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Stomach and duodenal ulcer as a cause of death in patients with cancer: a cohort study

Ramez M. Odat[1], Muhammad Idrees[2], Mohammed Dheyaa Marsool Marsool[3], Shahed Mamoun Oglat[1], Salma Omar Tbayshat[1], Zaid Ibrahim Adnan[1], Yousef Adeeb Alkhateeb[1], Ali O. Aldamen[4], Hritvik Jain[5], Dang Nguyen[6] and Hamdah Hanifa[7*]

Abstract

Introduction Non-cancer deaths are now becoming a significant threat to the health of cancer patients. Death from stomach and duodenal ulcer is linked to cancer due to the side effects of treatment and its pathogenesis. However, guidelines for identifying cancer patients at the highest risk of death from stomach and duodenal ulcer remain unclear.

Methods Data of all patients diagnosed with cancer between 2000 and 2021 were obtained from the Surveillance, Epidemiology, and End Results (SEER) database. Data regarding the causes of death and clinicopathological features such as sex, age, race, marital status, SEER stage, and treatment procedures were extracted. We calculated standardized mortality ratios (SMRs) using the SEER*Stat software V8.4.3.

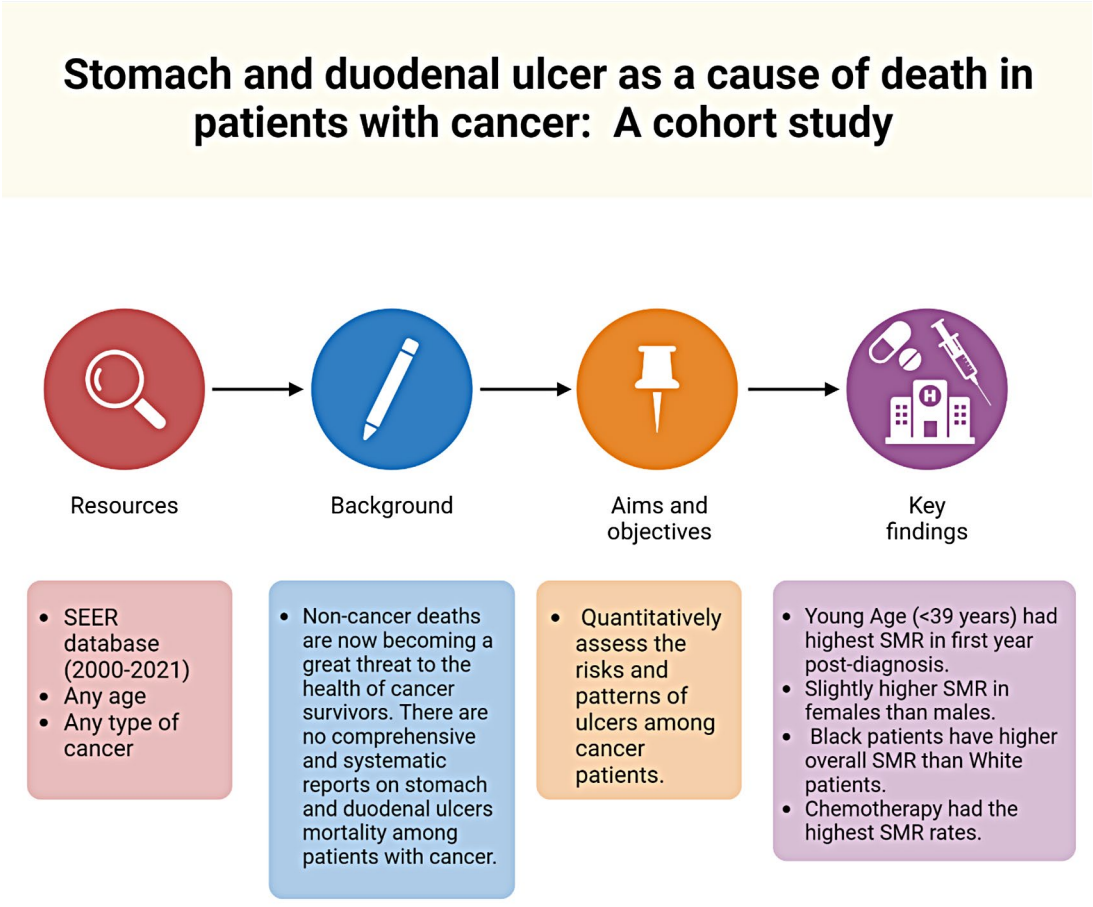
Results Of the 6,891,191 cancer patients, 2,318 died of stomach and duodenal ulcer, a rate higher than that in the general population (SMR = 1.58, 95% CI [1.52–1.65]). Stomach and duodenal ulcer-related deaths decreased over time from 870 deaths between 2000 and 2004 to 294 deaths between 2015 and 2019. Among the 2,318 stomach and duodenal ulcer deaths, the highest numbers were observed in patients with prostate cancer ($n = 389$, 16.8%), and lung and bronchus cancer ($n = 255$, 11%). Patients with liver and intrahepatic bile duct cancers (SMR = 10.53, 95% CI [8.3-13.18]), and pancreatic cancer (SMR = 6.84, 95% CI [5.11–8.97]) had a significantly higher rate of death from stomach and duodenal ulcer than the general population.

Conclusion Our study revealed a significantly higher risk of stomach and duodenal ulcer mortality among patients with cancer in the United States, underscoring the critical need for integrated care strategies that address both cancer and ulcer-related complications. To reduce ulcer-related mortality, we recommend the implementation of targeted prevention protocols, including routine gastrointestinal screenings for high-risk cancer patients, proactive management of ulcer risk factors, and collaboration between oncology, gastroenterology, and surgical teams.

*Correspondence:
Hamdah Hanifa
Hamdahhanifa@gmail.com

Full list of author information is available at the end of the article

Graphical abstract



Keywords Ulcer, Stomach, Liver, Lung, Peptic, Mortality, SEER

Introduction

Despite preventive and therapeutic oncologic advances, the United States has been challenged by debilitating cancer, with a projection of 611,720 deaths in 2024, demolishing the quality of life [1]. Non-cancer deaths are now becoming a significant threat to the health of cancer survivors. Among these, stomach and duodenal ulcers represent a critical yet underreported cause of mortality [2]. The accumulating trend of peptic ulcer disease (PUD) with an annual prevalence of 0.12–1.5% [3] further disorganizes physical, social, economic, and psychological domains predisposing the potentially life-threatening complications holding significant demise [4]. To be more specific, ulcer-related complications are at their peak, with an average reported incidence of up to 20%, of which perforation leading to hemorrhage enhanced the mortality risk by 15% [5]. Regular follow-up and timely detection of stomach and duodenal ulcers is crucial, as early intervention can mitigate severe outcomes and enhance patient survival [6].

Apart from the range of risk factors causing mucosal breach directly, its development under the cancer milieu might be direct or secondary to its metastatic nature [7, 8] which may get hyperactive while commencing modalities concerned with mitigating cancer and enhancing its survivability [9, 10]. Another aspect of ulcer development among cancer individuals is alterations in a balanced gastroduodenal mucosal homeostasis secondary to immunosuppression, stress, and cancer therapy. Suppression of physiologic immune power in cancer might be linked either with excessive interleukin-10, various growth factors like TGF-β and vascular endothelial growth factors (VEGF), or cells of innate /adaptive immunity, facilitating the evolution of more inflammation and oxidative stress [11]. Ischemic changes, inflammation, complement system activation, lymphocytic predominance, a decline in prostaglandin, harm to the enteric nervous system,

and disrupted gastrin-acid axis have been postulated as fundamental key players in cancer therapy-induced ulcerations [12]. Being a cancer survivor is considered a stressful situation that might be incremented by the addition of chemotherapy and radiotherapy-induced oxidative stress. Likewise, radiotherapy and chemotherapy-induced membrane damage, mitochondrial leak, endoplasmic reticulum stress (ERS), and DNA damage with ultimate apoptosis and necrosis may permanently disintegrate the mucosal defense and complicated non-healing ulcers [13].

Predictions claiming the persistent rise of cancers at an exponential rate, with an estimation of its occurrence among 26 million Americans by 2040, may produce the neglected attitude of health professionals towards cancer-related peptic ulcers, and thus mortalities [14]. Thus, its identification is fundamental, and this time, it supports our suggestion of quantifying cancer risk for ulcer and ulcer-related demise so that a solid and strategic plan could be designed for its prevention.

As narrated by many authors regarding the potential risk of cancer treatment for peptic ulcer, which may reduce survival in addition to the spectrum of other adverse events [15]. The National Comprehensive Cancer Network has intensified guidelines to reduce mortality and morbidity [16]. Few studies have emphasized the stratification of cancer-related ulcers, their diagnostic or therapeutic chain, and anticipated ulcer prevention among such patients. With a similar context, data is not able to set a guide for clinicians, oncologists, gastroenterologists, and pharmacists and thus they may fail for true identification of cancer survivors on the verge of death solely due to mortality risk of potential ulcer. Formulating a model with targeted stratification of cancer patients at high risk of ulcers and immediate execution of focused management by care physicians may protect cancer patients with improved quality of life [17]. With a yielding progression in therapeutic goals to overcome malignant proliferation, immune checkpoint inhibitors (CPIs) got great attention from immunologists, but not without some adverse events predominately involving gastro-duodenal mucosa [18]. Amongst the gastric patterns, ulcers, chronic active gastritis, severe hemorrhagic gastritis, intraepithelial lymphocytosis, and peri-glandular inflammation have been well explained embarking persistent injury to the gastric mucosa. Consistent pathologic manifestation in the duodenal i.e. duodenitis, villous atrophy, and reactive crypt hyperplasia under CPI therapy exposes the duodenum for ulceration with ultimate bleed. Concurrently, a vicious cycle of healing and non-healing ulcers with a broad spectrum may add complications of newer onset, worsening survivability [19]. The recently advanced cancer therapies also achieved promising outcomes in oncologic control but at the risk of mucosal ulcerations which may end with death before the death due to primary disease, the cancer [20]. While evaluating the prognosis, parallel commands must be furnished based on the risks versus benefits of administered therapy. Identifying such factors may aid in avoiding supplemented therapy-related stress apart of cancer burden, with neglecting attitude non-cancer mortality may prevail [21].

We conducted the current analysis to determine the risk factor for causing peptic ulcer and its contribution to poor survivability among cancer patients residing in the United States. Furthermore, characterizing disease patterns, demographics, cancer stage, and modality used for cancer is desirable. An in-depth evaluation of our goal may find our intentions for devising guidelines for healthcare physicians for alleviating ulcer-affiliated risks, an ultimate purpose for the decline in morbidity, and improved survival.

Methods

Data search and extraction

The Surveillance, Epidemiology, and End Results (SEER) program (available at http://www.seer.cancer.gov) is a comprehensive clinical database that compiles cancer incidence and survival statistics from various U.S. cancer registries, encompassing nearly 34.6% of the U.S. population. This study utilized SEER data to identify patients diagnosed with primary tumors between January 1, 2000, and December 31, 2021. Eligible participants included both male and female patients with primary tumor diagnoses. A total of 6,891,191 cancer patients were included from the SEER 17 Registries (2021), with complete data on demographic factors (such as sex and race), clinical variables (chemotherapy, radiation therapy, surgeries), and cause of death [22]. We used the International Classification of Diseases, 10th Revision (ICD-10) code for stomach and duodenal ulcer (ICD-10: K25-K28) to identify patients with stomach and duodenal ulcer listed as the cause of death in SEER data. Therefore, our definition of stomach and duodenal ulcer-related cause of death in cancer patients is dependent on the data recorded in SEER software. This research followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [23].

SEER stages variable was defined as follows: (A) Localized: Cancer is confined to the origin site, with no evidence of spreading to other areas. (B) Regional: Cancer has extended to nearby lymph nodes, tissues, or adjacent organs. (C) Distant: Cancer has metastasized to distant organs or tissues beyond the primary site.

Statistical analysis

We performed statistical analyses using SEER*Stat software, version 8.4.3. Standardized Mortality Ratios

Table 1 Comparison of mortality rates for stomach and duodenal ulcer among cancer patients

	0–11 months				12–59 months				60–119 months				120 + months				Total				
	Observed	SMR	CI Lower	CI Upper	Observed	SMR	CI Lower	CI Upper	Observed	SMR	CI Lower	CI Upper	Observed	SMR	CI Lower	CI Upper	Observed	SMR	CI Lower	CI Upper	Number of patients
Sex																					
Male	477	4.18#	3.82	4.58	398	1.31#	1.18	1.44	272	1.11	0.98	1.25	189	0.92	0.8	1.06	1,336	1.54#	1.46	1.62	3,519,156
Female	305	3.76#	3.35	4.21	296	1.40#	1.25	1.57	226	1.36#	1.19	1.55	155	1.12	0.95	1.31	982	1.65#	1.54	1.75	3,372,035
Age																					
< 39	5	16.06#	5.21	37.47	3	2.33	0.48	6.81	3	1.69	0.35	4.94	9	2.69#	1.23	5.1	20	2.97#	1.82	4.59	460,346
40–49	19	8.54#	5.14	13.34	18	2.18#	1.29	3.45	10	0.97	0.46	1.78	15	0.95	0.53	1.56	62	1.69#	1.3	2.17	648,964
50–59	87	7.19#	5.76	8.87	83	2.03#	1.62	2.51	55	1.28	0.96	1.66	41	0.77	0.55	1.04	266	1.78#	1.57	2.01	1,377,216
60–69	152	4.72#	4	5.53	174	1.72#	1.48	2	136	1.37#	1.15	1.62	112	0.95	0.79	1.15	574	1.64#	1.51	1.78	1,891,784
70–79	241	4.24#	3.72	4.81	215	1.27#	1.1	1.45	174	1.06	0.91	1.23	128	0.97	0.81	1.15	758	1.45#	1.35	1.55	1,562,122
> 80	278	3.04#	2.69	3.42	201	1.03	0.89	1.19	120	1.30#	1.08	1.56	39	1.87#	1.33	2.56	638	1.60#	1.48	1.73	945,075
Race																					
White	627	3.79#	3.5	4.1	583	1.33#	1.22	1.44	405	1.15#	1.04	1.26	290	0.97	0.86	1.09	1,905	1.52#	1.45	1.59	5,626,908
Black	69	4.14#	3.22	5.24	51	1.2	0.89	1.58	52	1.68#	1.25	2.2	30	1.31	0.89	1.87	202	1.79#	1.55	2.05	721,592
Marital status																					
Married	331	3.35#	3	3.74	346	1.23#	1.11	1.37	252	1.03	0.9	1.16	195	0.85#	0.74	0.98	1,124	1.32#	1.24	1.4	3,736,796
Unmarried	403	5.03#	4.55	5.54	291	1.55#	1.38	1.74	201	1.56#	1.35	1.79	128	1.43#	1.19	1.69	1,023	2.10#	1.98	2.23	2,656,476
SEER stage																					
Localized	177	2.52#	2.17	2.92	226	1	0.87	1.14	215	1.1	0.95	1.25	101	0.87	0.71	1.06	719	1.18#	1.1	1.27	2,627,104
Regional	131	4.61#	3.86	5.47	89	1.25#	1	1.53	64	1.24	0.95	1.58	27	0.94	0.62	1.37	311	1.73#	1.54	1.93	1,225,570
Distant	219	6.88#	6	7.85	136	2.54#	2.13	3.01	54	1.98#	1.49	2.58	7	0.63	0.25	1.3	416	3.36#	3.05	3.7	1,452,676
Year of diagnoses																					
2000–2004	227	3.76#	3.28	4.28	239	1.50#	1.32	1.71	178	1.26#	1.08	1.45	226	1.06	0.93	1.21	870	1.51#	1.41	1.62	1,434,443
2005–2009	155	3.57#	3.03	4.18	158	1.24#	1.06	1.45	163	1.18#	1.01	1.38	114	0.96	0.8	1.16	590	1.38#	1.27	1.5	1,526,620

Table 1 (continued)

	0–11 months				12–59 months				60–119 months				120 + months				Total				
	Observed	SMR	CI Lower	CI Upper	Observed	SMR	CI Lower	CI Upper	Observed	SMR	CI Lower	CI Upper	Observed	SMR	CI Lower	CI Upper	Observed	SMR	CI Lower	CI Upper	Number of patients
2010–2014	179	4.77#	4.1	5.53	160	1.34#	1.14	1.56	146	1.23#	1.04	1.45	4	0.34#	0.09	0.88	489	1.70#	1.55	1.86	1,582,029
2015–2019	150	3.68#	3.11	4.31	133	1.25#	1.04	1.48	11	0.87	0.43	1.55	0	0	0	0	294	1.84#	1.63	2.06	1,685,483
2020–2021	71	5.47#	4.27	6.9	4	1.15	0.31	2.95	0	0	0	0	0	0	0	0	75	4.56#	3.59	5.71	662,616
Treatment																					
surgery	250	2.42#	2.13	2.73	366	1.14#	1.03	1.27	311	1.15#	1.02	1.28	240	1	0.88	1.13	1,167	1.25#	1.18	1.32	3,863,232
chemotherapy	176	4.38#	3.76	5.08	169	1.95#	1.67	2.27	90	1.48#	1.19	1.82	60	1.2	0.92	1.55	495	2.09#	1.91	2.28	2,114,856
radiation	121	2.95#	2.44	3.52	159	1.46#	1.24	1.7	119	1.28#	1.06	1.53	96	1.17	0.95	1.43	495	1.52#	1.39	1.66	1,681,819

Standardized mortality ratios of stomach and duodenal ulcer and observed deaths among cancer patients grouped characteristics. SMRs: Standardized mortality ratios. SEER stage (2004–2015)

(SMRs) were calculated by dividing the observed number of stomach and duodenal ulcer-related deaths by the expected number of deaths in a comparable age-matched population during the same period. The end of follow-up time was the date of the last follow-up or death according to the recorded data in SEER software. U.S. population data, adjusted for age and race/ethnicity, were obtained from the National Center for Health Statistics. Additionally, SMRs were further stratified based on cancer type, age, sex, race, marital status, stage of cancer, year of diagnosis, treatment modalities, treatment sequence, and AJCC 6th edition for (T, N, M stages), with latency periods analyzed from 1 to 10 years post-diagnosis.

Ethical considerations

Since SEER data are publicly available and anonymized before access, obtaining ethical approval from local ethics boards was not required for this study.

Results

Demographic and clinical characteristics of the study population

Our cohort consisted of a total of 6,891,191 cancer patients, of whom 2,318 died of cancer-related stomach and/or duodenal ulcer. The population was mostly male, with 3,519,156 male participants and 3,372,035 female participants. The most prevalent age group was 60–69 years, totaling 1,891,784 patients. However, the <39 years group had the highest SMR during the first 0–11 months, with an SMR of 16.06 (95% CI: 5.21–37.47). The majority of the study's patients (5,626,908) were white. Black patients comprised a lesser fraction of the sample, totaling 721,592 participants. 3,736,796 people were married. Furthermore, localized tumors were the most reported stage in the study, affecting 2,627,104 patients. Finally, surgery was the most reported treatment method, with 3,863,232 patients undergoing surgical procedures. Chemotherapy was the second most frequent treatment, involving 2,114,856 patients Table 1.

Key risk factors contributing to cancer-related duodenal and stomach ulcer mortality

When it comes to risk factors responsible for cancer-related duodenal and stomach ulcer mortality, our analysis identified several key risk factors. Both males and females experienced elevated mortality risks related to duodenal and stomach ulcers. Males had an SMR of 1.54 (95% CI: 1.46–1.62), while females had a slightly higher SMR of 1.65 (95% CI: 1.54–1.75). Although both genders are affected, females may have a marginally higher mortality risk from ulcer-related complications in cancer cases.

Another significant risk factor we identified was the age group with the highest death rate, which was 50–59 years old, with an SMR of 2.97 (95% CI: 1.82–4.59). Patients aged 40–49 had an SMR of 1.65 (95% CI: 1.54–1.75), while those under 39 had a higher mortality risk with an SMR of 1.54 (95% CI: 1.46–1.62). The SMR remained elevated in elderly age groups, with patients aged 60 to 69 having an SMR of 1.64 (95% CI: 1.51–1.78).

Race was also revealed as a significant risk factor; throughout all periods combined, Black patients had a higher chance of dying from cancer-related duodenal and stomach ulcers, with an overall SMR of 1.79 (95% CI: 1.55–2.05). This is also seen in the early post-diagnosis period (within 1 year), as Black patients exhibited a higher SMR of 4.14 (95% CI: 3.22–5.24), as compared to White patients, who had an SMR of 3.79 (95% CI: 3.50–4.10). Both racial groups' SMRs decline over time. For White patients, the SMR drops to 1.33 (95% CI: 1.22–1.44), while for Black patients, it falls to 1.20 (95% CI: 0.89–1.58). Finally, over 10 years after the diagnosis, the SMR for White patients falls to 0.97 (95% CI: 0.86–1.09), comparable to that of the general population. In contrast, although not statistically significant, Black patients maintain a higher SMR of 1.31 (95% CI: 0.89–1.87).

Our analysis also found that marital status plays a significant role in the mortality rate from stomach and/or duodenal ulcers, as unmarried individuals faced consistently higher odds of dying from cancer-related duodenal and stomach ulcers throughout all time periods, from one year to over ten years with a total SMR of 2.10 (95% CI: 1.98–2.23), compared to 1.32 (95% CI: 1.24–1.40) for married individuals.

In terms of tumor stage, patients with localized tumors had the lowest overall SMR of 1.18 (95% CI: 1.10–1.27), pointing to a decreased mortality risk throughout the study period. Regional tumors had an SMR of 1.73 (95% CI: 1.54–1.93), whereas distant tumors had the highest overall SMR of 3.36 (95% CI: 3.05–3.70). In the first year after diagnosis, patients with localized tumors had an SMR of 2.52 (95% CI: 2.17–2.92). However, patients with regional tumors had a much higher risk, with an SMR of 4.61 (95% CI: 3.86–5.47). Patients with distant tumors had the highest risk, with an SMR of 6.88 (95% CI: 6.00–7.85). From 1 to 5 years, individuals with localized cancer had a significantly lower mortality risk, with an SMR of 1.00 (95% CI: 0.87–1.14), equivalent to the general population. In contrast, the SMR for individuals with regional tumors remained elevated at 1.25 (95% CI: 1.00–1.53), and those with distant tumors continued to have a greater mortality risk with an SMR of 2.54 (95% CI: 2.13–3.01). Over the course of ten years, patients with localized malignancies had an SMR of 0.87 (95% CI: 0.71–1.06). Regional tumors had a somewhat higher SMR of 0.94 (95% CI: 0.62–1.37), while distant tumors' SMR declined to 0.63 (95% CI: 0.25–1.30). We also conducted an analysis according to the AJCC staging system.

Table 2 Analysis of the mortality rate among cancer patients

	0–11 months				12–59 months				60–119 months				120 + months				Total			
	Observed	SMR	CI Lower	CI Upper	Observed	SMR	CI Lower	CI Upper	Observed	SMR	CI Lower	CI Upper	Observed	SMR	CI Lower	CI Upper	Observed	SMR	CI Lower	CI Upper
All Sites	782	4.01#	3.73	4.3	694	1.35#	1.25	1.45	498	1.21#	1.11	1.32	344	1	0.9	1.11	2,318	1.58#	1.52	1.65
Oral Cavity and Pharynx	31	7.19#	4.88	10.2	21	1.98#	1.23	3.03	13	1.71	0.91	2.92	10	1.86	0.89	3.43	75	2.69#	2.12	3.37
Esophagus	6	3.68#	1.35	8	5	2.51	0.81	5.85	2	1.96	0.24	7.09	1	1.57	0.04	8.74	14	2.65#	1.45	4.45
Stomach	50	15.87#	11.78	20.92	12	2.31#	1.19	4.04	4	1.24	0.34	3.19	4	1.98	0.54	5.06	70	5.15#	4.02	6.51
Small Intestine	12	15.39#	7.95	26.89	4	1.94	0.53	4.97	1	0.66	0.02	3.66	1	0.98	0.02	5.48	18	3.34#	1.98	5.29
Colon and Rectum	77	3.34#	2.63	4.17	59	0.96	0.73	1.24	60	1.31#	1	1.69	25	0.7	0.45	1.03	221	1.33#	1.16	1.52
Anus, Anal Canal and Anorectum	4	6.26#	1.71	16.04	1	0.61	0.02	3.42	1	0.84	0.02	4.66	2	2.19	0.27	7.92	8	1.83	0.79	3.6
Liver and Intrahepatic Bile Duct	51	21.90#	16.31	28.8	20	6.60#	4.03	10.19	4	3.27	0.89	8.37	1	1.58	0.04	8.8	76	10.53#	8.3	13.18
Pancreas	34	9.37#	6.49	13.09	13	5.09#	2.71	8.71	3	3.12	0.64	9.12	2	4.38	0.53	15.81	52	6.84#	5.11	8.97
Larynx	10	6.96#	3.34	12.8	13	3.39#	1.81	5.8	6	2.17	0.79	4.71	2	1.04	0.13	3.76	31	3.11#	2.11	4.42
Lung and Bronchus	143	7.19#	6.06	8.47	62	2.28#	1.75	2.93	36	2.78#	1.95	3.85	14	2.04#	1.12	3.42	255	3.81#	3.36	4.31
Skin excluding Basal and Squamous	10	1.05	0.5	1.93	23	0.79	0.5	1.19	14	0.61	0.33	1.02	18	0.94	0.56	1.49	65	0.81	0.62	1.03
Melanoma of the Skin	9	1.08	0.49	2.05	20	0.77	0.47	1.19	8	0.38#	0.17	0.75	17	0.96	0.56	1.54	54	0.74#	0.56	0.97
Breast	40	1.66#	1.19	2.26	80	1.01	0.8	1.25	77	1.1	0.87	1.37	63	0.98	0.75	1.26	260	1.09	0.96	1.23
Cervix Uteri	2	3.01	0.37	10.89	6	3.79#	1.39	8.26	2	1.47	0.18	5.33	7	4.40#	1.77	9.07	17	3.28#	1.91	5.24
Ovary	4	2.11	0.57	5.4	5	1.27	0.41	2.96	3	1.21	0.25	3.54	6	2.74#	1.01	5.96	18	1.71#	1.02	2.71
Prostate	39	0.96	0.68	1.31	128	0.93	0.78	1.11	121	0.92	0.77	1.1	101	0.82#	0.67	1	389	0.90#	0.81	0.99
Urinary Bladder	38	2.89#	2.04	3.96	54	1.49#	1.12	1.95	35	1.34	0.94	1.87	22	1.24	0.78	1.88	149	1.60#	1.35	1.88
Kidney and Renal Pelvis	23	4.09#	2.59	6.14	27	1.69#	1.11	2.46	23	1.82#	1.16	2.74	10	1.1	0.53	2.02	83	1.92#	1.53	2.37
Brain	5	4.74#	1.54	11.05	3	3.54	0.73	10.35	1	2.28	0.06	12.73	1	2.58	0.07	14.36	10	3.67#	1.76	6.74
Endocrine System	2	0.97	0.12	3.5	4	0.54	0.15	1.38	4	0.53	0.15	1.37	6	0.84	0.31	1.83	16	0.66	0.38	1.08
Thyroid	1	0.53	0.01	2.93	3	0.43	0.09	1.26	4	0.56	0.15	1.43	5	0.73	0.24	1.69	13	0.57#	0.3	0.97

Table 2 (continued)

	0–11 months				12–59 months				60–119 months				120 + months				Total			
	Observed	SMR	CI Lower	CI Upper	Observed	SMR	CI Lower	CI Upper	Observed	SMR	CI Lower	CI Upper	Observed	SMR	CI Lower	CI Upper	Observed	SMR	CI Lower	CI Upper
Lymphoma	71	8.06#	6.29	10.17	30	1.26	0.85	1.79	24	1.32	0.84	1.96	17	1.27	0.74	2.04	142	2.21#	1.86	2.6
Myeloma	16	5.06#	2.89	8.22	12	1.72	0.89	3.01	6	1.83	0.67	3.99	0	0	0	2.69	34	2.30#	1.59	3.22
Leukemia	20	3.81#	2.33	5.89	22	1.72#	1.08	2.61	11	1.27	0.63	2.27	1	0.18	0	1.01	54	1.68#	1.26	2.19
Mesothelioma	0	0	0	8.64	0	0	0	11.09	0	0	0	48.4	0	0	0	117.1	0	0	0	4.25
Kaposi Sarcoma	0	0	0	22.6	1	2.04	0.05	11.36	1	2.62	0.07	14.58	1	3.29	0.08	18.3	3	2.24	0.46	6.54

Standardized mortality ratios of stomach and duodenal ulcer and observed deaths among cancer patients grouped cancer site

Patients with metastasis, T4 stage, and N3 stage were at higher risk of death, with SMRs of 5.96 (95% CI: 4.88–7.21), 4.73 (95% CI: 3.77–5.84) and 4.84 (95% CI: 2.5–8.46), respectively (Tables S1-S3).

Finally, regarding the total SMRs across all time periods for the treatment method used for cancer patients, chemotherapy was associated with the highest overall mortality risk, with an SMR of 2.09 (95% CI: 1.91–2.28. Radiation therapy carries a moderate risk, with a total SMR of 1.52 (95% CI: 1.39–1.66). While still presenting some risk, surgery is associated with the lowest overall SMR of 1.25 (95% CI: 1.18–1.32). We also conducted an analysis according to the treatment sequence. Our results revealed that patients who received radiation after surgery are at higher risk of death, with a total SMR of 1.31 (95% CI: 1.15–1.48) (Table S4).

Cancer subsite-specific risks of duodenal and stomach ulcer mortality

Our investigation of the cancer subsites linked with the highest rates of duodenal and stomach ulcer death found considerable differences, with certain malignancies presenting particularly high mortality risks. Among the subsites, liver and intrahepatic bile duct, pancreatic, and lung malignancies have the greatest SMRs for ulcer-related mortality. Liver and intrahepatic bile duct malignancies have the greatest overall mortality rate, especially in the early stages after diagnosis. In the first year following diagnosis, the SMR for this subsite is 21.90 (95% CI: 16.31–28.80). This increased risk persists even after the first year, with an SMR of 6.60 (95% CI: 4.03–10.19) between 1 and 5 years and a total SMR of 10.53 (95% CI: 8.30–13.18) across all periods. Similarly, individuals with pancreatic cancer suffer a high risk of ulcer-related death. In the first year after diagnosis, the SMR for pancreatic cancer was 9.37 (95% CI: 6.49–13.09). This increased risk persists for 1–5 years, with an SMR of 5.09 (95% CI: 2.71–8.71), and a cumulative SMR of 6.84 (95% CI: 5.11–8.97). Lung and bronchus malignancies have also been linked to an increased risk of ulcer mortality. In the first year, the SMR for lung cancer is 7.19 (95% CI: 6.06–8.47). Although the risk decreases over time, it remains elevated, with a cumulative SMR of 3.81 (95% CI: 3.36–4.31). This is followed by stomach cancer patients, who are likewise more vulnerable to ulcer-related death. The SMR in the first year after diagnosis is 15.87 (95% CI: 11.78–20.92), placing it among the highest risks in the early period. During the entire observation period, the SMR for stomach cancer remained elevated at 5.15 (95% CI: 4.02–6.51) Table 2.

Temporal trends in cancer-related duodenal and stomach ulcer mortality

Our analysis of the temporal trends related to cancer-related duodenal and stomach ulcer mortality covered data from four major periods: 2005–2009, 2010–2014, 2015–2019, and 2020–2021.

From 2005 to 2009, the SMR in the first-year post-diagnosis was 3.57 (95% CI: 3.03–4.18). However, this risk gradually decreased in the 1–5 years range, where the SMR dropped to 1.24 (95% CI: 1.06–1.45), and it remained stable at 1.18 (95% CI: 1.01–1.38) for the 6–10 years period. Overall, the total SMR for 2005–2009 was 1.38 (95% CI: 1.27–1.50), which is relatively lower when compared to the first year. In the 2010–2014 period, for example, there was a noticeable increase in mortality risk in the 1-year window, with an SMR of 4.77 (95% CI: 4.10–5.53), which is significantly higher than the preceding period. Over time, the mortality risk decreased, as seen in the 1–5 years range, where the SMR was 1.34 (95% CI: 1.14–1.56), and 5–10 years, where the SMR was 1.23 (95% CI: 1.04–1.45). By the >10-years period, the SMR had significantly dropped to 0.34 (95% CI: 0.09–0.88). The total SMR for 2010–2014 was 1.70 (95% CI: 1.55–1.86), which has an overall increase in mortality risk compared to the previous period. For the period 2015–2019, the mortality risk remained elevated in 1 year period, with an SMR of 3.68 (95% CI: 3.11–4.31), though slightly lower than the peak in the 2010–2014 period. In the most recent period, 2020–2021, The total SMR for this period is 4.56 (95% CI: 3.59–5.71), the highest overall SMR among all periods Table 1.

Discussion

Several important demographic and clinical risk variables have been identified in our study's examination of cancer patients who died from stomach and duodenal ulcers. Patterns and trends with important therapeutic consequences were identified by analyzing a large cohort of 6,891,191 cancer patients using the SEER database from 2000 to 2021. Our analysis revealed higher SMR among the stomach cancer population following liver and intrahepatic malignancies during the first year after diagnosis, which remained consistent for hepatobiliary followed by pancreatic cancers but declined for stomach and lung subsites over the entire period. Of the treatment-linked mortality implied for cancer cure, surgery pronounced the lowest risk, while chemotherapy mounted the mortality risk.

While gender differences were modest, it is interesting to note that SMR was higher among younger patients, especially those under the age of 39. Even though younger people often have better cancer outcomes, the high SMR indicates that they could be more prone to ulcer-related problems. This could be because they are treated more aggressively, or their ulcers are detected later in life [24]. As for the gender differences, even though modest, they were noteworthy, with females exhibiting a slightly higher SMR than males. This could be related to hormonal factors, differences in health-seeking behavior, or variations in cancer types prevalent among females [25]. Previous studies have shown that estrogen may have a protective effect against gastric mucosal injury, but this protective effect may be diminished in the context of cancer and its treatments [25, 26].

The racial disparities observed, with Black patients experiencing higher SMRs than White patients, are consistent with existing literature highlighting health inequities. These disparities may be due to differences in access to healthcare, socioeconomic status, comorbid conditions, or genetic factors influencing susceptibility to ulcers and their complications [27, 28]. The persistently higher SMR in Black patients over time underscores the need for targeted interventions to address these inequities. A recent analytical study also revealed high ulcer-related SMR in females (2.03), unmarried (2.07), and black population (1.96) surviving with cancer, which was consistent with demographic factors (i.e., gender, marital status, and race) of our study.

Gastric mucosal ulceration under a malignant milieu could be possible with direct invasion, progressing to distant metastasis and consequent higher mortalities. A co-existing ascent of 44.7% in 2019 was observed relative to 33.1% in 1992 [28]. With the extensive progression of tumors likewise, distant metastasis always carried poor survival with higher mortalities due to its potential aggression as the findings in our case trending for 1–5 years [29]. Imbalance in systemic homeostasis with activation of multiple cancerous hazards to gastroduodenal mucosa may accumulate higher ulcers and deaths [30]. In addition to the physical burden, therapeutic and psychological stress may yield new-onset ulcerations without the healing older ones [31]. Such a repetitive cycle may pose tension in the form of higher mortalities with various complications. Lastly, body resistance to overcoming such challenges may cease predisposing to higher gastric ulcers, which end with the demise [32].

The increasing SMRs over the studied periods, culminating in the highest overall SMR during 2020–2021, may reflect changes in cancer treatment protocols, increased aggressive therapies, or healthcare access issues. The COVID-19 pandemic, occurring during the latest period, may have contributed to delayed medical care, reduced surveillance for ulcer symptoms, and increased stress levels, potentially exacerbating ulcer risks [33, 34]. However, a retrospective analysis revealed a decline in ulcer-related mortality by 59.4% in 2019 relative to 1990, signifying the positive role of modalities in this era [35].

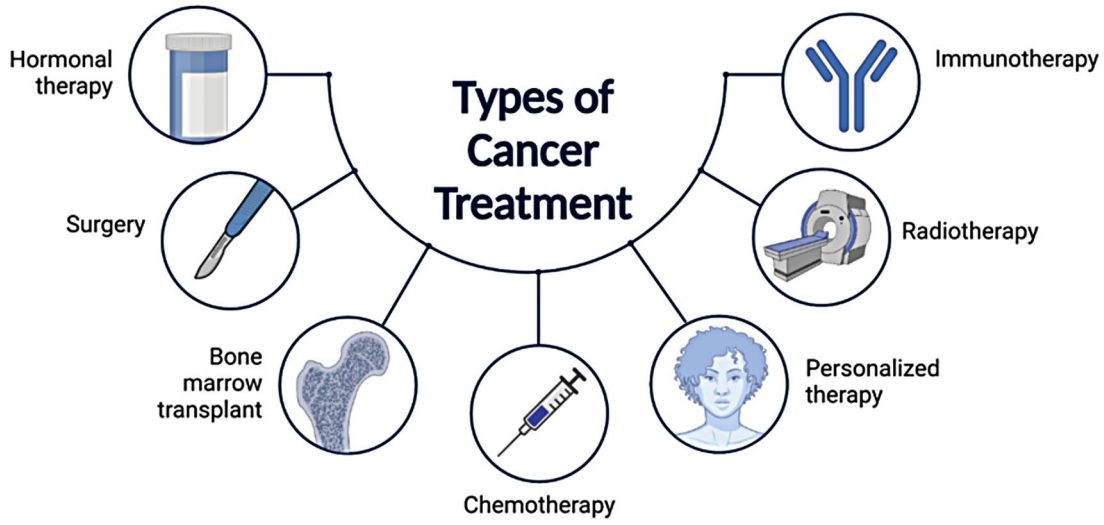


Fig. 1 Types of cancer treatment. Newer and conventional modalities for the treatment of cancer

Deadly complications with a shorter recovery window might be the causal association with a higher SMR secondary to the patients dominated with hepatobiliary involvement in our findings. Various mechanisms have been postulated behind this, of which portal hypertension leading to mucosal sloughing followed by ulcer bleed gained attention these days [36]. Additionally, chronic cirrhosis-induced HCC and cholangiocarcinoma may disrupt gut dysbiosis with resultant mucosal invasion and immunodeficiency may lead to ulceration, perforation, and hence increasing mortality [37]. Our saying for new-onset ulcers under the existing gastric malignancies might be less suggestive than that the ulcers act as a nidus for the malignant environment, thus causing higher mortalities [38, 39]. Different from gastric malignancy, direct invasion rather than involving mucosal disruption has been manifested in lung cancers with its detection at later stages, a possible postulation behind mortalities due to ulcers among such patients [40]. Peptic ulceration, either via direct left portal hypertension and gastric outlet obstruction or indirectly influenced by the loss of protective mucosal factors, pancreatic malignancies might be the possible reason for high mortality [41]. While comparing the life span of pancreatic versus hepatic cancer, the former carried a higher mortality risk due to its autophagic involution rather than spanning over the years, just like hepatic involvement [42, 43]. Many patients with esophageal cancers experience a risk of peptic ulcer-related deaths after radiotherapy [44]. Similar trends were noticed after radioembolization in hepatocellular carcinoma, which might be due to direct damage to the duodenal epithelium [7, 45].

The varying risk of peptic ulcers among cancer subtypes can be attributed to several mechanisms. Hepatobiliary cancers (e.g., liver, intrahepatic bile duct) and pancreatic cancers show the highest ulcer-related mortality, possibly due to direct mucosal injury from portal hypertension, chronic inflammation, and gut dysbiosis, which promote ulceration, bleeding, or perforation [17, 18]. For pancreatic cancer, gastric outlet obstruction and loss of protective mucosal factors also contribute to higher risks. In lung cancer, later-stage detection and systemic effects like immunosuppression may increase vulnerability to ulcers. Stomach cancers inherently involve mucosal compromise, exacerbating ulcer risks [17].

Regarding treatment modalities, newer modalities are continuously being discovered in the literature Fig. 1 [46]. Regarding our study, chemotherapy was associated with the highest overall SMR for ulcer-related mortality.

Chemotherapeutic agents can cause mucosal damage throughout the gastrointestinal tract, leading to ulcers and increasing the risk of bleeding or perforation [46]. Additionally, chemotherapy-induced immunosuppression may impair ulcer healing and increase the risk of infection. Radiation therapy also carries a moderate risk, possibly due to its direct effects on gastrointestinal mucosa when the treatment field includes the abdomen. Surgery, while associated with the lowest overall SMR among the treatment modalities, still presented some risk, potentially due to stress ulcers or postoperative complications [47]. Gao et al. reported improved survival of 11 months (9.8–12.2) with surgery when compared to the non-surgical group with 9 months survival (8.0–10.0) [48]. Trending reports have been marketed over the period, revealing the development of peptic ulcers with life-threatening complications throughout its execution. Wang et al. reported three cases with life-threatening problems that showed to have chemotherapy-induced peptic ulcers on upper GI endoscopy, if left untreated, may lead to death [49]. He reported 30 days mortality up

to 55.6%, which was inreased to 71.1% when extended to 90 days among cancer patients taking chemotherapy due to peptic ulcer.

Strengthens and limitations

To the best of our knowledge, our cohort is the first to comprehensively study the risk of death from stomach and duodenal ulcer in cancer patients and to examine the correlation between various outcomes and this risk. With a sample size of 6,891,191 cancer patients, it represents the largest cohort to date for assessing this risk. However, our study has limitations. The SEER database provides only basic patient characteristics and lacks detailed information on full treatment plans, prior surgeries, previous pathologies and co-morbidities. Additionally, data on tumor staging (T, N, M) using the AJCC 6th edition is available only for patients diagnosed between 2004 and 2015, which limits our analysis to this period. Similarly, SEER stage classifications (localized, regional, or distant) are also restricted to cases from 2004 to 2015. Finally, while peptic ulcers are common in gastrointestinal cancers, our findings indicate an association rather than a definitive causal relationship. Further research is needed to explore the underlying mechanisms and validate these findings in clinical practice.

Conclusion

Our study reveals a strong association between cancer and stomach and duodenal ulcer, showing an elevated risk of mortality from stomach and duodenal ulcer among cancer patients in the United States. We identified key demographic factors and cancer-related variables influencing this risk, including variations in cancer type, treatment modalities, and patient demographics. These findings highlight the critical need for integrated care strategies that address both cancer and surgery risks, aiming to enhance patient outcomes and reduce mortality from both cancer and other diseases within the oncologic population.

Supplementary Information

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Supplementary Material 1

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Author contributions
Ramez M. Odat: Study concept, Design, Data extraction, Analysis, Scientific writing and Drafting of the manuscript. Muhammad Idrees: Analysis, Scientific writing and Drafting of the manuscript. Mohammed Dheyaa Marsool Marsool, Shahed Mamoun Oglat, Salma Omar Tbayshat, Zaid Ibrahim Adnan, Yousef Adeeb Alkhateeb, Ali O. Aldamen: Scientific writing and Drafting of the manuscript. Hritvik Jain, Dang Nguyen, Hamdah Hanifa: Supervision, Validation, Editing.

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Data availability
Data is provided within the manuscript.

Declarations

Ethics approval and consent to participate
Ethical approval and consent to participate were not required for this study. Authorization and data were obtained through the SEER website and database, respectively.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Author details
[1]Faculty of Medicine, Jordan University of Science and Technology, Irbid, Jordan
[2]Lahore General Hospital, Lahore, Punjab, Pakistan
[3]Department of Medicine, Research Fellow, Mayo Clinic Arizona, Scottsdale, Phoenix, Arizona, USA
[4]Faculty of Medicine, Al Yarmouk University, Irbid, Jordan
[5]Department of Internal Medicine, All India Institute of Medical Sciences (AIIMS), Jodhpur, India
[6]Corrigan Minehan Heart Center, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA
[7]Faculty of Medicine, University of Kalamoon, Al_Nabk, Syria

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