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Causes of death in patients diagnosed with gastric adenocarcinoma in Sweden, 1970-2014: A population-based study

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Abstract

The causes of death in patients with gastric adenocarcinoma have not been well characterized. This nationwide population-based cohort study included 56 240 patients diagnosed with gastric adenocarcinoma in 1970-2014 in Sweden. We used competing-risks regression to compare cause-specific risks of death in patients with different characteristics and a multiple-cause approach to assess proportions of deaths attributable to each cause. Among 53 049 deaths, gastric cancer was the main (77.7% of all deaths) underlying cause. Other major underlying causes were nongastric malignancies (8.0%), ischemic heart disease or cerebrovascular disease (6.5%), and respiratory diseases (1.4%). Risk of death from gastric cancer steadily decreased in patients with cardia adenocarcinoma over the study period, but remained relatively stable in patients with noncardia adenocarcinoma since the 1980s. Risk of death from other malignancies increased during later calendar periods (subhazard ratio [SHR] = 2.16, 95% confidence interval [CI] 1.97-2.38, comparing 2001-2014 with 1970-1980). Compared with men, the risk of death in women with cardia adenocarcinoma was higher from gastric cancer (SHR = 1.18, 95% CI 1.10-1.27), but lower from other malignancies (SHR = 0.80, 95% CI 0.71-0.91). In multiple-cause models, 60.4%-71.2% of all deaths were attributable to gastric cancer and 9.5%-12.1% to other malignancies. The temporal trends of cause-specific risks from multiple-cause models were similar to those of underlying causes. Our findings suggest that although most deaths in patients with gastric adenocarcinoma are due to gastric cancer, other causes of death are common. Patients with cardia adenocarcinoma face considerable increasing risk of death from other causes over time, particularly from other malignancies.

KEYWORDS
cause of death, mortality, prognosis, stomach neoplasm, survival

1 | INTRODUCTION

Gastric cancer is the sixth most common type of cancer worldwide, and gastric adenocarcinoma comprises over 90% of the total number of cases.[1-3] Gastric adenocarcinoma carries a poor prognosis with an overall 5-year survival rate below 30% in European countries, after slight improvements in recent years.[4-6] Characterizing the specific causes of death in patients with gastric adenocarcinoma is essential for improving the treatment and follow-up. However, to our knowledge, this has not been done previously in a population-based setting.

Analyzing causes of death data is methodologically complex, particularly because of 2 main challenges. First, competing risks are often present in the analysis of survival data, ie the occurrence of the primary cause of death of interest is precluded by death from other causes.[7] Therefore, the analyses should ideally assess the influence of competing risks. Second, although the reporting of cause-specific mortality is usually based on the so-called underlying cause of death, it is debatable if it is appropriate to attribute each death to a single disease, particularly in an era of high prevalence of chronic diseases.[7,8] Furthermore, designating the underlying cause of death is often a subjective judgment of certifying physicians, which could lead to considerable rates of errors.[9,10] Therefore, the contribution of other causes recorded on a death certificate, in addition to the underlying causes, should also be evaluated.

Using data from nationwide health data registries with complete coverage and follow-up, we assessed the causes of death in patients diagnosed with gastric adenocarcinoma in Sweden during more than 4 decades. To avoid bias, we used a competing-risks model comparing cause-specific risks of death in patients with different characteristics and applied a multiple-cause approach assessing both underlying and contributing causes of death.

2 | METHODS

2.1 | Study design and participants

This was a population-based cohort study including all patients diagnosed with gastric adenocarcinoma (International Classification of Diseases, 7th edition [ICD-7] code 151; and histology code 096 according to WHO/HS/CANC/24.1 classification) in Sweden between 1 January 1970 and 31 December 2014. These patients were identified from the Swedish Cancer Registry, which has 98% national coverage of both cardia and noncardia gastric cancers and a rate of histological confirmation of virtually 100%.[11,12] We obtained information on causes of death of the cohort members through linkage to the Swedish Cause of Death Register, which covers all deaths of residents in Sweden with a nonreporting rate lower than 1%.[13] All participants were followed up from the date of gastric adenocarcinoma diagnosis until the date of death or the end of the study (31 December 2014), whichever occurred first. The unique personal identity number assigned to all Swedish residents enabled linkages

of the individual participants' data between the registers. The study was approved by the Regional Ethical Review Board in Stockholm, Sweden (Protocol Number: 2015/1916-31/1).

2.2 | Outcome ascertainment

We analyzed both underlying and contributing causes of deaths in patients with gastric adenocarcinoma. According to the definition from the WHO, the underlying cause of death refers to any disease or injury initiating the train of events leading directly to death, or the circumstances of the accident or violence producing the fatal injury; contributing causes are other significant conditions that have unfavorably influenced the course of the morbid process and thus contributed to the fatal outcome.[14] The specific ICD codes used for defining causes of death are listed in Tables S1 and S2. Causes of death were categorized into the following 5 major groups: (i) gastric cancer; (ii) malignancies other than gastric cancer; (iii) ischemic heart disease or cerebrovascular disease; (iv) nonmalignant diseases of the respiratory tract; and (v) other causes.

2.3 | Statistical analysis

We assessed the distribution of underlying causes of death in patients with gastric adenocarcinoma by categories of duration of follow-up (1 year or less, 1-5 years, or more than 5 years), which was calculated from the date of gastric adenocarcinoma diagnosis to the end of follow-up. Competing-risks regression was used to compare the cause-specific risks of death in patients with different characteristics. This method was preferred over the standard Cox proportional hazard regression because, in the latter method, competing events (deaths from other causes) are simply treated as censored observations. The competing-risks regression is based on the method of Fine and Gray and estimates the cause-specific cumulative incidence functions of death in the presence of competing risks.[15,16] The Fine and Gray competing-risks model also provides subhazard ratios (SHRs), which describe the relative effect of covariates on the subdistribution hazard function.[17] Variables included in the model were sex (male or female), age at diagnosis (less than 50, 50-59, 60-69, 70-79 years, or 80 years or older), and calendar period of diagnosis (1970-1980, 1981-1990, 1991-2000, or 2001-2014). Cumulative incidence functions of death from the 5 major groups of underlying causes within 5 years of diagnosis were calculated by calendar period.

In a multiple-cause model, we quantitatively assessed the total number and proportion of deaths attributable to each cause according to different values of weight (ω) assigned to the underlying cause of death.[7] For each death event with a total of k recorded causes (including underlying and contributing causes), a given larger weight ω (eg 0.75) was assigned to the underlying cause, and the rest of the weight ($1 - \omega$) was equally shared by other causes, ie the fraction of death attributable to each contributing cause being ($1-\omega$)/

(*k*-1). We then calculated the *sum* of fractions of death attributable to each cause from all deceased individuals and the corresponding proportion out of all deaths. In the absence of recorded contributing cause of death, the fraction for the underlying cause of death was given the value of 1. Three weighting approaches (ω = 0.75, 0.5, and ω = 1/*k*) were used separately. When ω = 1/*k*, it was assumed that all causes had contributed equally to the death.[7,18]

We further separately analyzed the data in patients with cardia adenocarcinoma (ICD-7 code 151.1) and those with noncardia adenocarcinomas. All statistical analyses were undertaken using SAS 9.4 for Windows (SAS Institute). A 2-sided *P* value below 0.05 was considered statistically significant.

3 | RESULTS

3.1 | Participants

This study comprised 56 240 patients diagnosed with gastric adenocarcinoma, including 7542 (13.4%) patients with cardia adenocarcinoma and 48 698 (86.6%) patients with noncardia adenocarcinoma. A majority of patients were men (61.6%) and the male predominance was stronger for cardia adenocarcinoma (76.3%). The mean age at diagnosis was 71.4 years (SD, 11.6 years). More detailed information about the participants is presented in Table 1.

3.2 | Underlying causes of death

A total of 53 049 (94.3%) patients with gastric adenocarcinoma died during follow-up. Among these deaths, 36 940 (69.6%) occurred within 1 year of diagnosis and 48 333 (91.1%) occurred within 5 years of diagnosis. Table 2 shows the distribution of the underlying causes of death by duration of follow-up. Gastric cancer was the underlying cause of death in 41 226 (77.7%) of all deceased patients. Malignancies other than gastric cancer were the second most common group (n = 4256, 8.0%). Other relatively common underlying causes of death were ischemic heart disease (n = 2595, 4.9%), cerebrovascular disease (n = 863, 1.6%), and nonmalignant respiratory diseases (n = 762, 1.4%). Among the 4716 patients who died after having survived for at least 5 years after gastric adenocarcinoma diagnosis, gastric cancer was a less common underlying cause of death (n = 976, 20.7%), while the frequencies of other common underlying causes of death were relatively higher, ie other malignancies (n = 770, 16.3%), ischemic heart disease (n = 816, 17.3%), cerebrovascular disease (n = 384, 8.1%), and nonmalignant respiratory diseases (n = 343, 7.3%). Separate analyses showed a lower proportion of deaths from gastric cancer and a higher proportion of other malignancies as the underlying causes of death in patients with cardia adenocarcinoma than in noncardia adenocarcinoma patients (Tables S3 and S4).

TABLE 1 Distribution of basic characteristics of all patients with gastric adenocarcinoma diagnosed in Sweden, 1970-2014

Characteristics	Total gastric adenocarcinoma		Cardia adenocarcinoma		Noncardia adenocarcinoma	
	Number (%)	Person-years	Number (%)	Person-years	Number (%)	Person-years
Total	56 240 (100)	120 261	7542 (100)	12 331	48 698 (100)	107 930
Gender						
Male	34 649 (61.6)	71 574	5756 (76.3)	9519	28 893 (59.3)	62 055
Female	21 591(38.4)	48 687	1786 (23.7)	2812	19 805 (40.7)	45 875
Age at diagnosis, y						
<50	2753 (4.9)	11 774	428 (5.7)	1040	2325 (4.8)	10 734
50-59	5556 (9.9)	20 552	1023 (13.6)	2617	4533 (9.3)	17 934
60-69	13 112 (23.3)	36 444	2107 (27.9)	4176	11 005 (22.6)	32 268
70-79	20 365 (36.2)	37 821	2487 (33.0)	3432	17 878 (36.7)	34 389
≥80	14 454 (25.7)	13 670	1497 (19.9)	1066	12 957 (26.6)	12 604
Mean ± SD	71.4 ± 11.6		69.3 ± 11.6		71.7 ± 11.5	
Calendar period at diagnosis						
1970-1980	18 486 (32.9)	37 934	1071 (14.2)	1265	17 415 (35.8)	36 669
1981-1990	15 516 (27.6)	37 590	1642 (21.8)	2923	13 874 (28.5)	34 667
1991-2000	11 175 (19.9)	26 589	1983 (26.3)	3793	9192 (18.9)	22 797
2001-2014	11 063 (19.7)	18 147	2846 (37.7)	4350	8217 (16.9)	13 796
Length of follow-up, y						
≤1	37 637 (66.9)	10 861	4925 (65.3)	1794	32 712 (67.2)	9068
1-5	12 425 (22.1)	26 640	2052 (27.2)	4186	10 373 (21.3)	22 453
>5	6178 (11.0)	82 760	565 (7.5)	6351	5613 (11.5)	76 409

Mortality status	Duration of follow-up, y			
	≤1	1-5	>5	All
Total[a]	56 240 (100)	18 603 (100)	6178 (100)	56 240 (100)
Alive throughout follow-up[b,c]	697 (1.2)	1032 (5.6)	1462 (23.7)	3191 (5.7)
All deaths[c]	36 940 (65.7)	11 393 (61.2)	4716 (76.3)	53 049 (94.3)
Cause-specific death[d]				
Gastric cancer	31 134 (84.3)	9116 (80.0)	976 (20.7)	41 226 (77.7)
Malignancies other than gastric cancer	2518 (6.8)	968 (8.5)	770 (16.3)	4256 (8.0)
Infectious and parasitic diseases	29 (0.1)	26 (0.2)	59 (1.3)	114 (0.2)
Nonmalignant blood diseases	15 (0.04)	10 (0.1)	13 (0.3)	38 (0.1)
Endocrine, nutritional, and metabolic diseases	34 (0.1)	26 (0.2)	81 (1.7)	141 (0.3)
Diabetes	24 (0.1)	20 (0.2)	62 (1.3)	106 (0.2)
Dementia and Alzheimer's disease	4 (0.01)	16 (0.1)	141 (3.0)	161 (0.3)
Ischemic heart disease	1337 (3.6)	442 (3.9)	816 (17.3)	2595 (4.9)
Cerebrovascular disease	314 (0.9)	165 (1.5)	384 (8.1)	863 (1.6)
Hypertensive disease	23 (0.1)	7 (0.1)	30 (0.6)	60 (0.1)
Nonmalignant diseases of respiratory system	292 (0.8)	127 (1.1)	343 (7.3)	762 (1.4)
Chronic obstructive pulmonary disease	87 (0.2)	30 (0.3)	116 (2.5)	233 (0.4)
Influenza and pneumonia	167 (0.5)	73 (0.6)	180 (3.8)	420 (0.8)
Nonmalignant diseases of digestive system	314 (0.9)	65 (0.6)	131 (2.8)	510 (1.0)
Nonmalignant diseases of urinary system	35 (0.1)	29 (0.3)	60 (1.3)	124 (0.2)
External causes, including suicide	33 (0.1)	32 (0.3)	97 (2.1)	162 (0.3)
Suicide	14 (0.04)	5 (0.04)	13 (0.3)	32 (0.1)
Other specified	828 (2.2)	359 (3.2)	811 (17.2)	1998 (3.8)

Data are shown as n (%).

[a]Patients alive at the beginning of the follow-up window.

[b]Patients alive at the beginning of the follow-up window who did not die during the specific period of follow-up.

[c]Percentage of all patients alive at the beginning of the follow-up window.

[d]Percentage of all deaths occurring during the specific period of follow-up.

Among all deaths with nongastric malignancies as underlying causes (n = 4256), 2586 (60.8%) deaths were due to cancers of digestive organs, 262 (6.2%) to lung cancer, and 256 (6.0%) to prostate cancer (Table 3). The distribution of nongastric malignancy-related deaths varied between patients with cardia adenocarcinoma and those with noncardia adenocarcinoma. Esophageal cancer was the most commonly recorded underlying cause of death from nongastric malignancies (n = 1406, 20.9% of all deaths) in patients with cardia adenocarcinoma. In patients with noncardia adenocarcinoma, common nongastric malignant underlying causes of death were colorectal cancer (13.6% of all deaths from nongastric malignancies), pancreatic cancer (11.2%),

lung cancer (9.3%), prostate cancer (8.7%), and esophageal cancer (7.3%; Table 3).

3.3 | Competing-risks regression

The estimated SHRs and their 95% confidence intervals (CIs) of cause-specific death within 5 years of gastric adenocarcinoma diagnosis in the competing-risks regression are presented in Table S5. Compared to male patients, female patients had slightly higher risk of death from gastric cancer (SHR 1.08; 95% CI, 1.05-1.10), but lower risks of death from other malignancies (SHR 0.75; 95% CI, 0.70-0.81)

TABLE 3 Number (%) of deaths with malignancies other than gastric cancer as underlying causes in patients diagnosed with gastric adenocarcinoma in Sweden, 1970-2014

Anatomic site	Total gastric adenocarcinoma	Cardia adenocarcinoma	Noncardia adenocarcinoma
Total	4256 (100)	1600 (100)	2656 (100)
Lip, oral cavity, and pharynx	25 (0.6)	2 (0.1)	23 (0.9)
Digestive organs	2586 (60.8)	1481 (92.6)	1105 (41.6)
Esophagus	1601 (37.6)	1406 (87.9)	195 (7.3)
Colon, rectum, and anus	383 (9.0)	23 (1.4)	360 (13.6)
Liver and biliary passages	177 (4.2)	12 (0.8)	165 (6.2)
Pancreas	316 (7.4)	19 (1.2)	297 (11.2)
Lung (including trachea and bronchus)	262 (6.2)	15 (0.9)	247 (9.3)
Breast	124 (2.9)	4 (0.3)	120 (4.5)
Uterus	29 (0.7)	1 (0.1)	28 (1.1)
Ovary	48 (1.1)	2 (0.1)	46 (1.7)
Prostate	256 (6.0)	24 (1.5)	232 (8.7)
Bladder	73 (1.7)	10 (0.6)	63 (2.4)
Kidney	47 (1.1)	3 (0.2)	44 (1.7)
Thyroid	8 (0.2)	0 (0)	8 (0.3)
Hodgkin lymphoma	4 (0.1)	0 (0)	4(0.2)
Non-Hodgkin lymphoma	63 (1.5)	3 (0.2)	60 (2.3)
Leukemia	60 (1.4)	0 (0)	60 (2.3)
Others and unspecified	671 (15.8)	55 (3.4)	616 (23.2)

and ischemic heart disease or cerebrovascular disease (SHR 0.72; 95% CI, 0.65-0.81). Separate analyses for cardia and noncardia adenocarcinomas (Tables S6 and S7) showed that the sex difference was limited to patients with cardia adenocarcinomas in deaths from gastric cancer (SHR 1.18; 95% CI, 1.10-1.27) and other malignancies (SHR 0.80; 95% CI, 0.71-0.91). The reduced risk of death from respiratory diseases in female patients was limited to non-cardia adenocarcinoma patients (SHR 0.67, 95% CI 0.51-0.87). Risks of death from ischemic heart disease or cerebrovascular disease and respiratory diseases increased with age, whereas no such age pattern was observed for death from gastric cancer or from other malignancies (Table S5).

Patients who were diagnosed in more recent calendar periods had lower risk of death from gastric cancer than those diagnosed in earlier periods; patients diagnosed in 2001-2014 had decreased risk of death from gastric cancer than those diagnosed in 1970-1980 (SHR 0.72; 95% CI, 0.70-0.74). Patients diagnosed in later calendar periods had higher risk of death from other malignancies (Table S5 and Figure 1). The decreased risk of death from gastric cancer and the increased risk of death from other malignancies were more pronounced in patients with cardia adenocarcinoma than in those with noncardia adenocarcinoma, showing steady changes over the whole study period (Table S6). Patients diagnosed with noncardia adenocarcinomas in 1981-1990 had lower risk of death from gastric cancer than those diagnosed in 1970-1980 (SHR 0.86; 95% CI, 0.84-0.88),

but the risk showed little reduction in patients diagnosed after the 1980s. The risk of death from malignancies other than gastric cancer in patients with noncardia adenocarcinoma was stable before the year 2000, but increased in 2001-2014 (SHR 1.27; 95% CI, 1.11-1.46, compared with 1970-1980; Table S7). Risks of death from ischemic heart disease or cerebrovascular disease and respiratory disease were highest in patients diagnosed in 1981-1990 and decreased over time thereafter (Table S5 and Figure 1).

3.4 | Multiple-cause model

Gastric cancer was recorded as either an underlying or a contributing cause of death in 83.2% of all deaths among patients with gastric adenocarcinoma; other malignancies were recorded as causes of death in 27.7%, respiratory diseases in 10.5%, ischemic heart disease in 10.3%, and cerebrovascular disease in 4.2% of all deaths (Table S8).

Table 4 presents the numbers and percentages of deaths attributable to each cause according to different values of weight (ω) assigned to the underlying cause of death. When $\omega = 0.75$, 71.2% of all deaths were attributable to gastric cancer, 9.5% to other malignancies, 6.6% to ischemic heart disease or cerebrovascular disease, and 2.4% were attributable to respiratory diseases. With the increasing value of ω, the number of deaths attributable to gastric cancer decreased, and that of other causes
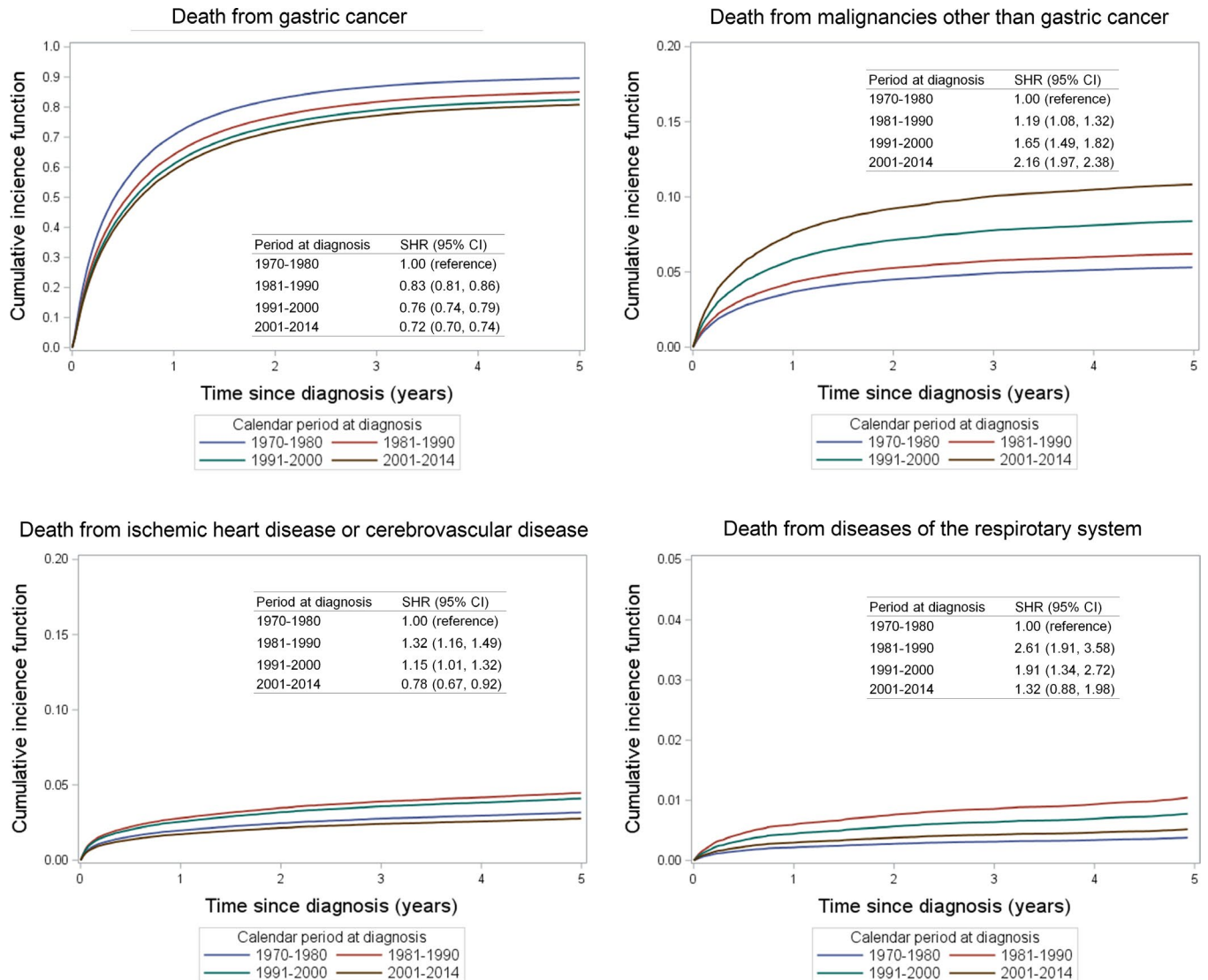
FIGURE 1 Cumulative incidence functions and subhazard ratios (SHRs) with 95% confidence intervals (CIs) for major causes of death by calendar period at diagnosis of gastric adenocarcinoma in Sweden, 1970-2014, from competing-risks regressions

increased. Under the "equal weights" approach, ie $\omega = 1/k$, gastric cancer accounted for 60.4% of all deaths, and other malignancies accounted for 12.1%. Separate analyses for cardia and noncardia adenocarcinomas showed similar patterns, except for substantially lower proportions of deaths attributable to gastric cancer (49.5%-60.3%) but higher proportions attributable to other malignancies (24.8%-26.4%) in patients with cardia adenocarcinoma (Tables S9 and S10).

The temporal trends in the proportions of deaths attributable to groups of causes in multiple-cause models had similar patterns to those observed for underlying causes in the competing-risks regressions. The proportion of deaths attributable to gastric cancer decreased over time and ranged from 67% to 75% in 1970-1980 compared with 55% to 71% in 2001-2014, depending on the value of weight (ω) assigned to the underlying cause. The proportion attributable to other causes, particularly nongastric malignancies, increased over time (Figure 2).

4 | DISCUSSION

This study found that gastric cancer was the main cause of death in short-term survivors of gastric adenocarcinoma, but accounted for a smaller proportion of deaths in long-term survivors. Other major causes of death were nongastric malignancies, particularly cancers of the digestive organs, as well as ischemic heart disease, cerebrovascular disease, and respiratory diseases. The cause-specific risks of death varied between patients with cardia and noncardia adenocarcinoma. Patients diagnosed in more recent calendar periods had a decreased risk of death from gastric cancer and were more likely to die from other causes, particularly from other malignancies, compared with those diagnosed in earlier periods.

To the best of our knowledge, this study is the largest and the first population-based study examining the causes of death in patients with gastric adenocarcinoma. The complete nationwide coverage and high quality of data from Swedish health data registers

TABLE 4 Number (%) of deaths attributable to each cause according to different values of weight (ω) assigned to the underlying cause of death, Sweden, 1970-2014

Cause of death	ω = 0.75	ω = 0.50	ω = 1/kᵃ
Gastric cancer	37 763 (71.2)	34 301 (64.7)	32 012 (60.4)
Malignancies other than gastric cancer	5021 (9.5)	5786 (10.9)	6409 (12.1)
Infectious and parasitic diseases	156 (0.3)	197 (0.4)	220 (0.4)
Nonmalignant blood diseases	105 (0.2)	172 (0.3)	216 (0.4)
Endocrine, nutritional, and metabolic diseases	256 (0.5)	371 (0.7)	448 (0.8)
Diabetes	195 (0.4)	284 (0.5)	337 (0.6)
Dementia and Alzheimer's disease	171 (0.3)	181 (0.3)	185 (0.3)
Ischemic heart disease	2592 (4.9)	2589 (4.9)	2439 (4.6)
Cerebrovascular disease	885 (1.7)	907 (1.7)	889 (1.7)
Hypertensive disease	102 (0.2)	144 (0.3)	177 (0.3)
Nonmalignant diseases of respiratory system	1266 (2.4)	1769 (3.3)	1988 (3.8)
Chronic obstructive pulmonary disease	279 (0.5)	324 (0.6)	349 (0.7)
Influenza and pneumonia	775 (1.5)	1130 (2.1)	1243 (2.3)
Nonmalignant diseases of digestive system	813 (1.5)	1117 (2.1)	1289 (2.4)
Nonmalignant diseases of urinary system	180 (0.3)	237 (0.4)	278 (0.5)
External causes, including suicide	365 (0.7)	568 (1.1)	786 (1.5)
Suicide	31 (0.1)	31 (0.1)	30 (0.1)
Other specified	3335 (6.3)	4672 (8.8)	5674 (10.7)

ᵃThis "equal weights" approach assumes that all causes have contributed equally to each death, where k is the total number of causes (including underlying and contributing causes).

lend validity to the findings. The comprehensive survival analyses used in this study, including the competing-risks model and multiple-cause model, took into account both underlying and contributing causes of death. Nevertheless, these methods have some limitations. The competing-risks model considers only the underlying causes of death, whereas the multiple-cause model does not solve the "competing risks" problem.[7] The magnitude of the SHRs obtained in the competing-risks model should be interpreted with caution because the SHRs cannot directly quantify the strengths of the associations between predictors and cause-specific risk of mortality.[17] In the multiple-cause model, the choice of weights assigned to the underlying cause of death was arbitrary. Finally, this study had limited statistical power in some subgroup analyses of patients with the sublocation cardia adenocarcinoma.

Few studies have investigated the causes of death in patients diagnosed with gastric cancer. A hospital-based study of 172 selected postoperative patients with gastric cancer in Italy and a similar study of 323 postoperative patients in China both showed that tumor recurrence was the most common cause of death, and other common causes of death were other primary cancers, cardiovascular disease, cerebrovascular disease, and respiratory diseases.[19,20] These observations are consistent with the findings of the present study, although the specific proportions of deaths due to each cause were not comparable because of substantial differences in patient characteristics, analytic methods, and sample sizes. No previous study has assessed the temporal trends in the cause-specific deaths or had adequate statistical power to undertake robust subgroup analyses.

The present study suggests that gastric cancer remains the predominant cause of death in patients with gastric adenocarcinoma, particularly within the first 5 years of diagnosis. During the last 3-4 decades, a steadily decreased risk of death from gastric cancer over time was seen in patients with cardia adenocarcinoma, whereas no such strong reduction was found for noncardia adenocarcinoma. These findings are consistent with a recent Swedish population-based analysis, which found that the relative survival improved for cardia adenocarcinoma, but not for noncardia adenocarcinoma, during 1990-2017.[4] The decreased disease-specific mortality in patients diagnosed with cardia adenocarcinoma in recent decades could be attributable to a better selection of patients for curative treatment, increased use of neoadjuvant therapies, introduction of multidisciplinary team meetings, and centralization of services.[21-23] The lack of improved disease-specific survival after noncardia adenocarcinoma in recent years in Sweden warrants closer investigation, but inadequate centralization of treatment could be one explanation.

Interestingly, the present study shows increasing risk of death from other malignancies over time in gastric adenocarcinoma patients.
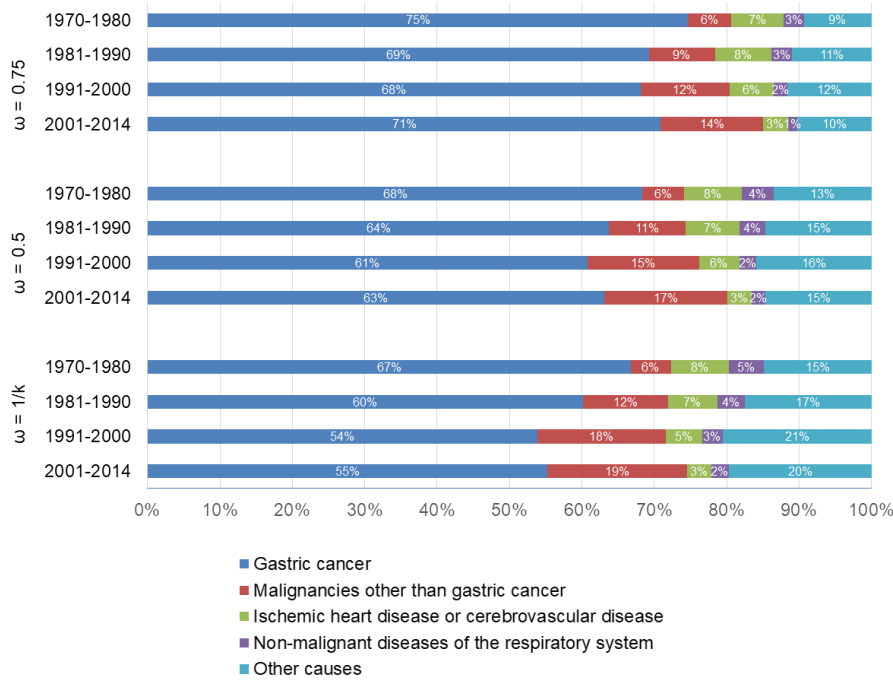
FIGURE 2 Proportions of deaths attributable to major groups of causes according to different values of weight (ω) assigned to the underlying cause by calendar period at diagnosis of gastric adenocarcinoma in Sweden, 1970-2014. The "equal weights" approach ($\omega = 1/k$) assumes that all causes contribute equally to each death, where k is the total number of causes, including underlying and contributing causes

These malignancies accounted for 14%-19% of all deaths in the latest period, 2001-2014, in the multiple-cause analyses. A large proportion of such deaths was due to cancers of other digestive organs, the lung and prostate. These findings could be explained by shared risk factors for gastric adenocarcinoma and other malignancies, eg tobacco smoking, dietary factors, and possibly treatments given to cancer patients, eg irradiative effects from radiotherapy.[2,3,24] The evidence concerning the role of *Helicobacter pylori* infection, the strongest risk factor for noncardia gastric adenocarcinoma, in the development of other cancers remains controversial.[25,26] Notably, esophageal cancer was recorded as the underlying cause for around one-fifth of deaths in patients with cardia adenocarcinoma, which is likely, to some extent, to be due to misclassification of these tumors.[11,12] However, the increasing risk of death from nongastric malignancies over time remained when analyses were restricted to patients with gastric noncardia adenocarcinoma, where tumor misclassification is not a major issue.

The higher risk of death from gastric cancer but lower risk of death from other malignancies in female patients, compared with male patients, is less likely to be explained by any misclassification in causes of death, which would have affected both sexes in the same manner. Thus, there should be an underlying mechanism, but this remains to be identified. The observed sex differences and age-dependent patterns in risks of death from ischemic heart disease or cerebrovascular disease and respiratory disease are in line with corresponding cause-specific mortality patterns in the general population.[27]

Despite all efforts to improve diagnostic procedures and therapy, the prognosis following diagnosis in patients with gastric adenocarcinoma has not improved much in European countries, with an overall 5-year survival still below 30% (18% in Sweden).[4-6] One possible explanation might be the increasing risks of death from other causes in addition to gastric adenocarcinoma recurrence, especially in an era when chronic diseases are increasingly common in an ageing population. Patients with gastric adenocarcinoma might be more vulnerable to death from other coexisting conditions, eg due to increased rates of immunodeficiency, malnutrition, and systemic inflammation.[28] Our multiple-cause analyses revealed that 29%-45% of all deaths were due to causes other than gastric cancer in patients diagnosed after the year 2000. These findings highlight the need to consider comorbidities in the clinical management of gastric adenocarcinoma patients for an improved overall prognosis.

In summary, this nationwide and population-based Swedish study reveals that, although patients diagnosed with gastric adenocarcinoma mainly die from this cancer, the disease-specific mortality has steadily decreased during the last 3-4 decades in patients with cardia adenocarcinoma. Patients diagnosed with gastric adenocarcinoma face considerable increasing risk of death from other causes over time, particularly from other malignancies.

DISCLOSURE

The authors declare that they have no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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