Second primary malignancy risk among patients with gastric cancer: a nationwide population-based study in Taiwan

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Abstract

Background Several studies have reported an increase in second primary malignancies (SPMs) among gastric cancer patients.

Methods Patients who were newly diagnosed with gastric cancer between 1997 and 2011 were recruited from the Taiwan National Health Insurance database. Those who had antecedent malignancies or gastrointestinal stromal tumor were excluded. Standardized incidence ratios (SIRs) of SPMs were calculated. Risk factors for cancer development were analyzed by Cox proportional hazards

models. Effects of treatments for gastric cancer were treated as time-dependent variables.

Results During the 15-year study period, 47,729 gastric cancer patients were recruited. Overall, 2,110 SPMs developed during a total follow-up of 137,798 person-years. The SIR for all cancers was 1.46. The SIRs for specific follow-up periods were 1.43, 1.41, and 1.21 at >10 years, 5–10 years, and 1–5 years, respectively. After excluding SPMs that developed within 1 year, significantly higher SIRs were seen for cancers of the head and neck (1.34), esophagus (2.16), colon and rectum (1.37), bones and soft tissues (1.95), ovaries (2.89), bladder (1.47), or kidneys (1.44), as well as non-Hodgkin's lymphoma (5.56). Multivariate analysis showed that age ≥ 70 years [hazard ratio (HR) 1.19], being male (HR 1.37), diabetes mellitus (HR 1.30), chronic obstructive pulmonary disease (HR 1.17), and liver cirrhosis (HR 1.94) were independent risk factors. Radiotherapy (HR 1.24) and chemotherapy (HR 1.87) were independent risk factors, but surgery (HR 0.67) was not.

Conclusions Patients with gastric cancer are at increased risk of developing SPM. Close surveillance of patients with risk factors over a longer period should be considered.

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Keywords Gastric cancer · Second primary malignancy · Population-based study

Introduction

Gastric cancer is the fourth most common cancer in the population worldwide. Its incidence is decreasing in Western countries; over 70 % of new cases are occurring in developing countries [1]. In Taiwan, gastric cancer mortality has shown a decreasing trend in the past few decades [2], a trend similar to those seen in Japan [3] and Korea [4],

the two nations with the highest gastric cancer incidences in Asia [5]. There are a number of reasons for the increased survival of gastric cancer patients, for instance more hygienic strategies for food conservation, increased screening using upper gastrointestinal panendoscopy, better surgical techniques, improved lymph node dissection, and advances in adjuvant chemotherapy and radiotherapy [6]. However, the risk of second primary malignancy (SPM) is of concern because patients with SPMs present lower survival rates than those without [7–9].

Several single institutes in Asia have reported that SPMs occur in gastric cancer patients at incidences of 0.9–3.4 % [9–11]. However, when group comparisons are performed, the relative risk or incidence ratios observed in large-scale (>5,000 patients) studies are inconsistent. The incidence of SPM at specific sites was found to be relatively high in a Japanese cancer registry study [12] and a Korean single-hospital case series [7], but not in another multicenter case series [13]. A population-based study in Sweden showed a high standardized incidence ratio (SIR) of SPM after gastric cancer, but this increase may have been caused by closer surveillance (i.e., surveillance bias) [14]. So far, no nationwide population-based studies on this topic in Asia have been reported. Thus, given the improvement in gastric cancer survival, a nationwide population-based study of SPM in gastric cancer patients in Taiwan was felt to be a worthwhile pursuit.

The National Health Insurance Research Dataset (NHIRD) in Taiwan possesses a nationwide population dataset for health research. All malignancies are registered precisely, meaning that the NHIRD is suitable for analyzing SPM. Besides age and sex, the NHIRD also includes complete information on major surgeries, chemotherapy, radiotherapy, and comorbidity—information that was not simultaneously integrated into most previous studies on gastric cancer. The aim of the study described in the present paper was to use the NHIRD to compare the overall incidence of SPM in gastric cancer patients with the expected incidence in an age-, sex-, and calendar-year-matched population. In addition, we investigated the potential predisposition of gastric cancer patients for chemotherapy, radiotherapy, and comorbidity.

Materials and methods

Data sources

Taiwan's National Health Insurance (NHI) program is a mandatory universal health insurance program that began in 1995. It supplies comprehensive medical care to all Taiwan's residents, with a coverage rate of more than 99 % [15]. This program provides coverage for outpatient,

emergency, inpatient, dental, and traditional Chinese medicine services, as well as prescription drugs. Our NHI program also allows all cancer patients to easily acquire treatment and surveillance after being diagnosed with cancer at a reasonably low cost, no matter what their socioeconomic background. The so-called “catastrophic illness” system exempts patients from copayment under the NHI program. Any patient certified for catastrophic illness can get appropriate outpatient follow-up, including all the necessary clinical tools, such as physical examinations, laboratory tests, endoscopies, and imaging studies such as a computed tomography (CT) scan and/or a magnetic resonance imaging (MRI) scan, for \$NT 100 dollars (~US\$ 3.2 or ¥ 370).

Our study used the NHIRD database, which is managed by the National Health Research Institute of Taiwan and available publicly. The NHI Database of Catastrophic Illness provides comprehensive information on the NHI enrollment of and health care resources for all patients with severe diseases. It integrates several NHI databases, including claims data, NHI enrollment files, and the registry for drug prescriptions. Gastric cancer and all other types of malignancies are categorized as catastrophic illnesses. Because of the possibility of exempting patients from most copayments, the insurance office strictly reviews the diagnosis. Registration as a cancer patient often requires pathological proof of the diagnosis. When there is no pathological confirmation, the clinical diagnosis must be supplemented by persuasive results from laboratory tests and imaging studies. In addition, since the referral system in Taiwan has not been fully enforced, patients with cancers of any stage or type can easily obtain access to all levels of hospitals, including medical centers for diagnosis and management—implying that they must be registered. Accordingly, the accuracy of cancer diagnoses from the catastrophic illness data is reliable, and the vast majority of all cancer patients in Taiwan are included in the data.

All information that could potentially identify an individual patient is encrypted. These data are confidential, as mandated by the Bureau of National Health Insurance and the National Health Research Institute. Because the NHI dataset contains unidentifiable secondary data for research purposes, our study is exempt from full review by the institutional review board of Taipei Veterans General Hospital (2013-10-002CE).

Study population

We conducted a nationwide population-based cohort study spanning January 1, 1997 to December 31, 2011. Newly diagnosed gastric cancer cases were retrieved from the Registry of Catastrophic Illness and diagnosed based on the International Classification of Diseases, Ninth Revision,

Clinical Modification (ICD-9-CM) code 151. Patients diagnosed with gastric cancer before January 1, 1997 were not enrolled. Patients aged <20 years at the time of diagnosis and those who had antecedent malignancies or gastrointestinal stromal tumor were excluded. Data on comorbidity and gastric cancer treatments such as surgery, radiation, and chemotherapy were collected for further analysis. The surgery was defined as curative gastrectomy.

Statistical analyses

The main dependent variable was development of SPM. Subjects identified from the Registry for Catastrophic Illness required histological evidence of malignant diagnosis. These patients were followed until the occurrence of SPM, death, or dropout from the NHI program before the end of the year 2011.

This study used the SIR, which is defined as the observed number of cancer occurrences divided by the expected number, to determine the risk of SPM among patients in this study cohort. The expected number of cancers was calculated by simply multiplying the cancer incidence in the general population by the number of patients in this study cohort who were in the corresponding age group. Each group was stratified according to sex, calendar year, and age in 5-year intervals by the corresponding stratum-specific person-time accrued in the cohort. The incidence of cancer among the general population was acquired from the Taiwan National Cancer Registry. The 95 % confidence intervals (CIs) of the SIRs were estimated according to the assumption that the observed number of cancers followed a Poisson probability distribution. We defined the SIRs for subgroups based on sex and age group. A subgroup analysis stratified by the time taken to develop the SPM was carried out to avoid surveillance bias. For the same reason, SIRs for different types of cancers were estimated by excluding SPMs that occurred within 1 year after the diagnosis of gastric cancer. Risk factors for the development of SPM in gastric cancer patients were analyzed using univariate and multivariate Cox proportional hazards models. We analyzed factors including not only age, sex, and comorbidities but also surgery, chemotherapy, and radiotherapy. Treatments after gastric cancer were treated as time-dependent variables to prevent immortal time bias. Factors with $p < 0.1$ in univariate analyses were included in the Cox multivariate analysis.

Data were extracted and computed using the Perl programming language (version 5.12.2; Perl Foundation, Walnut, CA, USA). Data linkage, processing, and sampling were conducted using Microsoft SQL Server 2008 (Microsoft Corp., Redmond, WA, USA). SAS 9.2 software (SAS Institute Inc., Cary, NC, USA) was used for all

statistical analysis. Statistical significance was defined as $p < 0.05$.

Results

Characteristics of the study population

We identified 50,598 patients with gastric cancer in the NHIRD's Catastrophic Illness Registry from 1997 to 2011. Among these, 25 patients were under the age of 20; 2,158 patients had antecedent malignancies before gastric cancer, 23 patients were lost to follow-up, and 663 patients were misclassified (see the flow chart in Fig. 1). Therefore, the final sample consisted of 47,729 patients, including 30,415 (63.7 %) males and 17,314 (36.3 %) females, with a median age of 69 years at diagnosis (interquartile range, 57–77 years). Overall, this cohort was observed for 137,798 person-years from 1997 to 2011. The characteristics of this cohort are shown in Table 1.

All cancers

During the observation period, 2,045 cancers developed. In comparison with the general population, patients with gastric cancer had a significantly increased risk of any type of cancer (SIR 1.46; 95 % CI 1.40–1.52, $p < 0.001$). The SIR was 1.38 (95 % CI 1.31–1.46, $p < 0.001$) for men and 1.67 (95 % CI 1.54–1.80, $p < 0.001$) for women. A subanalysis showed that patients who were relatively young at the time of diagnosis had the highest SIR for any cancer. Patients aged 20–39 had an SIR of 7.59 (95 % CI 5.29–10.56). Subgroup analysis based on the time taken to develop SPM after the diagnosis of gastric cancer showed that the SIRs for 0–1, 1–5, 5–10, and >10 years after the diagnosis of gastric cancer were 1.98 (95 % CI 1.83–2.13, $p < 0.001$), 1.21 (95 % CI 1.12–1.30, $p < 0.001$), 1.41 (95 % CI 1.29–1.54, $p < 0.001$), and 1.43 (95 % CI 1.21–1.69, $p < 0.001$), respectively. The results of this subanalysis are summarized in Table 2.

Specific cancer types

After excluding SPMs that developed within 1 year after the diagnosis of gastric cancer, significantly higher SIRs were observed for cancers of the head and neck (1.34, 95 % CI 1.09–1.63), esophagus (2.16, 95 % CI 1.61–2.84), colon and rectum (1.37, 95 % CI 1.21–1.54), bones and soft tissue (1.95, 95 % CI 1.11–3.16), ovaries (2.89, 95 % CI 1.71–4.57), bladder (1.47, 95 % CI 1.16–1.84), kidneys (1.44, 95 % CI 1.06–1.93), as well as non-Hodgkin's lymphoma (5.56, 95 % CI 4.68–6.55). SIRs for specific cancer types are shown in detail in Table 3.

Fig. 1 Flow chart for patient inclusion in the study **Table 1** Characteristics of patients with gastric cancer

	Total	Male	Female
No. of patients	47,729	30,415	17,314
Person-years at risk	137,798	84,700.2	53,098.2
Median follow-up, years (interquartile range)	1.25 (0.40–3.94)	1.20 (0.39–3.72)	1.33 (0.42–4.32)
Median age, years (interquartile range)	69 (57–77)	70 (59–78)	67 (53–77)
Age at diagnosis, years			
20–39	2,031	928	1,103
40–59	12,194	7,071	5,123
60–79	25,167	17,069	8,098
≥80	8,337	5,347	2,990

Table 2 Standardized incidence ratios according to sex, age at diagnosis, and follow-up time after gastric cancer diagnosis

Characteristics	Total			Male			Female		
	Observed	Expected	SIR (95 % CI)	Observed	Expected	SIR (95 % CI)	Observed	Expected	SIR (95 % CI)
All cancers	2,045	1,401.42	1.46 (1.40–1.52)	1,405	1,017.10	1.38 (1.31–1.46)	640	384.31	1.67 (1.54–1.80)
Age at diagnosis, years									
20–39	35	4.61	7.59 (5.29–10.56)	15	1.68	8.93 (5.00–14.73)	20	2.93	6.82 (4.17–10.54)
40–59	456	155.13	2.94 (2.68–3.22)	268	88.58	3.03 (2.67–3.41)	188	66.56	2.82 (2.44–3.26)
60–79	1,178	879.38	1.34 (1.26–1.42)	850	657.68	1.29 (1.21–1.38)	328	221.70	1.48 (1.32–1.65)
≥80	376	362.29	1.04 (0.94–1.15)	272	269.17	1.01 (0.89–1.14)	104	93.13	1.12 (0.91–1.35)
Follow-up period after gastric cancer diagnosis, years									
0–1	662	334.90	1.98 (1.83–2.13)	457	246.35	1.86 (1.69–2.03)	205	88.55	2.32 (2.01–2.65)
1–5	746	616.81	1.21 (1.12–1.30)	512	449.96	1.14 (1.04–1.24)	234	166.85	1.40 (1.23–1.59)
5–10	495	350.69	1.41 (1.29–1.54)	338	251.89	1.34 (1.20–1.49)	157	98.80	1.59 (1.35–1.86)
≥10	142	99.01	1.43 (1.21–1.69)	98	68.91	1.42 (1.15–1.73)	44	30.11	1.46 (1.06–1.96)

SIR standardized incidence ratio, CI confidence interval

Table 3 Standardized incidence ratios (SIRs) for specific cancer types in patients with gastric cancer (for follow-up periods of more than 1 year)

Site of cancers	Total		Male			Female		
	Observed	Expected	SIR (95 % CI)	Observed	Expected	SIR (95 % CI)	Observed	Expected
All cancers	1,383	1,066.52	1.30 (1.23–1.37)	948	770.75	1.23 (1.15–1.31)	435	295.77
Head and neck	101	75.41	1.34 (1.09–1.63)	92	67.46	1.36 (1.10–1.67)	9	7.95
Digestive system	526	418.08	1.26 (1.15–1.37)	378	308.30	1.23 (1.11–1.36)	148	109.78
Esophagus	51	23.59	2.16 (1.61–2.84)	46	21.92	2.10 (1.54–2.80)	5	1.67
Colon and rectum, anus	264	193.16	1.37 (1.21–1.54)	169	136.35	1.24 (1.06–1.44)	95	56.81
Liver and biliary tract	183	177.04	1.03 (0.89–1.19)	142	133.29	1.07 (0.90–1.26)	41	43.75
Pancreas	28	24.29	1.15 (0.77–1.67)	21	16.75	1.25 (0.78–1.92)	7	7.54
Lung and mediastinum	173	185.08	0.93 (0.80–1.08)	146	146.50	1.00 (0.84–1.17)	27	38.57
Bone and soft tissue	16	8.21	1.95 (1.11–3.16)	9	6.03	1.49 (0.68–2.83)	7	2.19
Skin	32	27.58	1.16 (0.79–1.64)	17	18.02	0.94 (0.55–1.51)	15	9.56
Breast	57	48.99	1.16 (0.88–1.51)	0	0.99	0.00 (0.00–3.74)	57	48.00
Genitourinary system	283	224.00	1.26 (1.12–1.42)	208	171.11	1.22 (1.06–1.39)	75	52.89
Cervix	15	18.97	0.79 (0.44–1.30)	N/A	N/A	N/A	15	18.97
Uterus	8	7.07	1.13 (0.49–2.23)	N/A	N/A	N/A	8	7.07
Ovaries	18	6.23	2.89 (1.71–4.57)	N/A	N/A	N/A	18	6.23
Prostate	120	108.29	1.11 (0.92–1.33)	120	108.29	1.11 (0.92–1.33)	N/A	N/A
Bladder	76	51.61	1.47 (1.16–1.84)	62	42.29	1.47 (1.12–1.88)	14	9.32
Kidneys	46	31.84	1.44 (1.06–1.93)	26	20.54	1.27 (0.83–1.86)	20	11.30
Thyroid	12	9.88	1.21 (0.63–2.12)	4	3.44	1.16 (0.32–2.98)	8	6.44
Hematologically related	165	50.86	3.24 (2.77–3.78)	83	36.92	2.25 (1.79–2.79)	82	13.94
Non-Hodgkin's lymphoma	141	25.37	5.56 (4.68–6.55)	64	18.10	3.54 (2.72–4.51)	77	7.26
Hodgkin's disease	0	0.76	0.00 (0.00–4.87)	0	0.60	0.00 (0.00–6.19)	0	0.16
Multiple myeloma	6	7.86	0.76 (0.28–1.66)	5	5.71	0.88 (0.28–2.04)	1	2.15
Leukemia	18	16.88	1.07 (0.63–1.69)	14	12.51	1.12 (0.61–1.88)	4	4.36
All others	18	18.43	0.98 (0.58–1.54)	11	11.98	0.92 (0.46–1.64)	7	6.45

SIR standardized incidence ratio, CI confidence interval, N/A not applicable

Table 4 Risk factors for SPM development in patients diagnosed with gastric cancer (for follow-up periods of more than 1 year) ($n = 26,420$)

Variables	Univariate analysis		Multivariate analysis ^a	
	HR (95 % CI)	<i>p</i> value	HR (95 % CI)	<i>p</i> value
Age ≥ 70	1.26 (1.13–1.40)	<0.001	1.19 (1.06–1.34)	0.002
Sex (male)	1.42 (1.26–1.59)	<0.001	1.37 (1.22–1.54)	<0.001
Comorbidities				
Diabetes mellitus	1.34 (1.18–1.52)	<0.001	1.30 (1.15–1.48)	<0.001
COPD	1.32 (1.16–1.49)	<0.001	1.17 (1.02–1.33)	0.020
Liver cirrhosis	2.15 (1.71–2.71)	<0.001	1.94 (1.54–2.45)	<0.001
Autoimmune diseases	1.22 (0.97–1.53)	0.093	1.14 (0.90–1.44)	0.284
Dyslipidemia	1.09 (0.94–1.26)	0.246		
ESRD	1.18 (0.87–1.59)	0.283		
Treatment ^b				
Surgery	0.73 (0.63–0.84)	<0.001	0.67 (0.58–0.78)	<0.001
Chemotherapy	1.25 (1.13–1.39)	<0.001	1.24 (1.10–1.39)	<0.001
Radiotherapy	2.01 (1.69–2.39)	<0.001	1.87 (1.56–2.24)	<0.001

COPD chronic obstructive pulmonary disease, *ESRD* end-stage renal disease

^a All factors with $p < 0.1$ in univariate analyses were included in the Cox multivariate analysis

^b Treatment was analyzed as a time-dependent covariate in the Cox regression model

Predictors of SPM risk

Univariate Cox proportional hazards analysis (see Table 4) showed that age ≥ 70 years, being male, diabetes mellitus, COPD, liver cirrhosis, and autoimmune disease were significantly associated with a higher risk of SPM development. Multivariate analysis showed that age ≥ 70 years [hazard ratio (HR) 1.19, 95 % CI 1.06–1.34, $p = 0.002$], being male (HR 1.37, 95 % CI 1.22–1.54, $p < 0.001$), diabetes mellitus (HR 1.30, 95 % CI 1.15–1.48, $p < 0.001$), COPD (HR 1.17, 95 % CI 1.02–1.33, $p = 0.020$), and liver cirrhosis (HR 1.94, 95 % CI 1.54–2.45, $p < 0.001$) remained independent predictors of SPM development. Risk of second primary cancer varied depending on the treatment instigated for gastric cancer, i.e., surgery (HR 0.67, 95 % CI 0.58–0.78, $p < 0.001$), radiotherapy (HR 1.24, 95 % CI 1.10–1.39, $p < 0.001$), or chemotherapy (HR 1.87, 95 % CI 1.56–2.24, $p < 0.001$).

Discussion

This is the first nationwide population-based study in Asia to clearly demonstrate a significantly increased SIR of metachronous SPM in patients with gastric cancer. Our main findings are that (1) gastric cancer patients have a significantly increased risk of SPM in cancer of the head and neck, esophagus, colon and rectum, bones and soft tissues, ovaries, bladder, or kidneys, as well as non-Hodgkin's lymphoma, and (2) the independent risk factors for SPM include age ≥ 70 years, being male, diabetes mellitus, COPD, liver cirrhosis, chemotherapy, and radiotherapy.

Previous studies have reported incidences of SPM following gastric cancer ranging from 0.9 to 9.5 % [7–14, 16–22]: 0.6–6.7 % for metachronous [7–10, 16–21] and 0.6–5.4 % for synchronous [8–11] SPM. Most of these studies were single-institute case series; only a few were nationwide or multiple-institute cohort studies that included a reference group to test the SIR or relative risk of SPM [7, 12–14]. Those cohort studies reported that co-occurrence of second primary cancer (i.e., within 6 months of the initial cancer) occurred in 0.9–1.0 % of the gastric cancer patients who underwent gastrectomy [9–11], and two other population-based studies also reported similar findings: in those studies, the incidence of another cancer in the first year after the diagnosis of gastric cancer was 1.1 [14] and 0.15 % [12]. For this reason, we excluded the SPMs found during the first year of follow-up after diagnosis of gastric cancer ($n = 662$ accounting for 1.39 % of all the gastric cancer patients in our cohort), but the results of the analysis remained unchanged (SIR 1.30, 95 % CI 1.23–1.37). Our results are highly credible due to our unbiased nationwide selection of patients, who were diagnosed based on reliable diagnostic criteria with histological evidence.

Because the NHI's database is so comprehensive, the follow-up period was long as 15 years. Our study was the first to show that the SIR of SPM was highest at >10 years follow-up (SIR 1.43), followed by 5–10 years (SIR 1.41), and then 1–5 years (SIR 1.21). In the subgroup analysis, we confirmed that those aged 20–39 years at diagnosis had the highest risk of SPM (SIR 7.59). Both Hiyama et al. [12] and the SEER database [23] obtained similar findings for younger patients. This implies that patients with gastric

cancer, especially those aged 20–39 years and those who have survived for more than 10 years (accounting for 7.6 % in our study cohort), are still at risk for SPM, and a circumspect follow-up and screening strategy is necessary for these patients.

Similar to the Japan Cancer Registry study, our findings showed an increased SIR of SPM, including head and neck and gastrointestinal malignancies [12]. Our data also showed significantly higher SIRs for non-Hodgkin's lymphoma (5.56) and cancers of the bone and soft tissues (1.95), ovaries (2.89), kidneys (1.44), and the bladder (1.47). It is not uncommon for gastric MALT lymphoma to occur after gastric cancer, since these two malignancies share a common etiology: *H. pylori* infection [24, 25]. To avoid clerical error, we excluded all cases with gastric lymphoma and gastrointestinal stromal tumors (GISTs), but the correlation between SPM of non-Hodgkin's lymphoma and gastric cancer remained. A reasonable possibility is a late effect of systemic chemotherapy [26, 27] or regional radiotherapy, or both [27]. Mauch reported that treatment with radiotherapy may pose an excessive risk of secondary non-Hodgkin's lymphoma (as high as 10.6 per 10,000 person-years), and the risk may be even higher (up to 16.1) with radiotherapy plus chemotherapy [27]. Secondary bone and soft tissue sarcomas have been widely reported after solid tumor therapies during childhood [28–31], and they have been attributed to multiple treatment modalities and a long latency period. However, since cancers of the bone and soft tissue are relatively rare events (estimated at 0.07 % in our cohort), the exact relationship and underlying mechanism merit further exploration and study.

Regarding multivariate analysis, this is the first study to demonstrate that comorbidities such as diabetes mellitus, COPD, and liver cirrhosis are independent risk factors for SPM after diagnosis of gastric cancer. In the general population, there is a higher overall risk of cancer in patients with diabetes [32], of non-liver malignancies in patients with cirrhosis [33], and of nonpulmonary malignancies in patients with COPD [34]. Furthermore, old age and being male are also risk factors, which is consistent with previous findings [9, 10, 18]. Follow-up and clinical decision-making for patients with these risk factors should be more aggressive.

Our study discovered that surgery (HR 0.67) lowers the risk of SPM while radiotherapy (HR 1.87) and chemotherapy (HR 1.24) increase it; all of these factors were regarded as time-dependent variables. Patients who received surgery for gastric cancer might have had earlier stages of the disease, which implies that the more advanced the gastric cancer, the more frequently SPM occurs. In addition, fewer patients who received surgery for gastric cancer might have undergone cytotoxic therapy. Some

studies have also shown that adjuvant chemotherapy may not increase the incidence of SPM [35–37]. Those studies were all from single institutes with relatively few SPM events (<200), so they may not have had the power to detect the impact of chemotherapy. Since they are derived from a nationwide gastric cancer cohort with long-term follow-up periods of up to 15 years, our results may serve to inform clinicians that these patients should be given optimal adjuvant therapy but should not be overtreated [35].

This retrospective study has several limitations. First, family history and several lifestyle factors such as obesity, tobacco use, and alcohol use may serve as potential confounders, and these factors were not included in the NHI database. However, we found that some comorbidities which are independent risk factors for SPM may be associated with such lifestyle factors. Second, the disease extent (i.e., stage) and microscopic features of the gastric cancer were not recorded in the NHI database. Nevertheless, about 80 % of the patients underwent surgery in our study, which means that most of the gastric cancers were operable. The relation between gastric cancer stage and SPM is unknown, although Kim [9] proposed that early-stage gastric cancer is a predictive factor for SPM. Finally, clinical symptoms and laboratory data were not available, so we were not able to analyze the predictive value of specific clinical situations.

In conclusion, we have demonstrated that the risk of SPM is significantly higher in gastric cancer patients: as survival and follow-up increases, SIR increases. Age, being male, comorbidity, chemotherapy, and radiotherapy are independent risk factors. Hence, after the first 5 years of surveillance for gastric cancer, longer, closer surveillance might be necessary for early detection of SPM.

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Conflict of interest The authors declare no conflict of interest.

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