

Second Primary Cancers After Gastric Cancer, and Gastric Cancer as Second Primary Cancer

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Background: Second primary cancers (SPCs) are increasing, which may negatively influence patient survival. Gastric cancer (GC) has poor survival and when it is diagnosed as SPC it is often the cause of death. We wanted to analyze the risk of SPCs after GC and the risk of GC as SPC after any cancer. Such bidirectional analysis is important in relation to fatal cancers because SPCs may be under-reported in the short-term survival period.

Methods: Cancers were obtained from the Swedish Cancer Registry from years 1990 through 2015. Standardized incidence ratios (SIRs) were used to estimate bidirectional relative.

Results: We identified 23,137 GC patients who developed 1042 SPCs (4.5%); 2158 patients had GC as SPC. While the risk for three SPCs was increased after GC, seven first primary cancers were followed by an increased risk of GC as SPC, including esophageal, colorectal, bladder, squamous cell skin and breast cancers and non-Hodgkin lymphoma. Breast cancer, which was followed by a diagnosis of second GC, showed an excess of lobular histology.

Conclusion: Multiple primary cancers in the same individuals may signal genetic predisposition. Accordingly, the association of GC with breast cancer may be related to mutations in the *CDH1* gene, and clustering of colorectal, small intestinal and bladder cancers could be related to Lynch syndrome. The third line of findings supports a contribution of immune dysfunction on the increased risk of GC as SPC after skin cancer and non-Hodgkin lymphoma. Early detection of GC in the risk groups could save lives.

Keywords: cancer incidence, relative risk, second primary cancer, cancer etiology, stomach cancer

Introduction

Gastric (stomach) cancer (GC) has historically been the most common cancer in the world.¹⁻³ Although the incidence of GC has gradually fallen it is still among the main fatal cancers, however with a large international variation.⁴ Although survival rates in GC have been improving, prognosis remains poor; the 5-year survival rate is at 20–25%.^{5,6} In Sweden, GC 5-year survival has increased in men from 12 to 24% between 1967 and 2016, and in women from 13 to 28% according to the NORDCAN database (<https://www-dep.iarc.fr/NORDCAN/english/frame.asp>). Survival is better in Japan and South Korea where population screening has been implemented.^{7,8} The anatomic location of the tumor has important pathophysiological implications. Tumors in the cardia at the gastroesophageal junction are rarer than non-cardia tumors; obesity and the related gastroesophageal reflux are risk factors for cardia cancer, while for non-cardia disease *Helicobacter pylori* infection and dietary factors (see below) are important.⁴ Distant metastases from GC are most commonly found in the liver; cardia

tumors additionally metastasize to the lung, nervous system and bone, whereas non-cardia cancers more frequently metastasize within the peritoneum.⁹ Treatment of GC involves endoscopic mucosal resection for localized disease and gastrectomy for advanced disease, supplemented with chemotherapy and radiotherapy, and in Her2 positive cases targeted therapy.¹⁰ The declining trend in GC incidence has been ascribed to the falling rates of non-cardia cancer concomitant with declining rates in *H. pylori* infections as a result of improved household hygiene and widespread antibiotic use.⁷ Other risk factors include tobacco smoking, high-salt diet, poorly preserved food, excess alcohol intake, obesity, and low intake of fresh fruits and vegetables.¹⁰ Family history is another rare risk factor; hereditary GC is associated with mutations in the *CDH1* gene, and GC is manifested in Lynch syndrome related to mutations in mismatch repair genes.^{11–14} Next-generation sequencing studies have identified rare germline variants in several other genes, including *BRCA2* and many other DNA repair genes.^{15–17}

Second primary cancers (SPCs) are increasing as improving survival increases the likelihood of being diagnosed with another cancer.¹⁸ Because survival in GC is poor, SPCs are less common and these may also be underreported as the care is focused on GC.^{19,20} Population-based literature on SPCs after GC is not extensive. Portugal is a high-risk area of GC, and an increase in SPCs was observed for esophageal, small intestinal and colon cancers in both sexes.²¹ The same authors reported an increased risk of GC as SPC when esophageal and colon cancers were first primary cancers (FPCs).²² In a Swedish study, the risk of GC as SPC was increased after esophageal, breast, ovarian, cervical, testicular and squamous cell skin cancers and non-Hodgkin lymphoma, Hodgkin lymphoma and myeloma.²³ Patients diagnosed with colon and breast cancers as FPC and with a family history of these cancers experienced an increased risk of second GC.²³ In a nation-wide analysis in Taiwan, increased risks for SPCs were found for cancer overall and cancers of the head and neck, esophagus, colon and rectum, bones and soft tissues, ovaries, bladder and kidneys, as well as non-Hodgkin lymphoma,²⁴ radiotherapy and particularly chemotherapy were independent risk factors.

Considering the modestly improved survival in GC we decided to examine the risks of any cancer after GC, and also systematically bidirectionally, the risk of GC as SPC after any FPC. Because of the concerns of possible underreporting of SPCs after GC, it is instructive to compare results to the inverse association, GC as SPC.²⁰ Cardia and non-cardia cancers were assessed separately.

Patients and Methods

Nation-wide population and cancer data were obtained from Statistics Sweden and the Swedish Cancer Registry, and these were delivered to us in a pseudonymized format. We have no access to any keys of the pseudonymized data including personal information, such as name, address, or personal ID numbers. GC was identified by the codes of the International Classification of Diseases revision 7 (ICD-7 and later revisions) distinguishing cardia and other parts (ie, non-cardia). Lauren's classification into diffuse and intestinal types was not used. Practically all cancers, including SPCs, are histologically verified in the Swedish Cancer Registry.²⁵ This should in most cases distinguish recurrences from independent primaries.

Data on GC and other cancers covered years 1990 through 2015. The other cancers include any of 23 common male and 24 female FPCs or SPCs. Patients were followed up from 1990 onward from the diagnosis of FPC until the end of 2015 or diagnosis of SPC, immigration or death, whichever came earliest. Only discordant (different) FPC-SPC pairs were included. Upper aerodigestive tract (UAT) included lip, oral cavity, pharynx and larynx. Kidney cancer included only renal cell carcinoma; renal pelvic and ureteral cancers were also considered but case numbers were few and not reported. For skin cancer, only melanoma and squamous cell carcinoma (SCC) were included.

Standardized incidence ratios (SIRs) for SPCs were estimated through the observed number of SPCs divided by the expected number of cases. The expected numbers of cancers were estimated by the person-years after first primary cancer diagnosis, multiplied by the incidence of the same cancer as FPC in the general population. The estimation was done for both sexes combined and separately, and adjusted for age, calendar year, place of residence and socioeconomic factors. The 95% confidence interval (95% CI) for SIR was calculated by assuming Poisson distribution. Chi-square test, or Fisher exact test if appropriate, was used to test the difference of frequency. The statistical tests were two-tailed and P value < 0.05 was regarded as significant, and an increase in risk was called only when P value was significant. All the analyses were performed in SAS 9.4.

Incidence, mortality and survival data were obtained from the NORDCAN database (<https://www-dep.iarc.fr/NORDCAN/english/frame.asp>), which is a compilation of data from the Nordic cancer registries, including the Swedish Cancer Registry, as described.²⁶

Results

A dramatic decrease in the incidence (and consequently in mortality) of GC is shown for Sweden in Figure 1, based on the NORDCAN database. Male and female incidence has declined to about 20% within 50 years.

During the follow-up period of 1990 to 2015, we identified 23,137 GC patients who developed 1042 SPCs (4.5%). Among GCs, 4764 patients had cardia cancer (75.6% male, median diagnostic age 78 years, interquartile range, IQR, 70–84) and 17,927 had non-cardia cancer (56.9% male, median diagnostic age 75 years, IQR 66–81). The total number of other cancers considered was 1,035,682 (51.7% male). The median (IQR) time from first GC to SPC was 34.5 (4–93) months and from FPC to second GC it was 41 (14–87) months.

SIRs for SPCs of combined sexes associated with GC are shown in Table 1. The overall risk for SPCs after GC was decreased (SIR 0.91), based on 1042 cases. Risks for three individual SPCs were significantly increased: small intestinal (4.12), esophageal (2.15) and kidney (1.62) cancers. The SIRs of also three cancers were decreased, including lung and prostate cancers and myeloma. In the reversed order, GC as SPC, the overall SIR was 1.05 with 2158 cases. Risks were increased for GC after seven FPCs,

most after esophageal (2.43), skin SCC (1.39) and UAT (1.35) cancers and non-Hodgkin lymphoma (NHL, 1.32). Three FPCs were followed by a decreased risk of GC; these were pancreatic and prostate cancers and melanoma.

Sex-specific analyses are presented in Tables 2 and 3. There are small differences to Table 1, considering the lower case numbers. Notably, the overall SIR for SPCs was 0.84 for men but it was 1.06 for women. Among women, colorectal cancer (CRC) was bidirectionally associated with GC, and female kidney cancer SIR was 2.38 as SPC.

Table 4 shows bidirectional results for cardia and non-cardia cancers. Cardia cancers are rare and so were significant associations. Esophageal cancer was bidirectionally associated with high SIRs. Risk of cardia cancer was increased after female genital cancer (4.89) and UAT cancer (1.72). After non-cardia cancer, risks of small intestinal and kidney cancers were increased as SPC. Small intestinal cancer showed a bidirectional association. Other FPCs which were associated with non-cardia cancer as SPC were CRC, breast, bladder and skin cancers, and thyroid cancer as a novel association (1.85).

We assessed histological distributions and diagnostic ages of probands for some cancers with increased SIRs when diagnosed after 1990; the hypothesis was to search

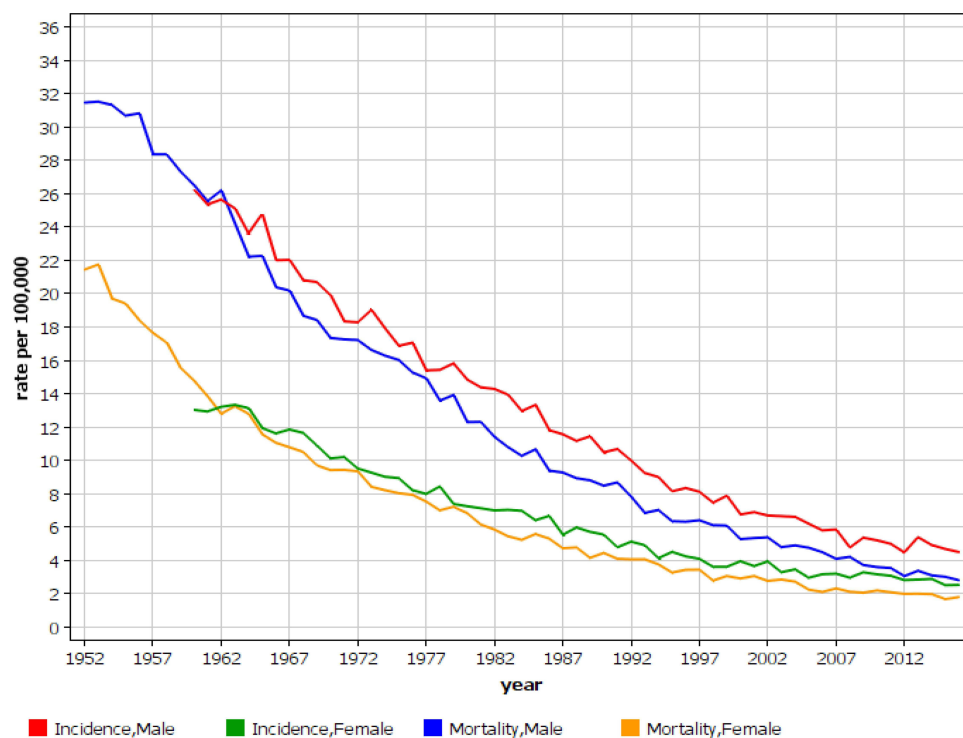


Figure 1 Incidence and mortality for gastric cancer among Swedish men and women. The data are derived from the NORDCAN database and are adjusted to the world standard population.

Table I Risks of SPC After Gastric Cancer and Risks of Gastric Cancer as SPC

Cancer	SPC After Gastric Cancer				Gastric Cancer as SPC			
	N	SIR	95% CI		N	SIR	95% CI	
UAT	21	0.85	0.53	1.3	57	1.35	1.02	1.75
Esophagus	28	2.15	1.43	3.11	24	2.43	1.56	3.63
Small intestine	22	4.12	2.58	6.24	12	1.60	0.82	2.8
CRC	169	1.09	0.93	1.27	288	1.15	1.02	1.29
Liver	27	0.83	0.55	1.21	21	0.98	0.61	1.5
Pancreas	29	0.93	0.62	1.33	6	0.33	0.12	0.72
Lung	78	0.77	0.61	0.96	68	0.88	0.68	1.11
Breast	79	0.95	0.76	1.19	249	1.18	1.03	1.33
Cervix	5	1.1	0.35	2.59	13	1.31	0.69	2.24
Endometrium	14	0.65	0.36	1.1	50	0.91	0.67	1.2
Ovary	12	1.02	0.52	1.78	23	1.11	0.7	1.67
Female genitals	3	0.73	0.14	2.15	8	1.27	0.54	2.51
Prostate	213	0.71	0.61	0.81	610	0.92	0.85	0.99
Testis	1	1.23	0	7.04	6	1.42	0.51	3.11
Male genitals	1	0.37	0	2.15	6	1.22	0.44	2.67
Kidney	32	1.62	1.11	2.29	33	0.96	0.66	1.36
Bladder	61	0.85	0.65	1.1	162	1.26	1.08	1.47
Melanoma	26	0.71	0.46	1.04	59	0.77	0.58	0.99
Skin SCC	71	0.82	0.64	1.04	158	1.39	1.19	1.63
Nervous system	12	0.60	0.31	1.05	28	0.80	0.53	1.16
Thyroid	8	1.76	0.75	3.48	16	1.70	0.97	2.76
Endocrine	12	1.04	0.54	1.83	44	1.25	0.91	1.68
Connective tissue	6	0.95	0.34	2.07	12	1.17	0.60	2.06
NHL	34	0.86	0.6	1.2	78	1.32	1.04	1.64
Myeloma	6	0.34	0.12	0.74	19	0.80	0.48	1.26
Leukemia	30	0.86	0.58	1.22	49	1.00	0.74	1.32
All	1042	0.91	0.86	0.97	2158	1.05	1.01	1.10

Notes: N= patient number. Bolding shows that the 95% CI does not overlap with 1.00.

Abbreviations: SIR, standardized incidence ratio; 95% CI, 95% confidence interval; SPC, second primary cancer; UAT, upper aerodigestive tract; CRC, colorectal cancer; SCC, squamous cell carcinoma; NHL, non-Hodgkin lymphoma.

evidence for mutations in *CDH1* (ie, proportion of lobular breast cancer) or *BRCA1/2* (ie, proportion of family members with breast cancer who had second breast or ovarian cancer) as genetic predisposing factors. For 246 female

breast cancer patients from Table 3, 19.1% (47/246) were diagnosed with lobular histology, while the proportion of lobular breast cancer for all women was 11.2% (13,531/120,810; Chi-square $P < 0.0001$). These 246 breast cancer

Table 2 Male Risk of SPC After Gastric Cancer and Risks of Gastric Cancer as SPC

Cancer	SPC After Gastric Cancer				Gastric Cancer as SPC			
	N	SIR	95% CI		N	SIR	95% CI	
UAT	17	0.89	0.51	1.42	44	1.32	0.96	1.77
Esophagus	20	1.88	1.15	2.91	20	2.50	1.52	3.86
Small intestine	11	3.08	1.53	5.53	8	1.61	0.69	3.18
CRC	97	0.94	0.76	1.14	178	1.08	0.93	1.25
Liver	19	0.91	0.55	1.43	14	1.02	0.56	1.72
Pancreas	17	0.86	0.5	1.38	4	0.35	0.09	0.89
Lung	53	0.71	0.53	0.92	50	0.87	0.65	1.15
Breast	2	1.66	0.16	6.09	3	1.37	0.26	4.05
Prostate	213	0.71	0.61	0.81	610	0.92	0.85	0.99
Testis	1	1.23	0	7.04	6	1.42	0.51	3.11
Male genital	1	0.37	0	2.15	6	1.22	0.44	2.67
Kidney	19	1.33	0.8	2.07	23	0.97	0.61	1.45
Bladder	46	0.75	0.55	1.01	141	1.28	1.08	1.51
Melanoma	17	0.68	0.4	1.10	33	0.66	0.45	0.93
Skin	48	0.79	0.58	1.05	116	1.49	1.23	1.79
Nervous system	8	0.65	0.28	1.30	16	0.86	0.49	1.40
Thyroid	2	0.95	0.09	3.48	6	1.54	0.55	3.37
Endocrine	5	0.96	0.30	2.25	14	0.98	0.54	1.66
Connective tissue	4	0.9	0.23	2.33	6	0.85	0.31	1.87
NHL	23	0.85	0.54	1.28	48	1.22	0.90	1.61
Myeloma	3	0.24	0.05	0.72	14	0.86	0.47	1.45
Leukemia	23	0.94	0.60	1.41	34	1.01	0.70	1.41
All	669	0.84	0.78	0.91	1436	1.02	0.97	1.08

Notes: N= patient number. Bolding shows that the 95% CI does not overlap with 1.00.

Abbreviations: SIR, standardized incidence ratio; 95% CI, 95% confidence interval; SPC, second primary cancer; UAT, upper aerodigestive tract; CRC, colorectal cancer; SCC, squamous cell carcinoma; NHL, non-Hodgkin lymphoma.

patients (Table 3) had 313 female family members, and 12 of them were diagnosed with breast cancer; of them, 4 (25%) were further diagnosed with second breast or second ovarian cancer. For all the women with breast cancer, 245,489 family members were found. Among them, 11,896 had breast cancer and 1400 (11.8%) were further diagnosed with second breast or second ovarian cancer; the difference to the GC probands was not significant (Fisher P=0.11).

Discussion

GC is a fatal cancer which is diagnosed at a high age (median age at diagnosis 76 years compared to all cancers of 70 years). According to the present results, it is likely that SPCs after GC are underreported among men as the overall SIR for SPCs was below 1.00 (0.84) while for women it was 1.06. SIRs below 1.00 were noted for fatal cancers (lung, pancreas, myeloma) or cancers in elderly men (prostate). This may imply some underestimation of

Table 3 Female Risk of SPC After Gastric Cancer and Risks of Gastric Cancer as SPC

Cancer	SPC After Gastric Cancer				Gastric Cancer as SPC			
	N	SIR	95% CI		N	SIR	95% CI	
UAT	4	0.73	0.19	1.88	13	1.45	0.77	2.48
Esophagus	8	3.30	1.41	6.54	4	2.16	0.56	5.57
Small intestine	11	6.22	3.09	11.16	4	1.57	0.41	4.07
CRC	72	1.39	1.09	1.75	110	1.28	1.05	1.54
Liver	8	0.69	0.30	1.37	7	0.91	0.36	1.88
Pancreas	12	1.04	0.53	1.81	2	0.30	0.03	1.12
Lung	25	0.96	0.62	1.42	18	0.89	0.53	1.41
Breast	77	0.94	0.75	1.18	246	1.17	1.03	1.33
Cervix	5	1.10	0.35	2.59	13	1.31	0.69	2.24
Endometrium	14	0.65	0.36	1.1	50	0.91	0.67	1.2
Ovary	12	1.02	0.52	1.78	23	1.11	0.70	1.67
Female genital	3	0.73	0.14	2.15	8	1.27	0.54	2.51
Kidney	13	2.38	1.26	4.09	10	0.96	0.46	1.77
Bladder	15	1.43	0.80	2.37	21	1.15	0.71	1.76
Melanoma	9	0.76	0.34	1.45	26	0.96	0.63	1.41
Skin	23	0.90	0.57	1.35	42	1.18	0.85	1.60
Nervous system	4	0.51	0.13	1.31	12	0.73	0.38	1.28
Thyroid	6	2.47	0.89	5.4	10	1.81	0.86	3.33
Endocrine	7	1.12	0.44	2.31	30	1.44	0.97	2.05
Connective tissue	2	1.05	0.10	3.86	6	1.88	0.68	4.12
NHL	11	0.88	0.44	1.58	30	1.52	1.02	2.17
Myeloma	3	0.55	0.10	1.64	5	0.67	0.21	1.58
Leukemia	7	0.66	0.26	1.37	15	0.98	0.55	1.63
All	373	1.06	0.96	1.18	722	1.12	1.04	1.21

Notes: N= patient number. Bolding shows that the 95% CI does not overlap with 1.00.

Abbreviations: SIR, standardized incidence ratio; 95% CI, 95% confidence interval; SPC, second primary cancer; UAT, upper aerodigestive tract; CRC, colorectal cancer; SCC, squamous cell carcinoma; NHL, non-Hodgkin lymphoma.

risks for male SPCs after GC. For women, there was no such indication of underreporting but their overall case numbers were smaller than those for men and statistical power was accordingly lower. In addition to the previously reported increases for esophageal and small intestinal cancers as SPCs, for which the anatomic proximity and the same kind of intestinal lining are likely to play a role, an association was observed for kidney cancer, particularly

among women and at the non-cardia location. As the association was noted only for kidney cancer as SPC, and not in reverse order, it may be a fortuitous finding during GC diagnostic work-up; carcinogenic effects of adjuvant radiation/chemoradiation for GC could also play a role.

GC is an associated cancer in Lynch syndrome, in which cumulative risk for GC in individuals with

Table 4 Risks of SPC After Gastric (Cardia and Non-Cardia) Cancer and Risks of Gastric Cancer as SPC

Gastric Cancer	Cancer	SPC After Gastric Cancer				Gastric Cancer as SPC			
		N	SIR	95% CI		N	SIR	95% CI	
Cardia	UAT	3	0.63	0.12	1.87	17	1.76	1.02	2.82
	Esophagus	17	6.64	3.86	10.65	10	4.49	2.14	8.29
	Gastric, non-cardia	3	0.62	0.12	1.82	6	1.04	0.37	2.27
	Small intestine	3	3.10	0.58	9.16				
	CRC	19	0.72	0.43	1.12	58	1.13	0.86	1.47
	Liver	3	0.54	0.10	1.60	2	0.48	0.05	1.76
	Pancreas	3	0.54	0.10	1.61	4	1.10	0.29	2.85
	Lung	11	0.58	0.29	1.03	13	0.78	0.41	1.33
	Breast	9	0.99	0.45	1.88	39	1.28	0.91	1.75
	Cervix					1	0.71	0	4.05
	Endometrium	1	0.44	0	2.54	6	0.79	0.28	1.72
	Ovary	1	0.79	0	4.53	4	1.39	0.36	3.6
	Female genitals					4	4.89	1.27	12.65
	Prostate	36	0.55	0.39	0.77	158	0.95	0.81	1.11
	Testis					3	2.04	0.38	6.03
	Male genitals					1	0.80	0	4.57
	Kidney	5	1.33	0.42	3.13	6	0.81	0.29	1.77
	Bladder	13	0.95	0.51	1.64	38	1.31	0.93	1.8
	Melanoma	7	1.01	0.40	2.09	12	0.68	0.35	1.19
	Skin SCC	5	0.37	0.12	0.87	29	1.29	0.86	1.85
	Nervous system	3	0.79	0.15	2.33	5	0.65	0.21	1.53
	Thyroid	3	4.17	0.79	12.35	2	1.07	0.10	3.95
	Endocrine	2	1.05	0.10	3.86	7	1.04	0.41	2.15
	Connective tissue					2	0.89	0.08	3.29
	NHL	8	1.14	0.49	2.25	18	1.41	0.83	2.23
	Myeloma					1	0.20	0	1.16
	Leukemia	5	0.80	0.25	1.87	12	1.12	0.58	1.97
	All	170	0.83	0.71	0.97	466	1.05	0.96	1.15

(Continued)

Table 4 (Continued).

Gastric Cancer	Cancer	SPC After Gastric Cancer				Gastric Cancer as SPC			
		N	SIR	95% CI		N	SIR	95% CI	
Non-cardia	UAT	18	0.90	0.53	1.43	40	1.22	0.87	1.67
	Esophagus	11	1.05	0.52	1.88	14	1.83	1.01	3.08
	Gastric, cardia	6	1.04	0.37	2.27	3	0.62	0.12	1.82
	Small intestine	19	4.34	2.61	6.8	12	2.04	1.05	3.57
	CRC	150	1.17	0.99	1.37	230	1.15	1.01	1.31
	Liver	24	0.89	0.57	1.33	19	1.1	0.66	1.72
	Pancreas	26	1.01	0.66	1.48	2	0.14	0.01	0.5
	Lung	67	0.82	0.63	1.04	55	0.9	0.68	1.17
	Breast	70	0.95	0.74	1.2	210	1.16	1.01	1.33
	Cervix	5	1.23	0.39	2.89	12	1.41	0.72	2.46
	Endometrium	13	0.68	0.36	1.16	44	0.93	0.67	1.24
	Ovary	11	1.04	0.52	1.87	19	1.07	0.64	1.67
	Female genitals	3	0.8	0.15	2.37	4	0.73	0.19	1.88
	Prostate	177	0.75	0.64	0.87	452	0.90	0.82	0.99
	Testis	1	1.66	0	9.53	3	1.09	0.21	3.23
	Male genitals	1	0.47	0	2.72	5	1.36	0.43	3.2
	Kidney	27	1.68	1.11	2.45	27	1.01	0.66	1.47
	Bladder	48	0.83	0.61	1.1	124	1.25	1.04	1.49
	Melanoma	19	0.64	0.38	1	47	0.79	0.58	1.05
	Skin SCC	66	0.91	0.7	1.16	129	1.42	1.19	1.69
	Nervous system	9	0.55	0.25	1.05	23	0.84	0.53	1.26
	Thyroid	5	1.31	0.41	3.07	14	1.85	1.01	3.11
	Endocrine	10	1.04	0.50	1.92	37	1.30	0.92	1.8
	Connective tissue	6	1.15	0.41	2.52	10	1.25	0.60	2.31
	NHL	26	0.80	0.52	1.18	60	1.29	0.99	1.66
	Myeloma	6	0.41	0.15	0.9	18	0.96	0.57	1.52
	Leukemia	25	0.87	0.56	1.29	37	0.97	0.68	1.33
	All	880	0.93	0.87	0.99	1701	1.05	1.00	1.10

Notes: N= patient number. Bolding shows that the 95% CI does not overlap with 1.00.

Abbreviations: SIR, standardized incidence ratio; 95% CI, 95% confidence interval; SPC, second primary cancer; UAT, upper aerodigestive tract; CRC, colorectal cancer; SCC, squamous cell carcinoma; NHL, non-Hodgkin lymphoma.

germline mutations in mismatch repair genes *MLH1* and *MSH2* was increased about 9-fold by age 75 years; yet the increased risk was observed only in patients aged 70 or more years.¹³ The observed associations of second GC with CRC, small intestinal (in non-cardia GC) and bladder cancers could be due to shared predisposition to mutations in mismatch repair genes.¹³ Yet the lacking risk of endometrial cancer contradicts this hypothesis. However, an explanation may be the relatively early median age of onset for endometrial cancer in Lynch syndrome (48 years).^{27,28} Thus, CRC with a median age of onset at 44 years, and a much commoner cancer than GC in Lynch syndrome, would be the likeliest SPC after endometrial cancer.²⁸

The association of GC with breast cancer poses the question if *CDHI* mutations may be involved, as lobular breast cancer manifests in *CDHI*-related cancers.¹¹ Indeed, lobular breast cancer was in excess as FPCs followed by GC, supporting the likelihood of *CDHI* predisposition. We tested also if some evidence for the role of *BRCA1/2* could be found, but low case numbers for pathognomonic clustering of cancers did not allow conclusions.

A further cluster of FPCs that showed a risk for GC as SPCs was skin SCC and NHL. High risk for this combination of neoplasms is known for immunocompromised individuals, such as kidney transplant patients.^{29–31} An increased risk of GC as SPC has been found in studies analyzing SPCs after NHL and skin SCC.^{32,33} It was also shown that family history of GC increased the likelihood of second GC in NHL patients.³⁴ We thus consider plausible that the increased risk for second GCs after skin SCC and NHL may have an immunological component. As an additional contributing factor could be mucosa-associated lymphoid tissue (MALT) lymphoma, for which the most commonly affected organ is the stomach. The underlying mechanism is chronic gastritis induced by *H. pylori*.³⁵ The Swedish Cancer Registry does not consider affected organs for lymphomas, and thus any MALT lymphoma would be classified under NHL. The median diagnostic age of MALT lymphoma is 67 years and it is quite possible that GC would be diagnosed after MALT lymphoma.³⁶ Even though MALT lymphoma is less than 10% of all NHL, the reported risk of GC (4.3) is relatively high.³⁷

Limitations of the study are several. A cancer registry has no information on individual treatment nor on lifestyle factors. However, we were able to adjust for socioeconomic factors, which reflect many aspects of lifestyle. While the overall reporting of SPCs is high, we have no

specific information on reporting after GC.^{25,38} As the distribution of GC has a large geographical variation, the results may be generalized only to regions with a similar GC incidence as Sweden. Finally, there is no information on the population frequency of *CDHI* mutations in Sweden. This being the case, it is not possible to evaluate how applicable the proposed guidelines for the management of mutation carriers would be.³⁹

In conclusion, multiple primary cancers in the same individual are one of the hallmarks of genetic predisposition, which in the present study suggested contribution by hereditary *CDHI*-related GC and Lynch syndrome. Lobular breast cancer is a manifestation of *CDHI* predisposition and we showed that breast cancers, which preceded GC had an over-representation of lobular histology. The signs of Lynch syndrome were found in an increased risk of second GC after CRC, small intestinal and bladder cancers. The third line of findings suggested immune dysfunction as a contributing mechanism for the excess GC as SPC after skin SCC and NHL. While GC is fatal as FPC, it is so also as SPC; for example, most breast or ovarian cancer and NHL patients who were diagnosed with second GC also died of GC.^{34,40,41} Even though Western countries, as opposed to Asian countries, have not adopted population screening for GC, application of early detection methods, such as gastroscopy, could be considered for risk groups.⁸ According to the present results, such risk groups could be breast and intestinal cancer patients with a family history of gastric cancer.

Statement on Ethics

The study was approved on 25 January, 2013 by the Regional Ethical Review Board in Lund without the requirement for informed consent (registration number 2012/795). Instead, the Ethical Review Board obliged us to advertise in the newspapers in order to inform the public that their data would be used for secondary purposes. After that, around 40 individuals were excluded (≈ 40 excluded individuals/ ≈ 10 million individuals in the Swedish population).

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Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it

critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

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Disclosure

A.H. is a shareholder in Targovax ASA. A.H. reports personal fees and is an employee and shareholder in TILT Biotherapeutics Ltd. The other authors declared no conflicts of interest.

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