166.19	1.31#	1.3	1.31	35.88	31,31,040
Race and origin							
Non-Hispanic White	5,47,611	4,68,885.51	1.17#	1.16	1.17	27.54	45,04,556
Non-Hispanic Black	63,471	56,334.86	1.13#	1.12	1.14	19.65	6,52,141
Non-Hispanic American Indian/Alaska Native	2,752	1,409.16	1.95#	1.88	2.03	80.37	30,258
Non-Hispanic Asian or Pacific Islander	36,897	25,144.42	1.47#	1.45	1.48	43.87	4,61,778
Hispanic (All Races)	55,927	55,091.61	1.02#	1.01	1.02	2	7,33,071
Age at diagnosis							
< 60 years	2,12,924	1,52,200.54	1.40#	1.39	1.4	32.89	24,01,063
60–69 years	2,34,824	2,17,549.51	1.08#	1.08	1.08	15.56	17,78,957
70 + years	2,58,910	2,37,115.51	1.09#	1.09	1.1	22.56	22,01,784
Marital status at diagnosis							
Single	2,22,634	1,74,505.23	1.28#	1.27	1.28	37.75	23,92,917
Married	4,25,404	3,81,528.71	1.11#	1.11	1.12	18.7	35,21,348
Unknown	58,620	50,831.62	1.15#	1.14	1.16	25.84	4,67,539
Latency							
2–11 months	1,03,632	66,894.30	1.55#	1.54	1.56	78.77	63,81,804
12–59 months	2,65,567	2,29,321.58	1.16#	1.15	1.16	23.34	51,22,879
60–119 months	1,98,017	1,79,173.24	1.11#	1.1	1.11	16.69	30,07,891
120 + months	1,39,442	1,31,476.44	1.06#	1.06	1.07	10.29	16,25,359
Surgery							
Yes	4,88,414	4,00,785.11	1.22#	1.22	1.22	31.11	37,85,417
None/Unknown	2,18,244	2,06,080.45	1.06#	1.05	1.06	10.99	25,96,387
Radiation							
Yes	2,06,610	1,85,320.20	1.11#	1.11	1.12	17.5	19,18,990
None/Unknown	5,00,048	4,21,545.36	1.19#	1.18	1.19	29.01	44,62,814
Chemotherapy							
Yes	1,67,904	1,19,196.80	1.41#	1.4	1.42	47.84	20,57,582
No/Unknown	5,38,754	4,87,668.77	1.10#	1.1	1.11	17.59	43,24,222

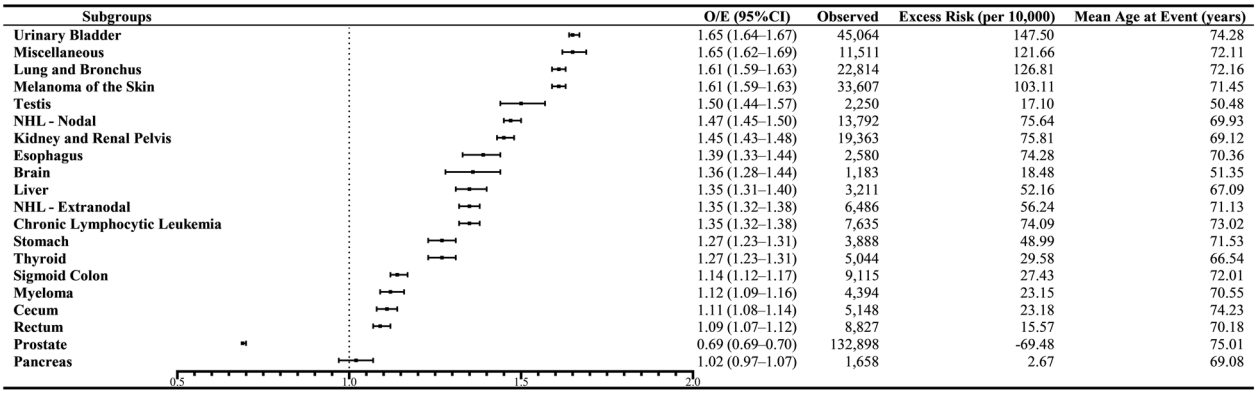
Excess risk is per 10,000

Confidence intervals are 95%

# P < 0.05

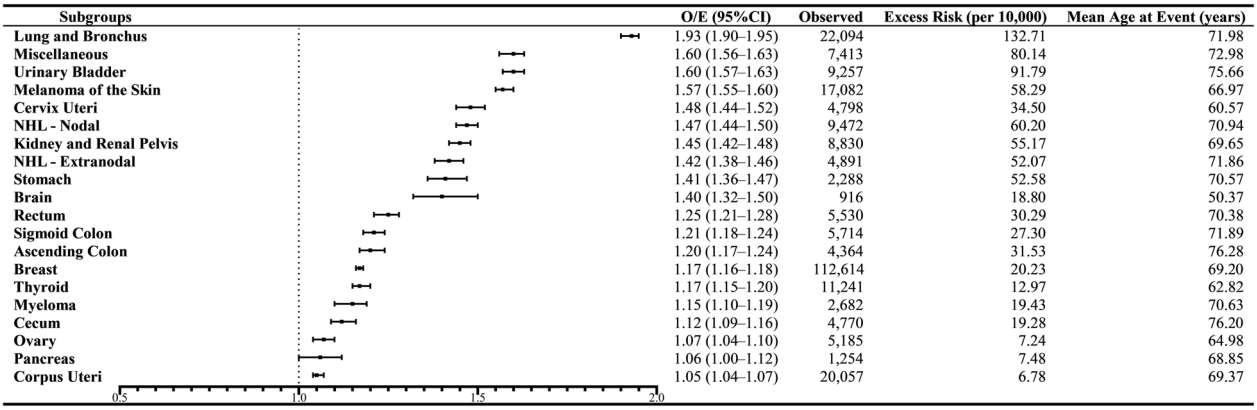
both researchers and clinicians in effectively documenting and addressing their unique healthcare needs [10]. The risk of developing secondary tumors in cancer survivors is now widely recognized [11–13] (Ref 20,231,496 30,102,558), yet the precise determinants of this risk remain elusive [14].

Aging may play a significant role in the development of subsequent cancers. Our study found that cancer survivors under 60 years of age exhibited the highest risk of subsequent cancers, differing from Murphy et al. [5], who reported a lower risk in survivors under 65 compared to older survivors. In Murphy's study, age was defined as the age at diagnosis of the subsequent cancer (the age at the event), whereas in our study, age was defined as the age at diagnosis of the primary cancer (the age at exposure). The higher risk observed in relatively younger patients may be attributed to their longer duration of exposure and the latency period between initial exposure and subsequent cancer development, and this may explain the observed discrepancy with previous studies. Radiation has been reported to be associated with an increased risk of secondary tumors[12, 15]. Some studies have demonstrated an association between chemotherapy and an increased risk of developing a second solid tumor



Subgroups	O/E (95%CI)	Observed	Excess Risk (per 10,000)	Mean Age at Event (years)
Urinary Bladder	1.65 (1.64–1.67)	45,064	147.50	74.28
Miscellaneous	1.65 (1.62–1.69)	11,511	121.66	72.11
Lung and Bronchus	1.61 (1.59–1.63)	22,814	126.81	72.16
Melanoma of the Skin	1.61 (1.59–1.63)	33,607	103.11	71.45
Testis	1.50 (1.44–1.57)	2,250	17.10	50.48
NHL - Nodal	1.47 (1.45–1.50)	13,792	75.64	69.93
Kidney and Renal Pelvis	1.45 (1.43–1.48)	19,363	75.81	69.12
Esophagus	1.39 (1.33–1.44)	2,580	74.28	70.36
Brain	1.36 (1.28–1.44)	1,183	18.48	51.35
Liver	1.35 (1.31–1.40)	3,211	52.16	67.09
NHL - Extranodal	1.35 (1.32–1.38)	6,486	56.24	71.13
Chronic Lymphocytic Leukemia	1.35 (1.32–1.38)	7,635	74.09	73.02
Stomach	1.27 (1.23–1.31)	3,888	48.99	71.53
Thyroid	1.27 (1.23–1.31)	5,044	29.58	66.54
Sigmoid Colon	1.14 (1.12–1.17)	9,115	27.43	72.01
Myeloma	1.12 (1.09–1.16)	4,394	23.15	70.55
Cecum	1.11 (1.08–1.14)	5,148	23.18	74.23
Rectum	1.09 (1.07–1.12)	8,827	15.57	70.18
Prostate	0.69 (0.69–0.70)	132,898	-69.48	75.01
Pancreas	1.02 (0.97–1.07)	1,658	2.67	69.08

Fig. 1 Standard incidence ratios of subsequent cancers in male cancer survivors stratified by primary cancer type



Subgroups	O/E (95%CI)	Observed	Excess Risk (per 10,000)	Mean Age at Event (years)
Lung and Bronchus	1.93 (1.90–1.95)	22,094	132.71	71.98
Miscellaneous	1.60 (1.56–1.63)	7,413	80.14	72.98
Urinary Bladder	1.60 (1.57–1.63)	9,257	91.79	75.66
Melanoma of the Skin	1.57 (1.55–1.60)	17,082	58.29	66.97
Cervix Uteri	1.48 (1.44–1.52)	4,798	34.50	60.57
NHL - Nodal	1.47 (1.44–1.50)	9,472	60.20	70.94
Kidney and Renal Pelvis	1.45 (1.42–1.48)	8,830	55.17	69.65
NHL - Extranodal	1.42 (1.38–1.46)	4,891	52.07	71.86
Stomach	1.41 (1.36–1.47)	2,288	52.58	70.57
Brain	1.40 (1.32–1.50)	916	18.80	50.37
Rectum	1.25 (1.21–1.28)	5,530	30.29	70.38
Sigmoid Colon	1.21 (1.18–1.24)	5,714	27.30	71.89
Ascending Colon	1.20 (1.17–1.24)	4,364	31.53	76.28
Breast	1.17 (1.16–1.18)	112,614	20.23	69.20
Thyroid	1.17 (1.15–1.20)	11,241	12.97	62.82
Myeloma	1.15 (1.10–1.19)	2,682	19.43	70.63
Cecum	1.12 (1.09–1.16)	4,770	19.28	76.20
Ovary	1.07 (1.04–1.10)	5,185	7.24	64.98
Pancreas	1.06 (1.00–1.12)	1,254	7.48	68.85
Corpus Uteri	1.05 (1.04–1.07)	20,057	6.78	69.37

Fig. 2 Standard incidence ratios of subsequent cancers in female cancer survivors stratified by primary cancer type

[16, 17]. Environmental and hormonal influences have also been identified as risk factors for secondary cancers among cancer survivors [14]. However, cancer is a remarkably complex disease characterized by its heterogeneity and multifaceted origins [18].

Prostate cancer is one of the most common cancers and the fifth most common cause of cancer-related death in males worldwide in men [19, 20]. Prior research has primarily focused on the influence of radiation therapy on the development of secondary cancers among prostate cancer survivors [21, 22]. Bagshaw et al. utilized the Veterans Affairs Corporate Data Warehouse to identify 154,514 male veterans aged 18 years and older with localized prostate cancer. Their findings indicated that radiotherapy-treated prostate cancer patients had a greater risk of developing a second primary cancer compared to those who did not receive radiotherapy [21]. Our study revealed a significantly lower risk of secondary cancer among male prostate cancer survivors compared to the general population, an unexpected finding given the generally increased risk of secondary cancer in individuals with a history of cancer. This finding warrants further investigation and may provide valuable insights into the underlying mechanisms of cancer development.

Previous similar studies have focused primarily on secondary cancers following specific primary cancer types [11, 12, 23, 24] or on the occurrence of specific secondary cancer subtypes [13]. Sung et al. conducted a retrospective cohort study utilizing the SEER 12 Registries database, encompassing 1,537,101 individuals aged 20–84 years who were diagnosed with cancer. These findings revealed a significant association between several primary cancer types and an increased risk of developing and succumbing to subsequent primary cancers [25]. Murphy et al. analyzed 765,843 incident cancer diagnoses from 2009 to 2013 and assessed the prevalence of prior cancer among these patients. Their findings revealed that a substantial proportion of individuals diagnosed with incident cancer in the United States had a history of prior cancer [5]. Compared with previous studies, our study utilized the most comprehensive dataset and analyzed the standard incidence ratios of secondary cancers among cancer survivors relative to the general population. This analysis included all types of primary

cancers and all subsequent cancer types, revealing several intriguing findings that may have implications for clinicians, researchers, and patients.

Several limitations of our research must be acknowledged. First, we employed the default setting of "multiple primary selection". This approach incorporates the initial tumor for each individual, provided that it meets the selection criteria. To mitigate the risk of misinterpreting cancers as secondary to benign tumors, we excluded patients whose first tumor was diagnosed as benign or borderline malignant. This study included all cancer survivors, including both short-term and long-term survivors, to provide a comprehensive overview. However, an analysis restricted to long-term survivors might reveal a greater risk of developing subsequent cancers. Third, this study employed an observational design, inherently susceptible to potential biases associated with retrospective data collection. While as one of the most comprehensive studies to date analyzing the risk of developing subsequent cancers among cancer survivors, we anticipate that this population-based study will provide valuable insights for future research endeavors.

Conclusion

This retrospective population-based analysis included all types of primary cancers and all subsequent cancer types. Our findings revealed a significant increase in the risk of developing subsequent cancers across nearly all groups of cancer survivors, with a notable exception: men with prostate cancer presented a 31% lower risk. Identifying these previously unexplored differential risk patterns can provide clinicians with evidence-based suggestions for implementing personalized surveillance and targeted prevention approaches, although further research is needed to elucidate the underlying mechanisms.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12967-025-06379-5.

Supplementary file1 (XLSX 14 KB)

Supplementary file2 (XLSX 18 KB)

Supplementary file3 (XLSX 17 KB)

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Author contributions

YBW drafted the manuscript. YBW, YNJ and YB acquired the data and conducted the analysis. YBW and HYX designed the study. All authors critically revised the manuscript.

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None.

Availability of data and material

The datasets analyzed in this research are publicly available in the SEER database.

Declarations

Conflict of interest

None.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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