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Authors

Murphy, James D

Ma, Grace L

Baumgartner, Joel M

et al.

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Increased Risk of Additional Cancers Among Patients with Gastrointestinal Stromal Tumors: A Population-Based Study

James D. Murphy, MD, MS[1,*], **Grace L. Ma**[2,*], **Joel M. Baumgartner, MD**[1], **Lisa Madlensky, PhD, CGC**[3], **Adam M. Burgoyne, MD, PhD**[4], **Chih-Min Tang, PhD**[2], **Maria Elena Martinez, PhD**[3], and **Jason K. Sicklick, MD**[2]

[1]Department of Radiation and Applied Sciences, Moores Cancer Center, University of California, San Diego

[2]Division of Surgical Oncology and Department of Surgery, Moores Cancer Center, University of California, San Diego

[3]Department of Family and Preventive Medicine, Moores Cancer Center, University of California, San Diego

[4]Division of Medical Oncology and Department of Internal Medicine, Moores Cancer Center, University of California, San Diego

Abstract

Purpose—Most gastrointestinal stromal tumors (GIST) are considered non-hereditary or sporadic. However, single-institution studies suggest that GIST patients develop additional malignancies with increased frequencies. We hypothesized that we could gain greater insight into possible associations between GIST and other malignancies using a national cancer database inquiry.

Methods—Patients diagnosed with GIST (2001–2011) in the Surveillance, Epidemiology, and End Results database were included. Standardized prevalence ratios (SPRs) and standardized incidence ratios (SIRs) were used to quantify cancer risks incurred by GIST patients before and after GIST diagnoses, respectively, when compared with the general U.S. population.

Results—Of 6,112 GIST patients, 1,047 (17.1%) had additional cancers. There were significant increases in overall cancer rates: 44% (SPR=1.44) before diagnosis and 66% (SIR=1.66) after GIST diagnoses. Malignancies with significantly increased occurrence both before/after diagnoses included other sarcomas (SPR=5.24/SIR=4.02), neuroendocrine-carcinoid tumors (SPR=3.56/SIR=4.79), non-Hodgkin's lymphoma (SPR=1.69/SIR=1.76), and colorectal adenocarcinoma (SPR=1.51/SIR=2.16). Esophageal adenocarcinoma (SPR=12.0), bladder adenocarcinoma (SPR=7.51), melanoma (SPR=1.46), and prostate adenocarcinoma (SPR=1.20) were significantly more common only before GIST. Ovarian carcinoma (SIR=8.72), small intestine adenocarcinoma

Corresponding Author: Jason K. Sicklick, MD, Division of Surgical Oncology, Moores UCSD Cancer Center, University of California, San Diego, 3855 Health Sciences Drive, MC 0987, La Jolla, CA 92093-0987, Tel: 858-822-6173, Fax: 858-228-5153, jsicklick@ucsd.edu.

*Authors contributed equally to this work

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(SIR=5.89), papillary thyroid cancer (SIR=5.16), renal cell carcinoma (SIR=4.46), hepatobiliary adenocarcinomas (SIR=3.10), gastric adenocarcinoma (SIR=2.70), pancreatic adenocarcinoma (SIR=2.03), uterine adenocarcinoma (SIR=1.96), non-small cell lung cancer (SIR=1.74), and transitional cell carcinoma of the bladder (SIR=1.65) were significantly more common only after GIST.

Conclusion—This is the first population-based study to characterize the associations and temporal relationships between GIST and other cancers, both by site and histological type. These associations may carry important clinical implications for future cancer screening and treatment strategies.

Keywords

GIST; Neoplasms; Second Primary; Multiple Primary Neoplasms; Neoplasms; Synchronous; Neoplasms; Metachronous; SEER

PURPOSE

Approximately 5% of all gastrointestinal stromal tumor (GIST), the most common mesenchymal tumor of the gastrointestinal (GI) tract, have a hereditary etiology [1]. Known heritable GIST syndromes are caused by germline mutations in KIT (c-KIT, CD117), PDGFRα, neurofibromin-1 (NF-1), and succinate dehydrogenase subunits (SDHx) [2]. Patients and families with these genomic alterations frequently develop multiple benign and malignant tumors. However, these syndromes only account for approximately 5% of GIST [2–6]; the remaining 95% are considered sporadic.

Results of several descriptive, single institution case series suggest that patients with sporadic GIST develop synchronous or metachronous malignancies with frequencies far exceeding the often-cited 1-in-9 lifetime chance of developing two primary cancers [5, 7–11]. A review of published case series of sporadic GIST, which included an additional set of cases from a single institution, is the largest study published to date and includes 4,813 patients [8]. In this review, the frequency of additional malignancies varied between 4.5% and 33% among the various series. A subsequent study by Trent and colleagues confirmed these findings, with 159 of 783 (20.3%) GIST patients developing one or more additional malignancies over the study period [7]. Other studies have also reported associations between GIST and desmoids [12], acute myeloid leukemia [9], and other GI malignancies discovered incidentally during resections for GIST, or GIST discovered incidentally during resections for other GI malignancies [13–15]. When considered in totality, the literature supports a possible association between GIST and other malignancies not typically associated with known hereditary disorders [16]. However, except for the link between GIST and leukemia [9], disease associations have only been reported in qualitative fashion, and none of these published reports were based on population-level data.

To address these important gaps in the literature, we used national cancer registry data to investigate the possibility of non-random associations between GIST and other malignancies. Specifically, we assessed risk of cancer by site and histology both before and after GIST diagnoses. As such, our report is the first population-based study to quantify the

frequency and temporal relationship of GIST and other cancer histologies not linked with known hereditary disorders.

METHODS

Patients

We utilized data from the National Cancer Institute's SEER database, which consists of 18 regional cancer registries that collect data on incident cancer diagnoses across the United States. These registries account for approximately 28% of the U.S. population and include patients with GIST diagnosed between 2001 and 2011. GIST before 2001 were excluded due to the high prevalence of misdiagnoses and miscoding in the 1990s [17]. We identified cases with histologically confirmed GIST using GI tumor site codes (C150-C189, C199, C209-C212, C218, C220-C221, C239-C260, C268-C269, C480-C482, C488) and the GIST histology code (ICD-O-3 code 8936). To exclude patients with high likelihood of hereditary syndromes, we eliminated those diagnosed under the age of 20. Of note, there were 16 patients who developed another GIST after their initial GIST diagnoses. However, we could not ascertain whether these were cases of metachronous, but sporadic GIST, miscoded cases of metastatic GIST, or GIST associated with multiple tumor syndromes. Therefore, we elected to include only the first diagnosis of GIST in our analysis.

Statistical Analysis

Cancer occurrence prior to GIST was estimated using standardized prevalence ratios (SPRs), defined as the number of observed cases of additional cancers divided by the number of expected cases [18]. The number of expected cases was calculated by multiplying the total at-risk person-years by the cancer prevalence specific to the patients' age (in 5-year intervals), sex, race, and SEER registry grouping. The registries were divided into groups based on the dates that they began collecting data (i.e., 1973, 1992, and 2000). The at-risk time period extended from the date that the registry started collecting data (or date of birth, if later) through the month prior to a patient's GIST diagnosis.

Cancer risk after GIST was estimated using standardized incidence ratios (SIRs), defined as the number of observed cases divided by the number of expected cases of additional cancers [19, 20]. The number of expected cases was estimated by multiplying the total at-risk person-years by the cancer incidence specific to the patient's age (in 5-year intervals), sex, race, year of GIST diagnosis (in 5-year intervals), and SEER registry grouping (defined above). The at-risk time period extended from the month of GIST diagnosis through date of death or last follow-up. The 2000 U.S. standard population [21] was used as the reference population when determining the expected prevalence (with SPR) and incidence (with SIR). We calculated SPRs and SIRs for any additional cancer as well as site-specific cancers. SPRs and SIRs over 1.0 indicated an excess in prevalence or incidence relative to the general population. We assumed the total number of observed events followed a Poisson distribution, which allowed us to estimate the 95% confidence intervals for SPR and SIR [22–25]. We conducted subgroup analyses by stratifying patients by demographic and disease-specific characteristics. The likelihood ratio test was used to assess for heterogeneity in standardized incidence ratios (SIR) or standardized prevalence ratios (SPR) between

different subgroups of patient characteristics [20, 26]. Additionally, we assessed occurrence of cancer at varying times before and after GIST diagnosis to elucidate the period of increased excess over time. All statistical tests were two-sided, and *P*-values less than 0.05 were considered significant. Data was acquired directly from SEER, imported into SAS, and all analyses were conducted with SAS (version 9.4, Cary, NC).

RESULTS

We identified 6,112 patients diagnosed with GIST between 2001 and 2011. The total observation period for additional cancers was 123,453 person-years, including 101,551 before and 21,902 after GIST diagnosis. There were 1,047 (17.1%, or 1-in-5.8 patients) patients with a total of 1,208 additional cancers. Specifically, 651 (62.2%) patients had other cancers diagnosed prior to GIST, 467 (44.6%) had other cancers diagnosed during the same month or after GIST, and 71 (6.8%) had other cancers diagnosed both before and after GIST. Among those with additional malignancies, 143 (13.7%) had more than one additional cancer, and 16 (1.5%) had more than two additional cancers. Table 1 demonstrates demographic and clinical characteristics for the GIST cohort.

Supplemental Figure 1 shows the distribution of additional cancers by anatomic site and/or organ system. Less common malignancies, such as sarcomas, neuroendocrine-carcinoid tumors, and mesotheliomas, were placed in distinct categories due to their unique histologies and clinical significance. Overall, the most common neoplasms before and after GIST were those of the genitourinary (GU) tract (35.8%)—specifically cancers of the prostate (57.4%), bladder (15.3%), and kidney (14.1%)—and the GI tract (17.2%)—specifically colorectal adenocarcinomas (73.1%) (Supplemental Figure 1A). Breast (11.9%) and respiratory (8.2%) cancers were also common, as were hematologic neoplasms (6.6%). Malignancies were then divided into those found before (Supplemental Figure 1B) and after (Supplemental Figure 1C) GIST.

We then compared the occurrence of additional cancers among GIST patients with that of the U.S. population. GIST patients in SEER had a 44% increased prevalence of cancers occurring before GIST diagnosis (SPR=1.44; 95% CI, 1.33–1.55) and a 66% increased relative risk of developing cancers after GIST diagnosis (SIR=1.66; 95% CI, 1.52–1.81) (Figure 1). Cancers with significantly increased occurrence both before and after GIST diagnosis included sarcomas, neuroendocrine-carcinoid tumors, colorectal adenocarcinoma, and non-Hodgkin’s lymphoma (NHL). Malignancies with significantly elevated prevalence only before GIST included esophageal adenocarcinoma, bladder adenocarcinoma, melanoma, and prostate adenocarcinoma. Malignancies with significantly elevated incidence only after GIST included small bowel adenocarcinoma, papillary thyroid cancer, renal cell carcinoma, gastric adenocarcinoma, hepatobiliary adenocarcinomas, pancreatic adenocarcinoma, non-small cell lung cancer (NSCLC), and transitional cell carcinoma (TCC) of the bladder. Among women, there was also an increased post-GIST incidence of ovarian carcinoma, uterine adenocarcinoma, and other GU cancers.

There were also several rare cancers that appeared significantly more often in the GIST cohort than in the general U.S. population. However, because some had only one reported

case in SEER, we elected to exclude them from Figure 1. These included prostatic TCC before GIST (SPR=51.5) and squamous cell carcinoma of the breast after GIST (SIR=42.8). Mesothelioma also exhibited increased co-occurrence both before and after GIST (SPR=7.35, SIR=2.43), but the ratios did not reach statistical significance. The complete list of all additional cancers, categorized by disease site and histology, is presented in Supplemental Table 1.

We observed notable differences between select demographic and clinical characteristics and the associated probability of developing additional malignancies (Table 2). We found elevated prevalence of other cancers before GIST among non-Hispanic (vs. Hispanic) patients (P=0.02). Moreover, differences by tumor size were notable, as patients with primary GIST ≤10 cm had higher probabilities of second cancers than patients with GIST >10 cm; in particular, patients with tumors ≤2 cm had the highest likelihood of having additional neoplasms before and after GIST. Overall, these findings suggest that ethnicity and tumor size impact the risk of developing additional cancers.

When we analyzed the period of increased occurrence for additional cancers, we found that maximum increase occurred within 1-year pre- and post-GIST diagnosis (Figure 2). The median latency period from the diagnosis of the first cancer to the diagnosis of GIST was 3.6 years for all patients, although it should be noted that SEER registries with longer follow-up (i.e., earlier data collection dates) also had longer median latencies: the median latency was 6.1 years in the 1973 registries, 3.5 years in the 1992 registries, and 1.5 years in the 2000 registries. The median time from the diagnosis of GIST to the diagnosis of a subsequent cancer was 10 months for the entire cohort.

CONCLUSION

To our knowledge, this is the first population-based study with present-day SEER ICD-O-3 coding to quantify occurrence of specific malignancies before and after GIST. While some of our results confirmed previous studies, we also refuted many earlier findings and identified several novel associations, providing a comprehensive description and statistical examination to support the existence of non-random associations between GIST and other malignancies.

Our results showed that the increased occurrence of other cancers was specific to anatomic site and histological type, as well as had a temporal relationship to GIST diagnosis. In particular, the data pointed to the possibility of many new, clinically relevant associations between GIST and cancers distinct from known disorders such Carney's triad/quadrad (e.g., gastric GIST, pulmonary chondroma, extra-adrenal paraganglioma, adrenal adenomas) [27–29], familial GIST syndromes (e.g., activating germline mutations in KIT and PDGFRα with multifocal GIST) [3, 30–33], neurofibromatosis type 1 (e.g., GIST, sarcomas, periampullary/pancreatic neuroendocrine tumors, and pheochromocytoma) [34–39], and Carney-Stratakis syndrome (e.g., GIST and paragangliomas) [40–42]. Because sarcomas and neuroendocrine tumors, which are found in neurofibromatosis, comprised only 4.0% and 3.1% of the 1,208 additional cancers, respectively, this suggests that other etiologies might be responsible for the observed trends.

In corroboration with single institution reports, our study shows that 17.1% of GIST patients developed additional cancers. Moreover, anatomic sites of additional malignancies were fairly similar to those reported in previous studies, including one multi-series analysis, which found second cancers in 13% of GIST patients and elevated risks of melanoma, gastrointestinal, lung, and prostate cancers [8]. A subsequent single institution study reported second neoplasms in 20.3% of GIST patients and elevated risk of renal cancers [7]. However, unlike earlier studies [7, 9], our population-based study did not reveal significantly increased risk of breast cancer or any leukemia. Moreover, unlike the MD Anderson study [7], we found higher prevalence of melanoma, prostate cancer, and esophageal adenocarcinoma before, rather than after, GIST, as well as higher relative risk of developing lung cancer after, rather than before, GIST. We also identified several novel and statistically significant associations between GIST and other malignancies, including NHL, thyroid, gastric, small intestine, colorectal, pancreatic, hepatobiliary, bladder, uterine, and ovarian cancers.

When compared with single institution databases, the SEER national cancer registry is less prone to biases due to geographic location or institutional referral patterns, which increases the generalizability of our results. Additionally, the larger sample size was particularly important for increasing precision of results and for studying associations between GIST and other relatively rare cancers. Also, unlike previous descriptive studies, we quantified risk of second malignancies by using SPRs and SIRs, which controlled for age, sex, race, year of GIST diagnosis, period of data collection, and length of follow-up. These are important distinctions from prior publications. Finally, we analyzed the frequency of cancers not only by anatomic site, but also by histology, allowing us to identify specific histopathologies, rather than just organ sites, that might be associated with GIST.

However, there were several limitations to our study. First, cancers were identified using histology and site-specific codes; as such, misdiagnosis or miscoding remained potential sources of error. Since the current ICD-O-3 histology code for GIST was instated in 2001, we also likely underestimated the actual number of patients with GIST in the database. Another limitation is that SEER does include data on the presence or absence of somatic mutations (e.g., KIT, PDGFRα, or SDHx), which may correlate with specific cancers. Additionally, while we attempted to eliminate patients with hereditary syndromes from our analysis by excluding those diagnosed before age 20, we had no way of directly identifying these patients. Moreover, as with all studies on second cancers, the elevated occurrence of additional cancers might be partially attributed to detection bias during evaluation for symptomatic patients and/or follow-up after GIST treatment, rather than a truly meaningful link (Figure 2). For instance, the increased pre-GIST prevalence of esophageal adenocarcinoma and increased post-GIST incidence of gastric and small bowel adenocarcinomas might be attributed, in part, to upper endoscopic evaluation for GIST or vice versa. Similarly, increased use of colonoscopy or chest X-rays during work-up might contribute to the higher incidence of post-GIST colorectal adenocarcinoma and NSCLC, respectively. Detection bias might also be particularly applicable to patients with papillary thyroid cancer, which is often diagnosed during imaging studies for other diseases [43]; as such, the increased incidence of thyroid cancers post-GIST might be more indicative of closer surveillance of GIST patients relative to the general population, rather than a true association between the two malignancies. Finally, the SEER dataset is limited by its

inability to capture non-melanoma skin cancers, such as basal cell and squamous cell carcinomas, as well as myeloproliferative neoplasms, as anecdotes and case reports suggested that these diseases might also be more common in the GIST population [16].

Proper identification of additional cancer histologies and their timing relative to GIST diagnosis leads to several possible implications for cancer screening. For instance, the increased incidence of post-GIST gastric, small bowel, and colorectal adenocarcinomas, as well as neuroendocrine-carcinoid tumors (many of which originate in the gut) may warrant greater consideration of upper and lower endoscopies among symptomatic patients who were previously considered to be cured following resection of localized GIST. At present, the current guidelines established by the National Comprehensive Cancer Network recommend chest imaging only during staging workup of GIST [44]. However, given the increased incidence of post-GIST NSCLC and results from a recent clinical trial showing reduced lung cancer mortality among high-risk individuals receiving routine low-dose chest CTs [45], practitioners may also consider employing chest CT scans to monitor certain GIST patients at higher risk for NSCLC. In addition, given the higher risk of bladder, renal, and uterine cancers after GIST diagnosis, secondary cancers should be included in the differential for hematuria or vaginal bleeding post GIST-diagnosis. Finally, since GIST rarely metastasizes to lymph nodes [46], but GIST patients face higher risk of developing NHL, new lymphadenopathy should warrant consideration for additional work-up. As such, our findings have the potential to alter certain cancer screening recommendations and management strategies.

There are many factors that may contribute to the development of additional cancers, but the exact mechanism(s) remain to be determined. These may include age, gender, possible hereditary (e.g., germline) tumor syndromes caused by mutations in oncogenes or tumor suppressor genes, spontaneous germline mutations, infectious causes, environmental risk factors (i.e., sedentary lifestyles, alcohol, smoking, and diet) exposure to toxic chemicals, treatment-related toxicities and detection bias associated with surveillance following an initial cancer. In addition, the prevalence of multiple malignancies increases with more advanced cancer treatments and higher probabilities of surviving the first malignancy. For example, there has been dramatic improvement in the survival of patients with metastatic GIST due to the widespread use of imatinib over the past decade [47]. Since little is known about risk factors for GIST beyond age and gender, and race [17, 48, 49], additional research is needed to further identify appropriate screening/surveillance recommendations, and elucidate possible hereditary factors that may result in increased cancer risk in GIST patients.

Our population-based analysis demonstrated many significant associations between GIST and other cancers, providing evidence for increased cancer risk among the GIST population. The proper identification and description of these links carry immense clinical implications, from screening and prevention to diagnosis and treatment. As such, further investigation is necessary to link the histologically confirmed, epidemiological findings from this and other population-based studies [49] with relevant clinical decision-making. In addition, the development of a national registry is necessary to capture patients with potential syndromes, raise awareness, identify prevention strategies, and elucidate the role of genetic counseling.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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ABBREVIATIONS

CI	Confidence interval
GIST	Gastrointestinal stromal tumor
GI	Gastrointestinal
GU	Genitourinary
SEER	Surveillance, Epidemiology, and End Results
NCCN	National Comprehensive Cancer Network
NHL	Non-Hodgkin's lymphoma
NSCLC	Non-small cell lung cancer
PDGFRα	Platelet derived growth factor receptor-alpha
SIR	Standardized incidence ratio
SPR	Standardized prevalence ratio
TCC	Transitional cell carcinoma

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Site	Observed	Expected	SPR/SIR (95% CI)
Cancers before GIST			
Esophageal adenocarcinoma	13	1.1	12.0 (6.40-20.6)
Bladder adenocarcinoma	3	0.4	7.51 (1.55-22.0)
Sarcoma	32	6.1	5.24 (3.58-7.39)
Neuroendocrine	20	5.6	3.56 (2.17-5.50)
Non-Hodgkin lymphoma	34	20.2	1.69 (1.17-2.35)
Colorectal adenocarcinoma	81	53.7	1.51 (1.20-1.88)
Melanoma	38	25.9	1.46 (1.04-2.01)
Prostate adenocarcinoma	184	153.9	1.20 (1.03-1.38)
All sites	*703*	*488*	*1.44 (1.33-1.55)*
Cancers after GIST			
Ovarian carcinoma	2	0.2	8.72 (1.06-31.5)
Small bowel adenocarcinoma	3	0.5	5.89 (1.22-17.2)
Other female GU*	6	1.0	6.00 (2.20-13.1)
Papillary thyroid cancer	16	3.1	5.16 (2.95-8.38)
Neuroendocrine	18	3.8	4.79 (2.84-7.56)
Renal cell carcinoma	35	7.8	4.46 (3.11-6.21)
Sarcoma	15	3.7	4.02 (2.25-6.64)
Hepatobiliary adenocarcinoma**	8	2.6	3.10 (1.34-6.10)
Gastric adenocarcinoma	14	5.2	2.70 (1.48-4.54)
Colorectal adenocarcinoma	71	32.8	2.16 (1.69-2.73)
Pancreatic adenocarcinoma	13	6.4	2.03 (1.08-3.47)
Uterine adenocarcinoma	12	6.1	1.96 (1.01-3.43)
Non-Hodgkin lymphoma	22	12.5	1.76 (1.11-2.67)
Non-small cell lung cancer	61	35.1	1.74 (1.33-2.23)
Bladder transitional cell carcinoma	27	16.4	1.65 (1.09-2.40)
All sites	*505*	*304*	*1.66 (1.52-1.81)*

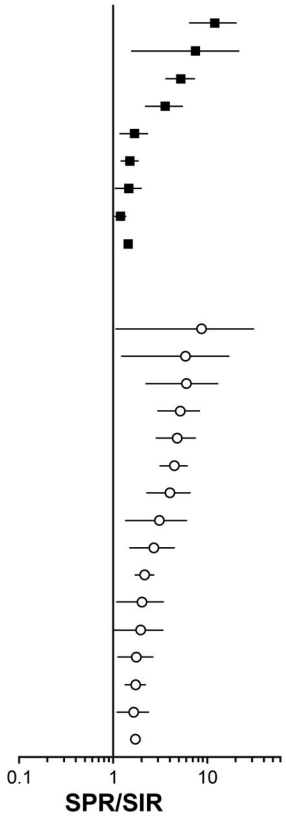

Figure 1. Cancer development before and after the diagnosis of GIST

Occurrence of each cancer before GIST is reported using the standardized prevalence ratio (SPR, solid squares) and that after GIST is reported as the standardized incidence ratio (SIR, white circles). Horizontal lines illustrate associated 95% CIs. Only cancers with statistically significantly elevated SPRs and SIRs ($P<0.05$), as well as more than one reported case within the cohort, are included.

* Other female genitourinary (GU) includes vulvar cancer (N=4), vaginal cancer (N=1), fallopian tube (N=2), and not otherwise specified (N=1).

** Hepatobiliary adenocarcinoma includes liver adenocarcinoma (N=2), intrahepatic cholangiocarcinoma (N=1), extrahepatic cholangiocarcinoma (N=1), and ampullary adenocarcinoma (N=4).

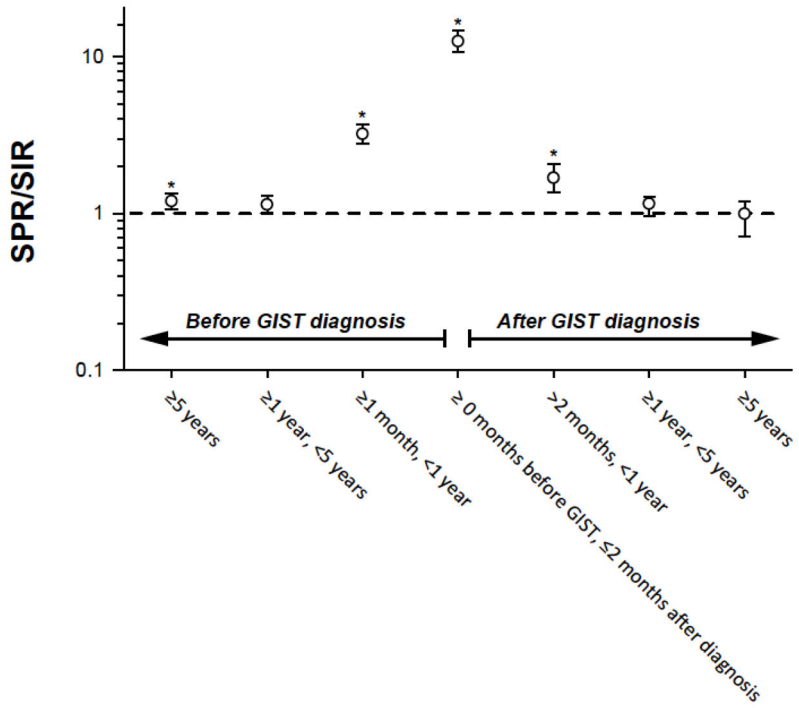

Figure 2. Timeline for the occurrence of additional cancers relative to the diagnosis of GIST

Occurrence of additional cancers relative to the time of GIST diagnosis is represented. Occurrence of cancer before the diagnosis of GIST is quantified using the standardized prevalence ratio (SPR) and that after GIST is quantified using the standardized incidence ratio (SIR). Error bars represent the 95% confidence intervals, and stars (*) represent $P<0.05$.

Table 1

Demographic and clinical characteristics in the GIST cohort (N=6,112).

Characteristic	Number (N)	Percent
Age at GIST Diagnosis		
20 – 39	325	5.3%
40 – 49	739	12.1%
50 – 59	1,289	21.1%
60 – 69	1,553	25.4%
70 – 79	1,398	22.9%
≥80	808	13.2%
Sex		
Female	2,860	46.8%
Male	3,252	53.2%
Race		
White / Unknown	4,320	70.7%
Black	1,079	17.7%
Other	713	11.7%
Ethnicity		
Hispanic	560	9.2%
Non-Hispanic / Unknown	5,552	90.8%
Year of Diagnosis		
2001	408	6.7%
2002	522	8.5%
2003	505	8.3%
2004	521	8.5%
2005	531	8.7%
2006	494	8.1%
2007	517	8.5%
2008	577	9.4%
2009	604	9.9%
2010	730	11.9%
2011	703	11.5%
GIST Location		
Esophagus	33	0.5%
Stomach	3,368	55.1%
Small Intestine	1,762	28.8%
Colorectal	343	5.6%
Hepatobiliary	5	0.1%
Pancreas	23	0.4%
Retroperitoneum	57	0.9%
Peritoneum, Omentum and Mesentery	126	2.1%
Other Digestive Organs	384	6.3%

Characteristic	Number (N)	Percent
GIST Size (cm)		
≤2	430	7.0%
>2, ≤5	1,351	22.1%
>5, ≤10	1,847	30.2%
>10	1,478	24.2%
Unknown	1,006	16.5%

Table 2

Occurrence of additional cancers before and after diagnosis of GIST, according to select patient characteristics.

	Cancers before GIST				Cancers after GIST			
	Observed	**Expected**	**SPR (95% CI)**	**P-value***	**Observed**	**Expected**	**SIR (95% CI)**	**P-value***
Age at GIST diagnosis								
20–39	5	1.8	2.82 (0.92–6.58)	0.11	6	2.1	2.86 (1.05–6.22)	0.71
40–49	22	11.8	1.87 (1.17–2.83)		24	13.7	1.75 (1.12–2.61)	
50–59	104	48.1	2.16 (1.77–2.62)		76	48.4	1.57 (1.24–1.97)	
60–69	192	125.5	1.53 (1.32–1.76)		144	97.5	1.48 (1.25–1.74)	
70–79	238	179	1.33 (1.17–1.51)		176	101.3	1.74 (1.49–2.01)	
≥80	142	118.5	1.20 (1.01–1.41)		79	38.6	2.05 (1.62–2.55)	
Sex								
Female	280	199.4	1.40 (1.24–1.58)	0.57	201	117.8	1.71 (1.48–1.96)	0.89
Male	423	285.2	1.48 (1.34–1.63)		304	183.8	1.65 (1.47–1.85)	
Race								
White / Unknown	526	369.3	1.42 (1.31–1.55)	0.41	357	228.3	1.56 (1.41–1.73)	0.26
Black	126	74.8	1.68 (1.40–2.01)		97	50.4	1.92 (1.56–2.35)	
Other	51	40.5	1.26 (0.94–1.66)		51	22.9	2.23 (1.66–2.93)	
Ethnicity								
Hispanic	33	37.6	0.88 (0.60–1.23)	0.02	31	22.2	1.40 (0.95–1.98)	0.47
Non-Hispanic / Unknown	670	447	1.50 (1.39–1.62)		474	279.4	1.70 (1.55–1.86)	
GIST size (cm)								
≤2	91	37	2.46 (1.98–3.02)	0.0009	66	19.1	3.46 (2.67–4.40)	0.02
>2, ≤5	187	109.8	1.70 (1.47–1.97)		119	71.3	1.67 (1.38–2.00)	
>5, ≤10	182	144.7	1.26 (1.08–1.45)		154	96.8	1.59 (1.35–1.86)	
>10	126	113.4	1.11 (0.93–1.32)		94	69.9	1.34 (1.09–1.65)	
Unknown	117	79.8	1.47 (1.21–1.76)		72	44.6	1.61 (1.26–2.03)	
GIST site								
Stomach	406	279	1.46 (1.32–1.60)	0.73	303	171.6	1.77 (1.57–1.98)	0.57
Small Intestine	192	126.2	1.52 (1.31–1.75)		140	86.9	1.61 (1.36–1.90)	
Other	105	79.4	1.32 (1.08–1.60)		62	43.1	1.44 (1.10–1.84)	

	Cancers before GIST				Cancers after GIST			
	Observed	Expected	SPR (95% CI)	P-value*	Observed	Expected	SIR (95% CI)	P-value*
Registry group								
1973–2011	339	243.4	1.39 (1.25–1.55)	0.81	183	106	1.73 (1.49–2.00)	0.94
1992–2011	108	76	1.42 (1.17–1.71)		71	42.3	1.68 (1.31–2.12)	
2000–2011	256	165.1	1.55 (1.37–1.75)		251	153.3	1.64 (1.44–1.85)	

* P-values represent a likelihood ratio test to assess for heterogeneity in standardized incidence ratios (SIR) or standardized prevalence ratios (SPR) between different subgroups of patient characteristics.