Cohort Study

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The risk and distribution of second primary cancers according to subsite of primary stomach cancer: a retrospective cohort population-based study

Ali Hemade, MD[a,*], Souheil Hallit, PharmD, MSc, MPH, PhD[b,c]

Background: The development of second primary cancers (SPCs) following a diagnosis of stomach cancer presents a significant clinical challenge, with varying risks depending on the anatomic subsite of the primary tumor, patient demographics, and treatment modalities. This study aims to assess the risk of SPCs in stomach cancer survivors, focusing on differences across anatomic subsites, sex, age, and treatment periods.

Methods: The authors conducted a retrospective cohort study using data from stomach cancer patients, analyzing the incidence of SPCs based on the anatomic location of the primary tumor, with stratifications by sex, age, latency period, and year of diagnosis. Standardized incidence ratios (SIRs) were calculated to compare the observed SPC rates with those expected in the general population.

Results: Elevated stomach SPC risk was observed across most anatomic subsites, particularly in the body (SIR 8.84) and fundus (SIR 7.34). Females exhibited higher SIRs compared to males, especially in the fundus (SIR 13.33 for females vs. 4.55 for males). Younger patients (< 50 years) had significantly higher SPC risks, particularly for cancers originating in the fundus (SIR 49.56). Notably, patients diagnosed after 2010 showed the highest SIRs, indicating a potential impact of advances in diagnostic and therapeutic modalities. Nonstomach SPCs, including colorectal, lung, and thyroid cancers, were significantly elevated, with distinct patterns based on the primary tumor site.

Conclusions: The study highlights the critical role of primary tumor location, sex, age, and treatment era in determining SPC risk in stomach cancer survivors. These findings underscore the need for tailored surveillance strategies to manage long-term cancer risks in this population.

Keywords: cancer, epidemiology, stomach, second primary, standardized incidence ratio

Introduction

Stomach cancer, or gastric cancer, is a significant global health concern, ranking as the fifth most common malignancy and the third leading cause of cancer-related mortality worldwide[1]. Despite substantial progress in the early detection and treatment of stomach cancer, the prognosis remains dismal, particularly in advanced stages, with a 5-year survival rate that varies significantly depending on the stage at diagnosis[2]. Over recent decades, advancements in surgical techniques, chemotherapies, and targeted therapies have improved outcomes for many patients, leading to an increasing number of long-term survivors[3,4].

HIGHLIGHTS

- Patients with primary stomach cancer, particularly those with tumors in the body and fundus, exhibit significantly elevated risks for developing second primary cancers, including colorectal and pancreatic cancers.
- Genetic predispositions such as Lynch syndrome, along with shared environmental risk factors like smoking and Helicobacter pylori infection, contribute to the increased incidence of colorectal and pancreatic SPCs in stomach cancer survivors.
- Radiotherapy and chemotherapy used in treating stomach cancer may increase the risk of secondary malignancies in adjacent organs, highlighting the need for tailored surveillance strategies in this patient population.

As the population of stomach cancer survivors grows, attention has shifted to the long-term health challenges these individuals face, particularly the risk of developing second primary cancers (SPCs)[5–10]. SPCs are defined as new malignancies that occur in patients who have survived a previous cancer, and they pose a significant risk of morbidity and mortality[11]. The development of SPCs in cancer survivors may result from a combination of factors, including genetic predisposition, shared environmental risk factors, lifestyle behaviors, and the late effects of cancer treatment such as chemotherapy, radiotherapy, or immunosuppression[12–16]. Cancer predisposition syndromes are also associated with a high risk of developing early SPCs[17].

[a]Faculty of Medicine, Lebanese University, Hadat, Lebanon, [b]School of Medicine and Medical Sciences, Holy Spirit University of Kaslik, Jounieh, Lebanon and [c]Applied Science Research Center, Applied Science Private University, Amman, Jordan

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*Corresponding author. Address: Hadat, Beirut, Lebanon. Tel.: +961 793 045 27. E-mail: alihemade3@gmail.com. (A. Hemade).

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Stomach cancer survivors are known to have an elevated risk of SPCs, particularly in organs with shared etiological factors or those that were exposed to carcinogenic treatment[18]. Previous studies have reported an increased incidence of SPCs in sites such as the esophagus, small intestine, colon, rectum, pancreas, and lungs[5,19–21]. However, the relationship between the anatomic subsite of the primary stomach cancer and the subsequent risk and distribution of SPCs remains underexplored. Stomach cancer can originate in various anatomical subsites, including the cardia, fundus, body, antrum, and pylorus, each of which may have different biological behaviors, risk factors, and treatment responses.

The anatomic subsite of the primary tumor may influence the risk of SPCs due to differences in tumor biology, genetic mutations, and the extent of treatment exposure[4,22]. For example, tumors located in the gastric cardia are often associated with different risk factors and genetic profiles compared to those in the distal stomach, as one study showed differences in Single Nucleotide Polymorphism between cardia and noncardia tumors of the stomach[23].

To the best of our knowledge, limited evidence exists on the role of the anatomic site of stomach cancer in determining the risk of SPCs. Understanding the risk and distribution of SPCs based on the anatomic subsite of the primary stomach cancer is crucial for improving surveillance strategies and tailoring preventive measures. This knowledge can guide clinicians in making more informed decisions regarding the long-term monitoring of stomach cancer survivors and in identifying those who may benefit from more intensive surveillance. In this study, we aim to assess the risk of SPCs in stomach cancer survivors, with a specific focus on the influence of the anatomic subsite of the primary tumor. We hypothesize that the risk for second primary cancer will be different across patients depending on the primary stomach cancer location. By leveraging data from a large, population-based cohort, we will evaluate whether certain subsites of stomach cancer are associated with higher risks of SPCs.

Materials and methods

Study population

This retrospective cohort study was conducted using data collected from the Surveillance, Epidemiology, and End Results (SEER) database supported by the National Cancer Institute. We utilized data from the SEER 8, which includes registries from eight geographic areas of the United States (Connecticut, Atlanta, San Francisco – Oakland, Hawaii, Iowa, New Mexico, Seattle – Puget Sound – Utah), providing a comprehensive and representative sample of the US population. The dataset utilized for this study was the November 2023 submission, covering the period from 1975 to 2021.

We included patients diagnosed with Stomach cancer as the first primary cancer. Specific primary stomach cancer anatomic sites included C16.0 – C16.9 codes as classified by the International Classification of Diseases, Tenth Revision, and Clinical Modification (ICD-10-CM). We included patients with primary stomach cancer originating in lymph nodes of the following regions only: C16.0 – 'Cardia', C16.1 – 'Fundus of stomach', C16.2 – 'Body of stomach', C16.3- 'Gastric antrum', C16.4- 'Pylorus'. Patients with first primary stomach cancer originating in regions classified as C16.5 – 'Lesser curvature of stomach, NOS (Not otherwise specified)', C16.6 – 'Greater curvature of stomach, NOS', C16.8 – 'Overlapping lesion of stomach', and C16.9 – 'Stomach, NOS' were not included in our study. Patients diagnosed with stomach cancer at autopsy or reported through death certificate only were not included. We chose the latency exclusion period to be 2 months; that is, all patients who were diagnosed with a second primary cancer within less than 2 months of diagnosis with primary stomach cancer were excluded. This is in compliance with the ICD's international rules for multiple primary cancers[24]. Some patients were diagnosed with an SPC at least 2 months following diagnosis with primary stomach cancer. All cancers following the primary stomach cancer were included in calculating the SIR values as will be described below. In addition, we extracted data pertinent to each patient's age, sex, race, and location of second primary cancer if applicable.

Statistical analysis

All statistical analyses were performed using SEERStat software (version 8.4.3, National Cancer Institute). We employed a Multiple Primary-Standardized Incidence Ratio (MP-SIR) session to calculate the Standardized Incidence Ratios (SIRs), Absolute Excess Risks (AERs), and Person-Years at Risk (PYRs), stratified by primary stomach cancer anatomic location, assuming a Poisson distribution for the observed number of SPC. The MP-SIR session in SEERStat compares the observed number of second primary cancers in the study cohort to the expected number based on general population cancer incidence rates, adjusted for age, sex, and calendar period. The SIR is the ratio of observed to expected cases. It is calculated by dividing the observed number of second primary cancers by the expected number, which is based on the incidence rates in the general population. The AER represents the excess number of cancer cases per 10 000 Person-Year at Risk (PYR). It is calculated by subtracting the expected number of cases from the observed number and then dividing by the PYR. PYR is the total amount of time that the cohort is at risk of developing a second primary cancer, calculated from the time of initial stomach cancer diagnosis to either the diagnosis of a second primary cancer, death, or end of the study period[25]. The SIR, AER, and PYR were calculated for each primary stomach cancer anatomic site. For SPC of the stomach, we stratified our analysis by latency period (2–59 months and 60+ months after primary cancer diagnosis), age at primary cancer diagnosis (less than 50 years old and older than 50 years old), sex, and year of primary cancer diagnosis (1975–1979, 1980–1989, 1990–1999, 2000–2009, and 2010–2021).

The statistical significance of the SIRs was determined using Poisson regression models to calculate 95% CIs. An SIR was considered statistically significant if the 95% CI did not include 1.0; that is, a two-sided *P*-value less than 0.05[26].

Ethical considerations

As this study extracted data from the SEER database, a publicly available cancer registry of deidentified and decoded data with no possibility of tracing back patient information, an institutional review board was not required.

Results

Study population

Our cohort included 33 951 patients. The majority were males (65.8%) and white (72.7%). 6.98% of these patients developed at least one second primary cancer. In these patients, 75.57% of SPCs occurred within 120 months of primary stomach cancer diagnosis. An overview of the characteristics of the cohort of our study are summarized in Table 1. Our reporting is compliant with the strengthening the reporting of cohort, cross-sectional, and case–control studies in surgery (STROCSS) guidelines[27].

Risk for second primary cancer

The risk for all-site SPCs was significantly elevated in patients with primary stomach cancer originating in the cardia (SIR, 1.28; 95% CI: 1.20–1.37), body (SIR 1.27; 95% CI: 1.14–1.41), and antrum (SIR 1.10; 95% CI: 1.02–1.18), while the risk was not significant in cancers originating in the fundus (SIR 1.12; 95% CI: 0.96–1.29) and pylorus (SIR 1.11; 95% CI: 0.93–1.33) (Table 2). When considering only nonstomach cancer SPCs, the risk was only significant in patients with primary stomach cancer originating from the cardia (SIR 1.20; 95% CI: 1.12–1.28). The results are represented in Table 2.

The SPC with the highest SIRs was second primary stomach cancer, the risk for which was consistently elevated for patients with primary stomach cancer originating in all anatomic sites of the stomach except the pylorus, with SIR values ranging from 8.84 (95% CI: 6.77–11.33) for primary cancer originating in the body to 7.34 (95% CI: 4.79–10.76) for primary cancers originating in the fundus. In our extended investigation, we noticed that these patterns were similar when stratified by sex, with SIR of stomach SPCs in patients with primary stomach cancer originating in the fundus and body being the highest and the risk for primary stomach cancer originating in the pylorus being nonsignificant (Fig. 1A).

Table 1

Cohort characteristics

Patient characteristics		Frequency (*n*)	Percentage (%)
Total number of patients included in our cohort		33 951	
Sex	Male	22 340	65.8
	Female	11 611	34.2
Race	White	24 682	72.7
	Black	2936	8.6
	Other	6220	18.3
	Unknown	113	0.3
Mean age at primary stomach cancer diagnosis (in years)	67.33		
Mean age at secondary primary cancer diagnosis (in years)	73.16		
Primary stomach cancer anatomic location	Antrum	9933	29.3
	Body	4239	12.5
	Cardia	15 555	45.7
	Fundus	2609	7.7
	Pylorus	1615	4.8
Patients that developed a second primary cancer		2371	6.98

Table 2

Standardized incidence ratio values for different second primary cancers across different stomach cancer primary sites

Second cancer site	All first primary sites			Cardia			Fundus			Body			Antrum			Pylorus		
	112 861.78			40 608.16			9704.31			16 577.09			39 674.74			6297.48		
Person-year risk	SIR	95% CI	AER	SIR	95% CI	AER	SIR	95% CI	AER	SIR	95% CI	AER	SIR	95% CI	AER	SIR	95% CI	AER
All sites	**1.19**	1.15–1.24	33.99	**1.28**	1.20–1.37	51.85	1.12	0.96–1.29	19.13	**1.27**	1.14–1.41	44.39	**1.10**	1.02–1.18	17.23	1.11	0.93–1.33	19.97
All nonstomach	**1.10**	1.06–1.15	17.74	**1.20**	1.12–1.28	36.68	0.98	0.83–1.14	−4.02	1.07	0.95–1.20	11.22	1.04	0.96–1.12	6.82	1.09	0.90–1.31	15.21
Esophagus	**3.29**	2.60–4.11	4.81	**5.55**	4.19–7.21	11.31	1.67	0.34–4.87	1.24	1.73	0.56–4.03	1.27	1.55	0.80–2.71	1.08	1.66	0.19–5.99	1.26
Stomach	**4.77**	4.18–5.42	16.25	**5.28**	4.16–6.61	15.17	**7.34**	4.79–10.76	23.14	**8.84**	6.77–11.33	33.17	**3.00**	2.30–3.84	10.41	2.00	0.73–4.36	4.77
Small intestine	**3.03**	1.98–4.45	1.54	**2.70**	1.23–5.13	1.40	4.16	0.84–12.15	2.35	**5.73**	2.30–11.81	3.49	2.10	0.77–4.57	0.79	2.29	0.03–12.75	0.90
Colon and rectum	**1.16**	1.02–1.31	3.14	**1.24**	1.00–1.52	4.48	1.35	0.87–2.01	6.44	1.01	0.68–1.43	0.14	1.13	0.92–1.37	2.84	0.97	0.53–1.62	−0.73
Pancreas	**1.62**	1.32–1.96	3.48	1.09	0.70–1.63	0.51	**2.55**	1.36–4.36	8.15	**1.86**	1.09–2.98	4.75	**1.63**	1.16–2.22	3.79	**2.78**	1.33–5.12	10.17
Lung and bronchus	**1.32**	1.19–1.46	8.17	**1.54**	1.31–1.79	14.26	0.84	0.50–1.31	−3.77	1.26	0.93–1.66	6.07	**1.25**	1.04–1.49	6.50	1.14	0.67–1.80	3.43
Trachea	**12.54**	2.52–36.64	0.24	**32.45**	6.52–94.82	0.72	0.00	0.00–192.68	−0.02	0.00	0.00–125.56	−0.02	0.00	0.00–43.54	−0.02	0.00	0.00–257.18	−0.02
Vulva	**2.78**	1.39–4.97	0.62	**4.97**	1.34–12.73	0.79	2.56	0.03–14.23	0.63	1.39	0.02–7.75	0.17	2.27	0.61–5.82	0.56	3.52	0.05–19.56	1.14
Urinary bladder	**1.27**	1.08–1.49	2.87	**1.42**	1.11–1.78	5.39	0.90	0.39–1.77	−0.93	1.11	0.64–1.81	0.99	1.31	0.97–1.73	2.98	0.66	0.18–1.70	−3.21
Kidney	1.20	0.92–1.54	0.90	**1.54**	1.06–2.16	2.85	0.97	0.26–2.48	−0.14	1.18	0.51–2.33	0.74	1.00	0.57–1.62	−0.02	0.00	0.00–1.50	−3.88
Thyroid	**2.45**	1.76–3.32	2.15	**3.36**	2.05–5.19	3.46	**3.26**	1.05–7.60	3.57	1.78	0.57–4.15	1.32	1.60	0.73–3.03	0.85	2.44	0.27–8.82	1.88

Bold values represent statistical significance (*P*-value < 0.05).
AER, absolute excess risk; SIR, standardized incidence ratio.

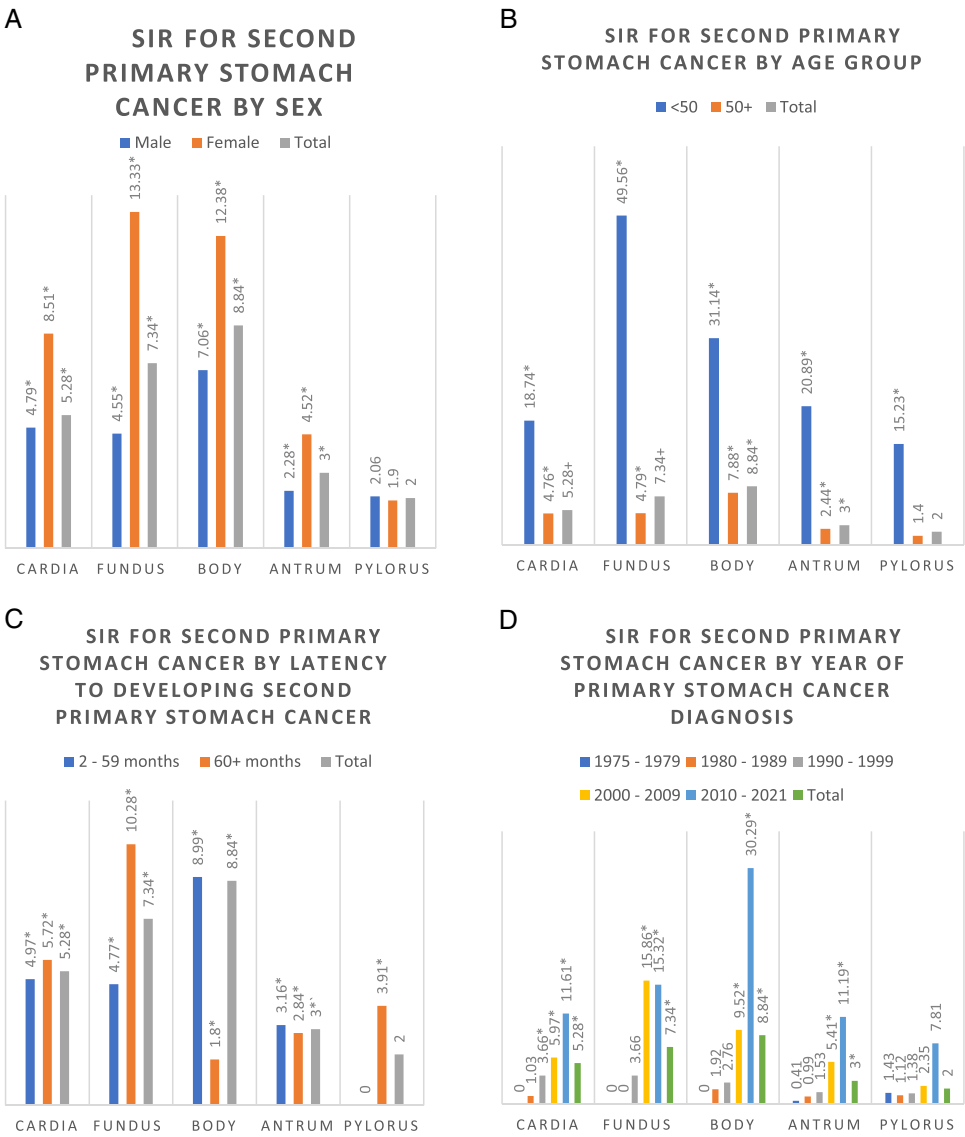

Figure 1. Standardized Incidence Ratios for second primary stomach cancers in patients with primary stomach cancer originating in different stomach anatomic sites stratified by (A) sex, (B) age group, (C) latency to developing second primary stomach cancer, and (D) year of primary stomach cancer diagnosis. SIR, standardized incidence ratio. * indicates statistically significant SIRs.

However, the SIR values for females were higher than those for male patients. For instance, the risk for stomach SPC in patients with primary stomach cancer originating in the fundus was higher in females (SIR 13.33; 95% CI: 7.45–21.99) compared to males (SIR 4.55; 95% CI: 2.27–8.15).

When stratified by age group (Fig. 1B), the risk for stomach SPC was much higher in patients less than 50 years of age at the time of diagnosis with primary stomach cancer, but the trends of SIR across primary stomach cancer anatomic sites remains similar, with the SIR being the highest in patients with primary stomach cancer originating in the fundus (49.56 for patients younger than 50 vs. 4.79 for patients older than 50). The risk for stomach SPC in patients with primary stomach cancer originating in the pylorus was significant only in patients less than 50 years of age (SIR 15.23), while that risk was not significant in other age groups.

When stratified by latency period (Fig. 1C), the trends of SIR were similar for SPCs diagnosed 2–59 months after primary stomach cancer compared to the total group. However, the risk for SPCs for stomach cancer originating in the body was much lower in patients diagnosed 60 months and later after the first primary cancer diagnosis compared to the total group (SIR 1.8 vs. 8.84). Also, the risk for SPCs for stomach cancer originating in the pylorus was only significant in the group of patients diagnosed with second primary stomach cancer 60 months and later after the first primary stomach cancer diagnosis (SIR 3.91).

When stratified based on the year of diagnosis of first primary stomach cancer (Fig. 1D), the risk of second primary stomach cancer differed. The risk was not significant in the 1975–1979 and 1980–1989 groups across all anatomic sites of primary stomach cancer. SIR values were highest for all second primary stomach cancers in the 2010–2021 group for all anatomic sites of

primary stomach cancer, with the SIR for the pylorus group remaining nonsignificant.

There was a significantly elevated risk of second primary esophageal (SIR 3.29; 95% CI: 2.6–4.11), small intestine (SIR 3.03; 95% CI: 1.98–4.45), colorectal (SIR 1.16; 95% CI: 1.02–1.31), pancreatic (SIR 1.62; 95% CI: 1.32–1.96), lung (SIR 1.32; 95% CI: 1.19–1.46), trachea (SIR 12.54; 95% CI: 2.52–36.64), vulva (SIR 2.78; 95% CI: 1.39–4.97), bladder (SIR 1.27; 95% CI: 1.08–1.49), and thyroid (SIR 2.45; 95% CI: 1.76–3.32) cancers. The risk of SPCs was not consistent across stomach cancer primary sites. The risk of second primary esophageal cancer was only significant in patients with primary stomach cancer originating in the cardia (SIR 5.55; 95% CI: 4.19–7.21), while the risk of second primary pancreatic cancer was significant in patients with primary stomach cancer originating in all anatomic sites of the stomach except the cardia. Overall, the cardia was the location of primary stomach cancer with the most consistently significant SIR for SPC development.

Discussion

Our study demonstrates that the risk of developing a stomach SPC in patients with primary stomach cancer is significantly elevated across most anatomic subsites of the primary tumor, with the exception of the pylorus. The highest SIRs were observed in patients with primary stomach cancer originating in the body and the fundus. These findings are consistent with previous research indicating that certain subsites, such as the body and fundus, are more susceptible to multiple primary stomach malignancies, likely due to chronic inflammation and Helicobacter pylori infection, which are known risk factors for gastric cancer[28,29].

Notably, our SIR values for all-site SPCs was comparable to other studies that did not use the SEER database[7,10]. One study conducted in Taiwan showed an SIR value of 1.21 for all-site SPCs, which is very close to our study (SIR of 1.19)[18]. Interestingly, the risk for second primary stomach cancer in the pylorus was not statistically significant in our study, a novel insight presented for the first time. One can speculate that this discrepancy might be due to underlying risk factors or treatment modalities that could influence the risk of SPC development in this specific subsite. Nonetheless, more research into the biology of pylorus cancers is encouraged.

In our extended analysis, when stratified by sex, we showed significant differences in the risk of second primary stomach cancer. Females consistently exhibited higher SIRs compared to males, particularly for tumors originating in the fundus and body of the stomach. For instance, the risk in females with primary cancer in the fundus was markedly elevated compared to males. This is contrary to other studies that demonstrated a higher risk for males to develop stomach SPCs after a primary stomach cancer[10,18,30]. Genetic and environmental factors between the samples might explain this contradiction, along with the fact that our study had a follow-up of more than 10 years compared to previous studies of less than 10 years. Previous studies have demonstrated an important role for CDH1 (E-Cadherin) mutations in the risk for hereditary diffuse gastric cancer, and this seems to be more prevalent in females[31].

Age at the time of primary stomach cancer diagnosis was another critical factor influencing the risk of second primary stomach cancers. Younger patients (< 50 years) exhibited significantly higher SIRs across most anatomic subsites compared to older patients. For example, the risk for stomach SPC in patients with primary cancer originating in the fundus was dramatically higher in those under 50 years of age (SIR 49.56) compared to those over 50 (SIR 4.79). This suggests that younger patients may have a more aggressive disease course or a greater genetic predisposition to multiple malignancies[32]. The significant risks observed in younger patients emphasize the importance of early and continuous surveillance in this group, as they are more likely to develop subsequent malignancies earlier in life.

The latency period between the diagnosis of primary and second primary stomach cancer also revealed important trends. The risk for SPCs remained high within the first 59 months after the initial diagnosis but was notably lower for stomach cancers originating in the body of the stomach after 60 months (SIR 1.8) compared to the overall group (SIR 8.84). This reduction in risk over time may reflect the impact of early detection and removal of precancerous lesions in the initial years following cancer treatment. Research has shown that intensive surveillance in the early years after cancer diagnosis can lead to the early identification and treatment of secondary malignancies, thereby reducing long-term cancer risks[18]. Conversely, the elevated risk observed in the pylorus after 60 months suggests a delayed but persistent risk, which might be linked to the biology of pyloric tumors or the effectiveness of long-term surveillance strategies in detecting SPCs[33].

Stratification by the year of diagnosis of the first primary stomach cancer revealed that the risk of second primary stomach cancer has increased over time, particularly in patients diagnosed after 2010. The highest SIRs for all SPCs were observed in this group, suggesting that advances in diagnostic technology, treatment regimens, and increased survival rates may contribute to this trend. For instance, the introduction of more sensitive diagnostic tools, such as endoscopic surveillance and advanced imaging techniques, may lead to the earlier detection of secondary cancers[34]. Additionally, improvements in cancer treatment, including the use of targeted therapies and immunotherapies, may have extended patient survival, thereby increasing the window of opportunity for secondary malignancies to develop[35].

Beyond the stomach, our study identified significantly elevated risks for second primary cancers in other organs, with particularly notable patterns based on the location of the primary stomach tumor.

Beyond the stomach, our study identified significantly elevated risks for second primary cancers in other organs, with particularly notable patterns based on the location of the primary stomach tumor. Other gastrointestinal cancers such as colorectal, small intestine, and pancreatic cancers were important SPCs in our study, which resonates with previous findings[7,8]. Genetic predispositions, such as Lynch syndrome, significantly increase the risk of both colorectal and gastric cancers, as these patients carry mutations in DNA mismatch repair genes, predisposing them to multiple primary malignancies across the gastrointestinal tract[36]. Shared lifestyle factors, including smoking, alcohol consumption, and diet, are also common risk factors for stomach, colorectal, and pancreatic cancers[37]. The risk of second primary tracheal cancer was strikingly high (SIR 32.45) but only observed in patients with primary tumors originating in the cardia. The risk of second primary lung cancer was significantly elevated in patients with primary stomach cancer originating in the cardia

and antrum. This may be due to the anatomical proximity of the gastric cardia to the trachea and esophagus, which could facilitate the spread of carcinogenic effects from treatments like radiotherapy or the influence of shared environmental risk factors, such as smoking, which is a known risk factor for cancers in both the upper gastrointestinal and respiratory tracts[21]. The elevated risk of second primary bladder cancer in patients with primary tumors in the cardia (SIR 1.27) could be related to shared carcinogenic exposures, such as smoking and occupational chemicals, which affect both gastric and bladder tissues. Additionally, bladder cancer has been associated with the long-term effects of systemic chemotherapy, often used to treat gastric cardia cancers, which may increase the risk of bladder malignancies[38]. The observed elevated risk of second primary vulvar cancer in patients with primary gastric cardia cancer (SIR 2.78) is intriguing and could be due to shared genetic predispositions or viral etiologies such as HPV, which has been implicated in both vulvar and certain gastric cancers. Moreover, systemic effects of treatments for cardia cancers, such as radiotherapy, might also contribute to an increased risk in distant sites like the vulva[39]. The elevated risk of second primary thyroid cancer was observed only in patients with primary tumors in the cardia and fundus (SIR 2.45 and SIR 2.67, respectively). This association might reflect the shared impact of radiotherapy, which is a common treatment for gastric cancers located in the cardia and fundus, and is known to increase the risk of secondary thyroid malignancies[40].

These findings have significant implications for clinical practice. The high risk of second primary stomach cancers, particularly in the fundus, body, and cardia, necessitates the development of targeted surveillance strategies tailored to the specific risk profiles of patients based on their primary tumor's location, age, and sex. Additionally, the observed risks for nonstomach SPCs in specific organs, such as the trachea, lungs, bladder, vulva, and thyroid, suggest that patients with primary stomach cancers, especially those located in the cardia, may require broader surveillance for secondary malignancies in these regions. This comprehensive approach is essential to mitigate the long-term risks and improve overall survival outcomes for these patients.

Several strengths of our study are worth of being highlighted. Our research is novel, and this is the first research to provide a comprehensive examination of SPCs in stomach cancer based on the anatomic site of primary stomach cancer. Also, the use of a large, population-based cohort enhances the statistical power of our research. The present study's extended follow-up period enabled the capture of long-term outcomes and late-onset SPCs, providing a more complete picture of the cancer trajectory in stomach cancer survivors. On the other hand, our study has several limitations that should be kept in mind when interpreting the results. Firstly, the retrospective design may introduce recall bias and affect data accuracy, particularly in capturing detailed patient history and treatment information. The lack of detailed treatment information, such as specific chemotherapy and radiotherapy doses, limited our ability to fully assess the impact of treatment regimens on SPC risk. Furthermore, the absence of genetic data restricts our understanding of the role of hereditary factors, which are known to influence multiple primary cancer risks. The study also focused on clinically diagnosed SPCs, potentially underestimating the true incidence due to undiagnosed or misclassified cases. Geographic and demographic limitations, as most data were derived from specific regions of the United States, may affect the generalizability of our findings.

Conclusion

In conclusion, our study highlights the critical role of the anatomic subsite of primary stomach cancer in determining the risk of SPCs. The significantly elevated risks associated with tumors located in the cardia, body, and antrum underscore the need for tailored surveillance strategies in these patients. Moreover, the increased risk of specific secondary malignancies in the trachea, lungs, bladder, vulva, and thyroid, particularly in patients with cardiac tumors, emphasizes the importance of a multidisciplinary approach to patient care, incorporating both targeted and broad surveillance strategies to manage the long-term health of stomach cancer survivors.

Ethical approval

As this study involves retrospective analysis of data deidentified and decoded by the Surveillance, Epidemiology, and End Results (SEER) Program and did not involve any direct or indirect patient contact or intervention, an Institutional Review Board (IRB) approval was not required.

Consent

Our study did not involve any direct or indirect human contact. The data was obtained from the SEER database, which is available publicly online in the form of decoded and deidentified data. Thus, obtaining a written consent is not applicable.

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Not applicable.

Author contribution

A.H.: conceptualization, data curation, formal analysis, investigation, methodology, and writing – original draft; S.H.: supervision and writing – review. All writers agreed on the final manuscript.

Conflicts of interest disclosure

The authors declare no conflicts of interest.

Research registration unique identifying number (UIN)

1. Name of the registry: research registry.
2. Unique identifying number or registration ID: researchregistry10608.
3. Hyperlink to your specific registration (must be publicly accessible and will be checked): https://researchregistry.knack.com/researchregistry#home/registrationdetails/66c0521d132237027cd2634f/.

Guarantor

Ali Hemade.

Data availability statement

Data utilized in our study is publicly available as part of the SEER database.

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