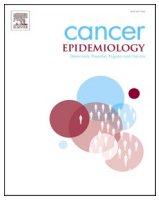
Cancer Epidemiology 85 (2023) 102399

Contents lists available at ScienceDirect

Cancer Epidemiology

journal homepage: www.elsevier.com/locate/canep



Mortality in small bowel cancers and adenomas – A nationwide, population-based matched cohort study

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ARTICLE INFO

Keywords:
Prognosis
Small bowel neoplasia
Small bowel adenomas
Cohort study

ABSTRACT

Background: Small bowel adenocarcinoma (SBA), neuroendocrine tumors (NET) and gastrointestinal stromal tumors (GIST) are neoplastic lesions of the small bowel while small bowel adenomas are precursors of SBA.
Aim: To examine mortality in patients diagnosed with SBA, small bowel adenomas, NET and GIST.
Methods: We performed a population-based matched cohort study encompassing all individuals with SBA (n = 2289), adenomas (n = 3700), NET (n = 1884) and GIST (n = 509) in the small bowel diagnosed at any of Sweden's 28 pathology departments between 2000 and 2016 (the "ESPRESSO study"). Each case was matched by sex, age, calendar year and county of residence to up to 5 comparators from the general population. Through Cox regression we estimated hazard ratios (HRs) and 95% confidence intervals (95%CIs) for death and cause-specific death adjusting for education.
Results: During follow-up until December 31, 2017, 1836 (80%) deaths occurred in SBA patients, 1615 (44%) in adenoma, 866 (46%) in NET and 162 (32%) in GIST patients. This corresponded to incidence rates of 295, 74, 80 and 62/1000 person-years respectively and adjusted HRs of 7.60 (95%CI=6.95–8.31), 2.21 (2.07–2.36), 2.74 (2.50–3.01) and 2.33 (1.90–2.87). Adjustment for education had a substantial impact on the HR for death in SBA but not for other neoplasias. The predominant cause of excess death was cancer in all groups.
Conclusion: This study confirms earlier findings of increased death rates in patients with SBA and NET in a modern study population. We also demonstrate a more than 2-fold increased risk of death in both GIST and the SBA precursor adenoma.

1. Introduction

The American cancer society estimates that 11–12,000 individuals in the US will be diagnosed with incident small bowel cancer (SBC) in 2022 [1], and that about 2000 individuals will die from SBC, with a roughly equal proportion of men (1110 expected deaths) and women (850 expected deaths) [1].

SBC consists of a range of neoplasia with different clinical and histological features [2], with potentially different prognosis. Small bowel adenocarcinoma (SBA) histologically resembles colorectal adenocarcinoma [3], but with a poorer prognosis at the same disease stage [4]. In most countries, NET constitute the second most common SBC [5]. Neuroendocrine tumors (NET) are typically polypoid and small, while jejunal forms are more often multicentric. Gastrointestinal stromal tumours (GIST) often debut through diffuse abdominal pain due to obstruction, anemia or gastrointestinal bleeding. Metastases are common [2], and in one of the larger cases series (n = 3363 patients with completed follow-up), recurrence-free survival 5 years after radical resection was 78.8% [6].

A number of studies have focused on SBC especially SBA and NET, generally demonstrating a poor survival [7–9]. With the exception of the Bojesen et al. paper, few have focused on modern-day SBC [9]. A

Abbreviations: aHR, adjusted Hazard Ratio; CI, Confidence Interval; SBA, Small Bowel Adenocarcinoma; SBC, Small Bowel Cancer; GIST, Gastrointestinal Stromal Tumor; NET, Neuroendocrine Tumor; HR, Hazard Ratio; TPR, Total Population Register.

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https://doi.org/10.1016/j.canep.2023.102399
Received 17 May 2023; Received in revised form 6 June 2023; Accepted 11 June 2023
Available online 14 June 2023

Swedish study by Landerholm recently examined survival in adenocarcinoma and NET based on the Swedish cancer register [10], but with most follow-up occurring prior to year 2000, since the study spanned a full 55 years (1960–2015). Cancer survival is highly dependent on cancer management and hence, that Swedish study may have underestimated survival in SBA diagnosed in the 21st century. Besides, considering the old age at median diagnosis of SBA (often around 70 years), death is frequent also in the general population, but the Landerholm study did not compare death rates in SBA with that in the general population [10]. Finally, the earlier Swedish paper did not report on GIST, or take socioeconomic status into account when evaluating mortality. Socioeconomic status has been strongly linked to cancer survival [11].

This study aimed to examine relative and absolute mortality in individuals with SBA, small bowel NET and GIST in a sample of individuals diagnosed 2000–2017. However, since gastrointestinal investigation for suspected cancer often ends with the detection of an adenoma, a cancer *precursor* rather than a cancer, we also examined mortality for this condition.

2. Methods

2.1. Study population

In Sweden, the SNOMED-CT classification system (Systematized Nomenclature of Medicine Clinical Terms), a standardized healthcare terminology is used to classify histopathology. Between 12 October, 2015 and 10 April, 2017 we collected data on all computerized gastrointestinal histopathology reports form Sweden's all 28 pathology departments. These data formed the basis of the ESPRESSO (Epidemiology Strengthened by histoPathology Reports in Sweden) cohort [12]. From this cohort we retrieved all small bowel biopsies identifying an overall 8382 cases (relevant topography and morphology codes are found in the Appendix): 2289 (27.3%) individuals with SBA, 3700 (44.1%) with adenoma, 1884 (22.5%) with NET and 509 (6.1%) diagnosed with GIST (Table 1). We did not consider lymphoma or non-specified SBC.

2.2. Comparators

Through the Swedish Total Population Register (TPR) [13], each patient with SBA was then matched on age, sex, county of residence, and birth year with ≤ 5 comparators (to optimize power and allow most individuals a full set of 5 comparators), alive at the index date of the corresponding patient. Comparators were not allowed to have an earlier record of the same small bowel neoplasia at date of matching but were allowed to develop future neoplasia (if and when they did, their follow-up was censored at date of small bowel neoplasia).

2.3. Outcome measure

We retrieved data on date of death according to the TPR. The TPR is maintained by the Swedish government agency Statistics Sweden, and contains information on births, deaths, and migration (91% of emigrations are registered within the TPR within 30 days and with a higher proportion over time). The register covers virtually all deaths in Swedish residents [13]. To determine cause of death the Swedish Cause of Death Register was used [14]. This register covers almost all deaths in Sweden since 1952. Causes of death were divided into five categories: cardiovascular disease, any cancer, respiratory disease, suicide and other diseases.

2.4. Other covariates

Models were also adjusted for education. We divided educational level (from the LISA database [15]), into four categories: compulsory (≤9 years), upper secondary (10–12 years), college or university (≥13 years) and missing.

Table 1
CHARACTERISTICS OF PATIENTS WITH SMALL INTESTINAL NEOPLASIA IN SWEDEN 2000–2017 AND THEIR COMPARATORS.

	Adenocarcinoma*		Adenoma*		NET*†		GIST*‡	
	Neoplasia	Comparators	Neoplasia	Comparators	Neoplasia	Comparators	Neoplasia	Comparators
N. Total	2 289 (100.0%)	10 819 (100.0%)	3 700 (100.0%)	17 366 (100.0%)	1 884 (100.0%)	9 019 (100.0%)	509 (100.0%)	2 461 (100.0%)
WOMEN	1 102 (48.1%)	5 238 (48.4%)	1 767 (47.8%)	8 349 (48.1%)	854 (45.3%)	4 124 (45.7%)	232 (45.6%)	1 126 (45.8%)
MEN	1 187 (51.9%)	5 581 (51.6%)	1 933 (52.2%)	9 017 (51.9%)	1 030 (54.7%)	4 895 (54.3%)	277 (54.4%)	1 335 (54.2%)
MEAN (SD)	70.3 (12.0)	69.7 (12.0)	67.2 (14.7)	66.5 (14.7)	67.1 (12.3)	66.7 (12.3)	65.1 (13.5)	64.7 (13.5)
MEDIAN	71.6	70.9	69.5	68.7	68.5	67.9	66.3	65.9
(INTERQUARTILE)	(62.7–79.2)	(62.2–78.5)	(59.5–78.0)	(58.8–77.2)	(59.8–76.0)	(59.4–75.6)	(57.7–75.3)	(57.3–74.8)
AGE RANGE	15.7–102.4	15.6–103.0	2.6–96.4	2.2–96.3	13.8–96.8	13.0–96.5	0.1–93.6	0.0–94.1
AGE GROUP (YEARS)								
0–39	39 (1.7%)	188 (1.7%)	217 (5.9%)	1 083 (6.2%)	50 (2.7%)	257 (2.8%)	26 (5.1%)	130 (5.3%)
40–59	392 (17.1%)	1 951 (18.0%)	750 (20.3%)	3 706 (21.3%)	429 (22.8%)	2 127 (23.6%)	127 (25.0%)	636 (25.8%)
60–69	607 (26.5%)	3 001 (27.7%)	936 (25.3%)	4 576 (26.4%)	559 (29.7%)	2 707 (30.0%)	155 (30.5%)	777 (31.6%)
70–79	738 (32.2%)	3 444 (31.8%)	1 077 (29.1%)	4 980 (28.7%)	588 (31.2%)	2 760 (30.6%)	143 (28.1%)	668 (27.1%)
> =80	513 (22.4%)	2 235 (20.7%)	720 (19.5%)	3 021 (17.4%)	258 (13.7%)	1 168 (13.0%)	58 (11.4%)	250 (10.2%)
EDUCATION (YEARS)								
< 9	609 (26.6%)	4 162 (38.5%)	1 290 (34.9%)	5 897 (34.0%)	612 (32.5%)	3 281 (36.4%)	134 (26.3%)	756 (30.7%)
10–12	628 (27.4%)	3 953 (36.5%)	1 323 (35.8%)	6 604 (38.0%)	734 (39.0%)	3 431 (38.0%)	197 (38.7%)	980 (39.8%)
≥ 13	324 (14.2%)	2 242 (20.7%)	750 (20.3%)	4 122 (23.7%)	392 (20.8%)	2 013 (22.3%)	137 (26.9%)	634 (25.8%)
missing	728 (31.8%)	462 (4.3%)	337 (9.1%)	743 (4.3%)	146 (7.7%)	294 (3.3%)	41 (8.1%)	91 (3.7%)
CALENDAR YEAR								
2000–2004	612 (26.7%)	2 943 (27.2%)	935 (25.3%)	4 444 (25.6%)	452 (24.0%)	2 159 (23.9%)	52 (10.2%)	258 (10.5%)
2005–2008	540 (23.6%)	2 550 (23.6%)	845 (22.8%)	3 976 (22.9%)	454 (24.1%)	2 169 (24.0%)	88 (17.3%)	421 (17.1%)
2009–2012	601 (26.3%)	2 812 (26.0%)	970 (26.2%)	4 487 (25.8%)	485 (25.7%)	2 334 (25.9%)	180 (35.4%)	863 (35.1%)
2013–2016	536 (23.4%)	2 514 (23.2%)	950 (25.7%)	4 459 (25.7%)	493 (26.2%)	2 357 (26.1%)	189 (37.1%)	919 (37.3%)
DEATH								
≤ 30 days	203 (8.9%)	33 (0.3%)	63 (1.7%)	46 (0.3%)	46 (2.4%)	20 (0.2%)	10 (2.0%)	4 (0.2%)
≤ 90 days	500 (21.8%)	85 (0.8%)	178 (4.8%)	130 (0.7%)	89 (4.7%)	64 (0.7%)	26 (5.1%)	14 (0.6%)
≤ 1 year	1 089 (47.6%)	411 (3.8%)	497 (13.4%)	514 (3.0%)	193 (10.2%)	253 (2.8%)	47 (9.2%)	65 (2.6%)
ever during follow-up	1 836 (80.2%)	3 440 (31.8%)	1 615 (43.6%)	4 739 (27.3%)	866 (46.0%)	2 259 (25.0%)	162 (31.8%)	434 (17.6%)

* All values refer to n (%) except age (mean, median and range) † NET Neuroendocrine tumor ‡GIST, Gastrointestinal stromal tumour

2.5. Statistical analysis

We used a population-based, nationwide matched cohort design, comparing individuals with small bowel neoplasia with up to 5 general population comparators, matched on age, sex, county of residence, and calendar year. Study follow-up ended with death, emigration, or end of follow-up (December 31, 2017), whichever occurred first. We used Cox proportional hazard modeling to calculate hazard ratios (HRs) and 95% confidence interval (95%CI) for overall and cause-specific mortality, on the time scale of days, internally stratified by the matching variables, i.e. each patient was only compared to their five population comparators. Furthermore we calculated absolute risks (deaths per 1000 person-years of follow-up) and risk differences according to follow-up period, sex, age group, presence of any previous cancer diagnosis and level of education. We also plotted Kaplan-Meier calculate survival curves comparing the different small bowel neoplasia subtypes to each other.

Statistics were carried out using the SAS statistical software (9.4). Statistical significance was set to $p < 0.05$.

2.6. Ethics

This study was approved by the Stockholm Ethics Review Board. Informed consent was waived since the study was strictly register-based [16].

3. Results

3.1. Background data

The median age at diagnosis was 72 years for SBA, 70 for adenomas, 69 for NET and 66 for GIST (Table 1). All neoplasia subtypes were more frequent in men, with the largest sex difference seen in NET (men constituting 54.7%). Some 47.6% of SBA patients died within the first year (vs. 13%, 10% and 9% of patients with adenomas, NET and GIST respectively, Table 1). For this reason, median follow-up differed substantially between neoplasia subtypes (Table 2).

3.2. Survival and mortality in different small bowel neoplasia subtypes and adenomas

The median survival was just above one year for SBA but considerably longer (>8 years) for adenomas, NET and GIST (Fig. 1). Mortality rates per 1000 person-years were 295 for SBA, 74 for adenomas, 80 for NET and 62 for GIST (Table 2). The adjusted Hazard Ratios (aHRs) (95% CI) for any death were of 7.60 (95%CI=6.95–8.31) for SBA, 2.21 (2.07–2.36) for adenoma, 2.74 (2.50–3.01) for NET and 2.33 (1.90–2.87) for GIST (Table 3).

3.3. Cause-specific mortality

Cancer was the most common cause of death in all neoplasia subtypes (Tables 2 and 3). For SBA patients, cancer death was the overwhelming contributor to excess death with an aHR of 27.6, all other cause-specific mortality aHRs ranged from 0.96 for respiratory death to 1.52 (non-significant) for suicide (Table 3). In adenoma patients the aHR for any death was 2.21 and significantly increased for all cause-specific mortality groups except for suicide, ranging from 1.56 for cardiovascular death to 3.71 for cancer (Table 3). The aHR for cancer death was 7.19 in patients with NET, and 5.35 in GIST patients (Table 3).

3.4. Stratified analyses

For all neoplasia subtypes, aHRs decreased with age, but were largely of similar magnitude in both women and men (Tables 4 and 5). Presence (aHR=8.55) vs. absence (aHR=6.32) of any cancer diagnosed before study entry was associated with a higher aHR for any death in SBA, but had no major impact in patients with other small bowel neoplasia (Tables 4 and 5). Low education, as well as missing data on education, was associated with increased mortality rates in all small bowel neoplasia subtypes and comparators, but with no clear link to aHRs (Tables 4 and

Table 2
Number of deaths and incidence rates for cause-Specific death among all swedish patients with small intestinal neoplasia IN 2000–2017 and their comparators.

	Adenocarcinoma		Adenoma		NET*		GIST†	
	Neoplasia	Comparators	Neoplasia	Comparators	Neoplasia	Comparators	Neoplasia	Comparators
PARTICIPANTS, N	2 289	10 819	3 700	17 366	1 884	9 019	509	2 461
DEATHS, N (%)	1 836 (80.2%)	3 440 (31.8%)	1 615 (43.6%)	4 739 (27.3%)	866 (46.0%)	2 259 (25.0%)	162 (31.8%)	434 (17.6%)
FOLLOW-UP								
AGGREGATE, PERSON-YEARS	6 225	79 970	21 763	127 789	10 850	66 829	2 606	15 171
MEAN FOLLOW-UP (SD)	2.7 (3.7)	7.4 (4.5)	5.9 (4.6)	7.4 (4.6)	5.8 (4.2)	7.4 (4.5)	5.1 (3.6)	6.2 (3.9)
median follow-up (INTERQUARTILE RANGE)	1.1 (0.3–3.5)	6.7 (3.6–10.7)	4.8 (2.0–8.9)	6.6 (3.5–10.8)	4.8 (2.3–8.4)	6.8 (3.7–10.6)	4.6 (2.3–7.1)	5.3 (3.1–8.4)
ANY DEATH, INCIDENCE ‡ (95%CI)	294.9 (281.4–308.4)	43.0 (41.6–44.5)	74.2 (70.6–77.8)	37.1 (36.0–38.1)	79.8 (74.5–85.1)	33.8 (32.4–35.2)	62.2 (52.6–71.7)	28.6 (25.9–31.3)
DEATH FROM CVD, N (%)	93 (4.1%)	1 306 (12.1%)	411 (11.1%)	1 736 (10.0%)	123 (6.5%)	805 (8.9%)	15 (2.9%)	126 (5.1%)
CVD MORTALITY: INCIDENCE ‡ (95%CI)	16.2 (12.9–19.5)	18.0 (17.1–19.0)	21.0 (18.9–23.0)	15.1 (14.4–15.8)	12.6 (10.3–14.8)	13.4 (12.5–14.4)	6.7 (3.3–10.0)	9.6 (7.9–11.3)
DEATH FROM CANCER, N (%)	1 554 (67.9%)	690 (6.4%)	638 (17.2%)	979 (5.6%)	566 (30.0%)	523 (5.8%)	98 (19.3%)	98 (4.0%)
CANCER, INCIDENCE RATE ‡ CANCER (95%CI)	270.3 (256.9–283.8)	9.5 (8.8–10.2)	32.5 (30.0–35.0)	8.5 (8.0–9.0)	57.8 (53.0–62.5)	8.7 (8.0–9.5)	43.5 (34.9–52.1)	7.5 (6.0–9.0)
RESPIRATORY DEATHS, N (%)	16 (0.7%)	210 (1.9%)	99 (2.7%)	269 (1.5%)	12 (0.6%)	130 (1.4%)	2 (0.4%)	23 (0.9%)
RESPIRATORY DEATH, INCIDENCE ‡ (95%CI)	2.8 (1.4–4.1)	2.9 (2.5–3.3)	5.0 (4.1–6.0)	2.3 (2.1–2.6)	1.2 (0.5–1.9)	2.2 (1.8–2.5)	0.9 (−0.3 to 2.1)	1.8 (1.0–2.5)
SUICIDES, N (%)	4 (0.2%)	14 (0.1%)	9 (0.2%)	30 (0.2%)	4 (0.2%)	13 (0.1%)	1 (0.2%)	5 (0.2%)
SUICIDE, INCIDENCE RATES ‡ (95%CI)	0.7 (0.0–1.4)	0.2 (0.1–0.3)	0.5 (0.2–0.8)	0.3 (0.2–0.4)	0.4 (0.0–0.8)	0.2 (0.1–0.3)	0.4 (−0.4 to 1.3)	0.4 (0.0–0.7)
OTHER DEATH, N (%)	107 (4.7%)	894 (8.3%)	337 (9.1%)	1 252 (7.2%)	92 (4.9%)	558 (6.2%)	33 (6.5%)	116 (4.7%)
OTHER DEATH, INCIDENCE RATE ‡ (95%CI)	18.6 (15.1–22.1)	12.3 (11.5–13.1)	17.2 (15.3–19.0)	10.9 (10.3–11.5)	9.4 (7.5–11.3)	9.3 (8.5–10.1)	14.7 (9.7–19.7)	8.8 (7.2–10.5)

* NET neuroendocrine tumor †GIST, Gastrointestinal stromal tumour ‡ Incidence per 1000 person-years

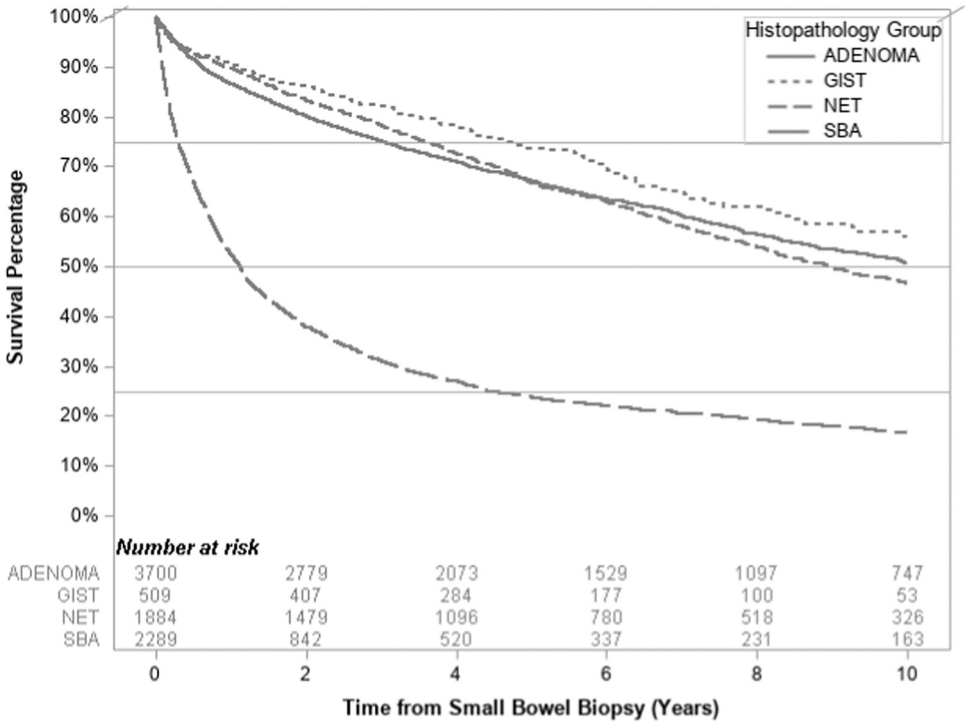


Fig. 1. Kaplan-Meier Survival Curve. SBA, Small bowel adenocarcinoma; NET Neuroendocrine tumor; GIST, Gastrointestinal Stromal tumor.

Table 3
Unadjusted and adjusted Hazard ratios for Any and cause-specific Death among individuals with small intestinal neoplasia in sweden 2000–2017.

	Adenocarcinoma, HR (95%CI)	Adenoma, HR (95%CI)	NET*, HR (95%CI)	GIST†, HR (95%CI)
ANY DEATH	9.87 (9.07–10.73)	2.31 (2.17–2.47)	2.82 (2.58–3.09)	2.43 (1.99–2.96)
ANY DEATH, ADJ EDUCATION	7.60 (6.95–8.31)	2.21 (2.07–2.36)	2.74 (2.50–3.01)	2.33 (1.90–2.87)
CAUSE-SPECIFIC				
Cardiovascular	1.11 (0.87–1.41)	1.55 (1.38–1.75)	1.08 (0.88–1.33)	0.75 (0.43–1.32)
CARDIOVASCULAR ‡	1.02 (0.80–1.31)	1.56 (1.38–1.77)	1.05 (0.85–1.30)	0.85 (0.47–1.52)
CANCER	37.06 (31.85–43.11)	4.22 (3.77–4.72)	7.58 (6.59–8.71)	5.98 (4.38–8.16)
CANCER ‡	27.60 (23.58–32.31)	3.71 (3.29–4.17)	7.19 (6.23–8.30)	5.35 (3.86–7.39)
RESPIRATORY DISEASE	1.10 (0.62–1.96)	2.34 (1.80–3.04)	0.48 (0.24–0.95)	0.64 (0.14–2.98)
RESPIRATORY DISEASE ‡	0.96 (0.53–1.73)	2.27 (1.73–2.97)	0.52 (0.26–1.06)	0.73 (0.15–3.54)
SUICIDE	1.88 (0.57–6.17)	1.77 (0.80–3.90)	2.71 (0.74–9.95)	1.37 (0.14–13.32)
SUICIDE ‡	1.52 (0.45–5.15)	1.69 (0.75–3.81)	3.61 (0.78–16.64)	1.37 (0.14–13.46)
OTHER CAUSE	1.76 (1.39–2.23)	1.86 (1.62–2.13)	1.18 (0.93–1.51)	1.83 (1.20–2.79)
OTHER CAUSE ‡	1.44 (1.11–1.86)	1.80 (1.56–2.07)	1.16 (0.90–1.49)	1.72 (1.10–2.69)

* NET Neuroendocrine tumor †GIST, Gastrointestinal stromal tumour. ‡Adjusted for education (for explanation, see main text) HR, Hazard ratio.

5).

3.5. Cancer mortality in adenoma patients

Death due to SBC occurred in 65 (1.8%) adenoma patients and five (0.0%) matched comparators with corresponding incidence rates of 3.3 (2.5–4.1) and 0.0 (0.0–0.1) per 1000 person-years respectively. Death from other gastrointestinal cancer was identified in 144 (3.9%) adenoma patients (incidence rate 7.3 (6.1–8.5)) and 148 (0.9%) comparators (incidence rate 1.3 (1.1–1.5)). Prostate cancer death was diagnosed in 40 (1.1%) vs. 149 (0.9%), breast cancer death in 15 (0.4%) vs. 50 (0.3%), lung cancer death in 59 (1.6%) vs. 140 (0.8%) and all other cancers death in 315 (8.5%) adenoma patients vs. 487 (2.8%) in matched comparators. Incidence rates for other cancer deaths were 16.1 (14.3–17.8) in adenoma patients and 4.2 (3.9–4.6) in matched comparators. The corresponding aHRs for the cancer death subgroups were all significant and ranging from 1.59 for prostate, 1.90 for breast, 2.39 for lung, 3.62 for other, 5.34 for other gastrointestinal and 103 for SBC. Approximately 85% of adenomas were detected in the duodenum.

4. Discussion

We performed a nationwide study of more than 4600 individuals diagnosed with SBC, among them > 2000 with SBA. Individuals with SBA were at increased risk of death, and especially death from cancer.

The highest mortality rates in small bowel neoplasia subtypes were seen in SBA (295/1000 person-years). The poor prognosis of this cancer is further underlined by the short median follow-up, to a large extent due to early death. Our findings of a 5-year-survival of about 25% (Fig. 1) are consistent with US SEER data (non-specific SBA 5-year survival: 21.1%) [8], Danish data from 1994 to 2010 (22%) [9], the Landerholm study (21–28%) [10] and data from Qubaiah et al. (non-specific SBA: 28.1%) [8].

Compared to the general population, the highest HRs for death in our study were seen in young people (e.g. SBA diagnosed at 40–59 years (HR=35.72), 60–69 (HR=11.71); 70–79 (HR=6.70) and ≥ 80 years (HR=3.87). However, this contrasts with *absolute* rates, where younger patients had the lowest absolute mortality: 40–59 years (mortality Incidence rate/1000 person-years=169), 60–69 (IR=248); 70–79 (333)

Table 4
Stratified number of events, incidence rate (IR), hazard ratios (HRs) for death in adenocarcinoma and adenoma patients diagnosed in 2000–2017 and their matched comparators.

	Adenocarcinoma								Adenoma							
	Study population, n (%)		Deaths, n (%)		Incidence rates per 1000 py (95%CI)		Hazard ratios (95%CI)		Study population, n (%)		Deaths, n (%)		Incidence rates per 1000 py (95%CI)		Hazard ratios (95%CI)	
	Cancer patient	Comparator	Cancer patient	omparator	Cancer patient	Comparator	Crude	Adj. for education	Cancer patient	Comparator	Cancer patient	omparator	Cancer patient	Comparator	Crude	Adj. for education
all	2 289 (100.0%)	10 819 (100.0%)	1 836 (80.2%)	3 440 (31.8%)	294.9 (281.4–308.4)	43.0 (41.6–44.5)	9.87 (9.07–10.73)	7.60 (6.95–8.31)	3 700 (100.0%)	17 366 (100.0%)	1 615 (43.6%)	4 739 (27.3%)	74.2 (70.6–77.8)	37.1 (36.0–38.1)	2.31 (2.17–2.47)	2.21 (2.07–2.36)
Follow-up (years)																
0–1	2 289 (100.0%)	10 819 (100.0%)	1 089 (47.6%)	411 (3.8%)	684.0 (643.4–724.6)	38.7 (35.0–42.5)	22.00 (19.06–25.39)	14.43 (12.02–17.32)	3 700 (100.0%)	17 366 (100.0%)	497 (13.4%)	514 (3.0%)	146.0 (133.2–158.8)	30.1 (27.5–32.7)	4.92 (4.33–5.60)	4.14 (3.45–4.97)
1–5´	1 197 (52.3%)	10 381 (96.0%)	617 (51.5%)	1 346 (13.0%)	222.5 (205.0–240.1)	38.7 (36.6–40.8)	7.31 (6.41–8.34)	7.44 (6.51–8.49)	3 180 (85.9%)	16 728 (96.3%)	637 (20.0%)	1 893 (11.3%)	65.3 (60.3–70.4)	34.3 (32.7–35.8)	1.99 (1.81–2.20)	1.99 (1.80–2.20)
5–10	412 (18.0%)	6 804 (62.9%)	94 (22.8%)	1 119 (16.4%)	70.5 (56.2–84.7)	46.2 (43.5–48.9)	1.87 (1.43–2.45)	1.88 (1.44–2.46)	1 797 (48.6%)	10 800 (62.2%)	342 (19.0%)	1 524 (14.1%)	56.1 (50.2–62.1)	39.6 (37.6–41.6)	1.69 (1.47–1.94)	1.69 (1.47–1.95)
> 10	163 (7.1%)	3 075 (28.4%)	36 (22.1%)	564 (18.3%)	68.4 (46.0–90.7)	54.3 (49.8–58.8)	1.61 (1.03–2.51)	1.57 (1.00–2.46)	747 (20.2%)	4 953 (28.5%)	139 (18.6%)	808 (16.3%)	55.3 (46.1–64.4)	47.5 (44.3–50.8)	1.40 (1.12–1.74)	1.37 (1.10–1.70)
> 1	1 197 (52.3%)	10 381 (96.0%)	747 (62.4%)	3 029 (29.2%)	161.2 (149.7–172.8)	43.7 (42.1–45.2)	5.14 (4.59–5.74)	5.19 (4.64–5.80)	3 180 (85.9%)	16 728 (96.3%)	1 118 (35.2%)	4 225 (25.3%)	60.9 (57.3–64.5)	38.2 (37.0–39.3)	1.82 (1.68–1.96)	1.81 (1.68–1.95)
Sex																
Women	1 102 (48.1%)	5 238 (48.4%)	879 (79.8%)	1 615 (30.8%)	274.7 (256.6–292.9)	40.9 (38.9–42.9)	10.36 (9.16–11.71)	8.05 (7.08–9.15)	1 767 (47.8%)	8 349 (48.1%)	710 (40.2%)	2 148 (25.7%)	64.2 (59.4–68.9)	34.0 (32.5–35.4)	2.15 (1.96–2.37)	2.11 (1.92–2.33)
Men	1 187 (51.9%)	5 581 (51.6%)	957 (80.6%)	1 825 (32.7%)	316.3 (296.2–336.3)	45.1 (43.0–47.2)	9.45 (8.42–10.60)	7.31 (6.45–8.27)	1 933 (52.2%)	9 017 (51.9%)	905 (46.8%)	2 591 (28.7%)	84.6 (79.1–90.1)	40.1 (38.6–41.7)	2.46 (2.25–2.68)	2.28 (2.08–2.50)
Age group (years)																
0–39	39 (1.7%)	188 (1.7%)	25 (64.1%)	(0.0%)	136.3 (82.8–189.7)	0.0 (0.0–0.0)	7.312E12 (0.00-.)	7.173E12 (0.00-.)	217 (5.9%)	1 083 (6.2%)	11 (5.1%)	8 (0.7%)	6.6 (2.7–10.5)	0.9 (0.3–1.5)	6.87 (2.77–17.09)	5.89 (2.04–17.05)
40–59	392 (17.1%)	1 951 (18.0%)	258 (65.8%)	104 (5.3%)	169.3 (148.6–189.9)	5.8 (4.6–6.9)	42.93 (29.24–63.03)	35.18 (23.77–52.05)	750 (20.3%)	3 706 (21.3%)	139 (18.5%)	216 (5.8%)	23.1 (19.3–27.0)	6.4 (5.6–7.3)	3.68 (2.94–4.59)	3.41 (2.70–4.31)
60–69	607 (26.5%)	3 001 (27.7%)	455 (75.0%)	491 (16.4%)	248.2 (225.4–271.0)	20.2 (18.4–22.0)	14.69 (12.16–17.74)	11.71 (9.62–14.27)	936 (25.3%)	4 576 (26.4%)	332 (35.5%)	694 (15.2%)	56.0 (50.0–62.0)	19.2 (17.7–20.6)	3.22 (2.79–3.72)	3.05 (2.62–3.54)
70–79	738 (32.2%)	3 444 (31.8%)	615 (83.3%)	1 290 (37.5%)	332.9 (306.6–359.2)	52.7 (49.8–55.5)	8.94 (7.75–10.31)	6.70 (5.76–7.79)	1 077 (29.1%)	4 980 (28.7%)	587 (54.5%)	1 759 (35.3%)	103.9 (95.5–112.3)	51.4 (49.0–53.8)	2.26 (2.03–2.51)	2.18 (1.95–2.43)
> =80	513 (22.4%)	2 235 (20.7%)	483 (94.2%)	1 555 (69.6%)	576.9 (525.5–628.4)	140.6 (133.6–147.6)	5.29 (4.57–6.11)	3.87 (3.31–4.53)	720 (19.5%)	3 021 (17.4%)	546 (75.8%)	2 062 (68.3%)	218.2 (199.9–236.5)	137.6 (131.7–143.5)	1.70 (1.52–1.90)	1.63 (1.45–1.83)

(*continued on next page*)

Table 4 (*continued*)

	Adenocarcinoma								Adenoma							
	Study population, n (%)		Deaths, n (%)		Incidence rates per 1000 py (95%CI)		Hazard ratios (95%CI)		Study population, n (%)		Deaths, n (%)		Incidence rates per 1000 py (95%CI)		Hazard ratios (95%CI)	
Earlier cancer*																
No	672 (29.4%)	3 175 (29.3%)	575 (85.6%)	1 327 (41.8%)	260.7 (239.4–282.0)	45.7 (43.2–48.1)	7.82 (6.39–9.55)	6.32 (5.13–7.78)	1 025 (27.7%)	4 837 (27.9%)	546 (53.3%)	1 817 (37.6%)	71.1 (65.1–77.1)	40.4 (38.5–42.3)	2.17 (1.88–2.50)	2.04 (1.76–2.37)
Yes	1 617 (70.6%)	7 644 (70.7%)	1 261 (78.0%)	2 113 (27.6%)	313.7 (296.4–331.0)	41.5 (39.7–43.3)	11.36 (10.07–12.81)	8.55 (7.52–9.72)	2 675 (72.3%)	12 529 (72.1%)	1 069 (40.0%)	2 922 (23.3%)	75.9 (71.3–80.4)	35.3 (34.0–36.6)	2.48 (2.27–2.71)	2.32 (2.12–2.55)
Calendar year																
2000–2004	612 (26.7%)	2 943 (27.2%)	545 (89.1%)	1 558 (52.9%)	248.4 (227.6–269.3)	48.2 (45.8–50.6)	6.76 (5.89–7.77)	5.49 (4.75–6.34)	935 (25.3%)	4 444 (25.6%)	607 (64.9%)	2 195 (49.4%)	74.7 (68.8–80.6)	43.4 (41.5–45.2)	2.07 (1.86–2.29)	2.03 (1.82–2.25)
2005–2008	540 (23.6%)	2 550 (23.6%)	461 (85.4%)	956 (37.5%)	271.6 (246.8–296.4)	42.2 (39.6–44.9)	8.77 (7.46–10.31)	6.85 (5.78–8.12)	845 (22.8%)	3 976 (22.9%)	451 (53.4%)	1 326 (33.4%)	74.2 (67.3–81.0)	36.6 (34.7–38.6)	2.35 (2.08–2.65)	2.24 (1.98–2.54)
2008–2012	601 (26.3%)	2 812 (26.0%)	465 (77.4%)	663 (23.6%)	309.6 (281.5–337.8)	38.3 (35.3–41.2)	14.11 (11.69–17.04)	11.04 (9.02–13.53)	970 (26.2%)	4 487 (25.8%)	376 (38.8%)	910 (20.3%)	74.7 (67.1–82.2)	32.6 (30.5–34.7)	2.41 (2.11–2.76)	2.27 (1.97–2.61)
2010–2016	536 (23.4%)	2 514 (23.2%)	365 (68.1%)	263 (10.5%)	438.6 (393.6–483.6)	34.3 (30.2–38.4)	16.90 (13.49–21.18)	12.97 (10.04–16.75)	950 (25.7%)	4 459 (25.7%)	181 (19.1%)	308 (6.9%)	71.7 (61.2–82.1)	23.6 (20.9–26.2)	3.12 (2.56–3.79)	2.81 (2.27–3.48)
Education (years)																
≤ 9	609 (26.6%)	4 162 (38.5%)	479 (78.7%)	1 798 (43.2%)	227.4 (207.0–247.8)	58.0 (55.4–60.7)	5.65 (4.70–6.80)	5.65 (4.70–6.80)	1 290 (34.9%)	5 897 (34.0%)	663 (51.4%)	2 345 (39.8%)	83.3 (76.9–89.6)	53.9 (51.7–56.1)	1.82 (1.61–2.06)	1.82 (1.61–2.06)
10–12	628 (27.4%)	3 953 (36.5%)	435 (69.3%)	956 (24.2%)	177.7 (161.0–194.4)	31.5 (29.5–33.5)	10.20 (7.85–13.24)	10.20 (7.85–13.24)	1 323 (35.8%)	6 604 (38.0%)	435 (32.9%)	1 444 (21.9%)	50.4 (45.6–55.1)	29.0 (27.5–30.5)	1.92 (1.63–2.26)	1.92 (1.63–2.26)
≥ 13	324 (14.2%)	2 242 (20.7%)	203 (62.7%)	367 (16.4%)	147.1 (126.8–167.3)	21.8 (19.5–24.0)	18.69 (10.30–33.90)	18.69 (10.30–33.90)	750 (20.3%)	4 122 (23.7%)	195 (26.0%)	550 (13.3%)	40.0 (34.4–45.6)	17.8 (16.3–19.3)	3.70 (2.64–5.19)	3.70 (2.64–5.19)
Education missing	728 (31.8%)	462 (4.3%)	719 (98.8%)	319 (69.0%)	2471.6 (2290.9–2652.	180.1 (160.4–199.9)	4.86 (3.38–6.99)	4.86 (3.38–6.99)	337 (9.1%)	743 (4.3%)	322 (95.5%)	400 (53.8%)	1113.4 (991.8–1235.0	110.7 (99.8–121.5)	2.35 (1.49–3.71)	2.35 (1.49–3.71)

* Cancer outside the small intestine was present at baseline (before small intestinal cancer diagnosis and corresponding date in matched controls)

Table 5
Stratified number of events, incidence rate (IR), hazard ratios (HRs) for deaths in patients with small bowel NET* and GIST‡ patients diagnosed in 2000–2017 and their matched comparators.

	NET*								GIST†							
	Study population, n (%)		Deaths, n (%)		Incidence rates per 1000 py (95%CI)		Hazard ratios (95%CI)		Study population, n (%)		Deaths, n (%)		Incidence rates per 1000 py (95%CI)		Hazard ratios (95%CI)	
	Cancer patient	Comparator	Cancer patient	Comparator	Cancer patient	Comparator	Crude	Adj. for education	Cancer patient	Comparator	Cancer patient	omparator	Cancer patient	Comparator	Crude	Adj. for education
all	1 884 (100.0%)	9 019 (100.0%)	866 (46.0%)	2 259 (25.0%)	79.8 (74.5–85.1)	33.8 (32.4–35.2)	2.82 (2.58–3.09)	2.74 (2.50–3.01)	509 (100.0%)	2 461 (100.0%)	162 (31.8%)	434 (17.6%)	62.2 (52.6–71.7)	28.6 (25.9–31.3)	2.43 (1.99–2.96)	2.33 (1.90–2.87)
Follow-up (years)																
0–1	1 884 (100.0%)	9 019 (100.0%)	193 (10.2%)	253 (2.8%)	109.8 (94.3–125.3)	28.5 (25.0–32.0)	3.86 (3.18–4.68)	2.82 (2.15–3.70)	509 (100.0%)	2 461 (100.0%)	47 (9.2%)	65 (2.6%)	98.6 (70.4–126.8)	26.8 (20.3 –33.3)	3.81 (2.58–5.63)	2.97 (1.75–5.03)
1–5´	1 683 (89.3%)	8 730 (96.8%)	379 (22.5%)	828 (9.5%)	73.4 (66.0–80.8)	28.4 (26.5–30.3)	2.73 (2.40–3.12)	2.80 (2.46–3.20)	458 (90.0%)	2 380 (96.7%)	72 (15.7%)	198 (8.3%)	52.2 (40.1–64.2)	26.2 (22.6–29.9)	2.16 (1.62–2.89)	2.23 (1.66–2.99)
5–10	909 (48.2%)	5 716 (63.4%)	212 (23.3%)	793 (13.9%)	71.0 (61.5–80.6)	38.9 (36.2–41.6)	2.25 (1.88–2.70)	2.26 (1.88–2.70)	232 (45.6%)	1 352 (54.9%)	36 (15.5%)	121 (8.9%)	57.9 (39.0–76.8)	30.3 (24.9–35.6)	2.02 (1.33–3.06)	1.97 (1.29–3.01)
> 10	326 (17.3%)	2 520 (27.9%)	82 (25.2%)	385 (15.3%)	86.9 (68.1–105.7)	45.7 (41.2–50.3)	3.08 (2.23–4.24)	3.08 (2.23–4.26)	53 (10.4%)	404 (16.4%)	7 (13.2%)	50 (12.4%)	55.1 (14.3–95.9)	41.9 (30.3–53.5)	1.76 (0.69–4.48)	1.83 (0.70–4.81)
> 1	1 683 (89.3%)	8 730 (96.8%)	673 (40.0%)	2 006 (23.0%)	74.0 (68.4–79.6)	34.6 (33.1–36.1)	2.60 (2.35–2.88)	2.63 (2.38–2.91)	458 (90.0%)	2 380 (96.7%)	115 (25.1%)	369 (15.5%)	54.0 (44.1–63.9)	29.0 (26.0–31.9)	2.09 (1.66–2.63)	2.14 (1.69–2.70)
Sex																
Women	854 (45.3%)	4 124 (45.7%)	392 (45.9%)	988 (24.0%)	78.9 (71.1–86.8)	32.2 (30.2–34.2)	3.20 (2.79–3.66)	3.11 (2.71–3.56)	232 (45.6%)	1 126 (45.8%)	57 (24.6%)	140 (12.4%)	48.6 (36.0–61.2)	20.6 (17.2–24.0)	3.10 (2.20–4.37)	3.12 (2.16–4.51)
Men	1 030 (54.7%)	4 895 (54.3%)	474 (46.0%)	1 271 (26.0%)	80.6 (73.3–87.8)	35.1 (33.2–37.1)	2.57 (2.28–2.89)	2.49 (2.20–2.82)	277 (54.4%)	1 335 (54.2%)	105 (37.9%)	294 (22.0%)	73.3 (59.3–87.3)	35.2 (31.1–39.2)	2.16 (1.69–2.75)	2.05 (1.59–2.64)
Age group (years)																
0–39	50 (2.7%)	257 (2.8%)	6 (12.0%)	3 (1.2%)	14.5 (2.9–26.0)	1.2 (0.0–2.6)	30.00 (3.61–249.17)	74.12 (4.65–1182.74)	26 (5.1%)	130 (5.3%)	4 (15.4%)	(0.0%)	19.0 (0.4–37.6)	0.0 (0.0–0.0)	1.09E13 (0.00-.)	1.09E13 (0.00-.)
40–59	429 (22.8%)	2 127 (23.6%)	126 (29.4%)	129 (6.1%)	39.2 (32.4–46.1)	6.7 (5.5–7.9)	7.43 (5.62–9.83)	7.41 (5.53–9.94)	127 (25.0%)	636 (25.8%)	28 (22.0%)	32 (5.0%)	40.0 (25.2–54.8)	7.3 (4.8–9.9)	6.50 (3.65–11.58)	6.44 (3.55–11.69)
60–69	559 (29.7%)	2 707 (30.0%)	209 (37.4%)	375 (13.9%)	64.1 (55.4–72.8)	18.6 (16.7–20.5)	3.65 (3.03–4.39)	3.53 (2.92–4.27)	155 (30.5%)	777 (31.6%)	40 (25.8%)	80 (10.3%)	46.7 (32.2–61.1)	15.8 (12.4–19.3)	3.48 (2.31–5.26)	3.43 (2.23–5.28)
70–79	588 (31.2%)	2 760 (30.6%)	333 (56.6%)	960 (34.8%)	113.0 (100.9–125.1)	50.8 (47.6–54.0)	2.66 (2.31–3.07)	2.63 (2.27–3.05)	143 (28.1%)	668 (27.1%)	53 (37.1%)	186 (27.8%)	82.2 (60.1–104.4)	51.5 (44.1–58.9)	1.62 (1.16–2.24)	1.50 (1.06–2.12)
> =80	258 (13.7%)	1 168 (13.0%)	192 (74.4%)	792 (67.8%)	188.8 (162.1–215.5)	131.8 (122.6–141.0)	1.59 (1.32–1.91)	1.50 (1.24–1.81)	58 (11.4%)	250 (10.2%)	37 (63.8%)	136 (54.4%)	191.1 (129.6–252.7)	127.5 (106.1–149.0)	1.68 (1.10–2.55)	1.62 (1.03–2.54)
Earlier cancer ‡																
No	566 (30.0%)	2 493 (27.6%)	312 (55.1%)	847 (34.0%)	76.2 (67.8–84.7)	35.9 (33.5–38.4)	2.82 (2.32–3.42)	2.77 (2.27–3.39)	110 (21.6%)	485 (19.7%)	47 (42.7%)	141 (29.1%)	65.0 (46.4–83.6)	34.9 (29.2–40.7)	3.35 (1.97–5.70)	3.46 (1.98–6.05)
Yes	1 318 (70.0%)	6 526 (72.4%)	554 (42.0%)	1 412 (21.6%)	82.0 (75.2–88.8)	32.6 (30.9–34.3)	2.99 (2.64–3.39)	2.86 (2.52–3.26)	399 (78.4%)	1 976 (80.3%)	115 (28.8%)	293 (14.8%)	61.1 (49.9–72.2)	26.3 (23.3–29.3)	2.56 (1.99–3.31)	2.45 (1.87–3.20)
Calendar year																

(*continued on next page*)

Table 5 (*continued*)

	NET*								GIST†							
	Study population, n (%)		Deaths, n (%)		Incidence rates per 1000 py (95%CI)		Hazard ratios (95%CI)		Study population, n (%)		Deaths, n (%)		Incidence rates per 1000 py (95%CI)		Hazard ratios (95%CI)	
	Cancer patient	Comparator	Cancer patient	Comparator	Cancer patient	Comparator	Crude	Adj. for education	Cancer patient	Comparator	Cancer patient	omparator	Cancer patient	Comparator	Crude	Adj. for education
2000–2004	452 (24.0%)	2 159 (23.9%)	338 (74.8%)	1 012 (46.9%)	93.5 (83.6–103.5)	40.3 (37.8–42.8)	3.01 (2.60–3.49)	2.94 (2.53–3.42)	52 (10.2%)	258 (10.5%)	33 (63.5%)	108 (41.9%)	77.2 (50.8–103.5)	35.0 (28.4–41.6)	2.90 (1.83–4.59)	2.86 (1.78–4.60)
2005–2008	454 (24.1%)	2 169 (24.0%)	251 (55.3%)	670 (30.9%)	77.0 (67.5–86.5)	33.8 (31.3–36.4)	2.63 (2.23–3.10)	2.62 (2.22–3.10)	88 (17.3%)	421 (17.1%)	45 (51.1%)	120 (28.5%)	70.5 (49.9–91.1)	30.6 (25.1–36.1)	2.40 (1.64–3.50)	2.22 (1.49–3.33)
2008–2012	485 (25.7%)	2 334 (25.9%)	187 (38.6%)	441 (18.9%)	71.6 (61.3–81.9)	29.9 (27.1–32.7)	2.57 (2.13–3.09)	2.38 (1.96–2.90)	180 (35.4%)	863 (35.1%)	53 (29.4%)	133 (15.4%)	52.4 (38.3–66.5)	24.6 (20.4–28.8)	2.12 (1.51–2.97)	2.19 (1.54–3.12)
2010–2016	493 (26.2%)	2 357 (26.1%)	90 (18.3%)	136 (5.8%)	65.9 (52.3–79.5)	19.0 (15.8–22.2)	3.45 (2.61–4.54)	3.35 (2.48–4.52)	189 (37.1%)	919 (37.3%)	31 (16.4%)	73 (7.9%)	58.6 (38.0–79.2)	26.5 (20.4–32.6)	2.68 (1.71–4.20)	2.33 (1.44–3.76)
Education (years)																
≤ 9	612 (32.5%)	3 281 (36.4%)	322 (52.6%)	1 183 (36.1%)	89.8 (80.0–99.6)	48.4 (45.6–51.1)	2.11 (1.78–2.50)	2.11 (1.78–2.50)	134 (26.3%)	756 (30.7%)	46 (34.3%)	215 (28.4%)	61.2 (43.5–78.9)	45.5 (39.4–51.6)	1.37 (0.90–2.08)	1.37 (0.90–2.08)
10–12	734 (39.0%)	3 431 (38.0%)	277 (37.7%)	644 (18.8%)	60.2 (53.1–67.3)	24.6 (22.7–26.5)	3.32 (2.64–4.17)	3.32 (2.64–4.17)	197 (38.7%)	980 (39.8%)	56 (28.4%)	118 (12.0%)	54.3 (40.1–68.5)	19.2 (15.7–22.6)	2.81 (1.76–4.48)	2.81 (1.76–4.48)
≥ 13	392 (20.8%)	2 013 (22.3%)	128 (32.7%)	263 (13.1%)	50.9 (42.1–59.7)	17.8 (15.6–20.0)	3.01 (2.02–4.50)	3.01 (2.02–4.50)	137 (26.9%)	634 (25.8%)	26 (19.0%)	53 (8.4%)	34.6 (21.3–47.9)	13.6 (9.9–17.3)	3.13 (1.38–7.11)	3.13 (1.38–7.11)
Education missing	146 (7.7%)	294 (3.3%)	139 (95.2%)	169 (57.5%)	926.2 (772.2–1080.2)	117.6 (99.8–135.3)	3.26 (1.56–6.84)	3.26 (1.56–6.84)	41 (8.1%)	91 (3.7%)	34 (82.9%)	48 (52.7%)	466.0 (309.4–622.7)	122.8 (88.1–157.6)	5.04 (1.32–19.19)	5.04 (1.32–19.19)

NET Neuroendocrine tumor †GIST, Gastrointestinal stromal tumour. ‡ Cancer outside the small intestine was present at baseline (before small intestinal cancer diagnosis and corresponding date in matched controls)

and ≥ 80 years (577), confirming earlier US data of better survival before 60 years of age [8]. Our mortality data on NET were similar to that of earlier papers [9].

Our paper contains new information on mortality in GIST. While Bojesen et al. present survival in sarcomas (not only including GIST) their sample size was limited [9] (n = 132, as compared to 509 GIST cases in our study). Mortality rates in GIST were substantially higher than in matched comparators (62.2 vs. 28.6/1000 person-years respectively), translating into an HR adjusted for education of 2.33 (1.90–2.87). An increase in GIST mortality was seen independent of sex and calendar period. Of note, there was a trend towards higher HRs for death among GIST patients with longer education, as compared to those with ≤ 9 years of attained education. While we did not examine the independent role of socioeconomic factors for survival in small bowel neoplasia, Ecker et al. have reported an increased mortality in patients with SBA and low median income [17].

Our study may also be one of the first to explore mortality in adenomas, an SBC precursor. Adjusting for education, adenoma patients were at a 2.12-fold increased risk of death. HRs for death in adenomas were particularly high during the first year of follow-up (HR=4.14) but remained statistically significant even after more than ten years' follow-up (HR=1.37; 95%CI=1.10–1.70). The risk of death was similar in men and women, and present across all age groups although HRs were highest among the youngest patients, with opposite findings for absolute mortality rates. We also found significant HRs for death from all major cancer subtypes after diagnosis of adenomas. The detection of these adenomas may have been due to clinical work-up of anemia or other cancer symptoms.

We also examined cause-specific mortality in SBC. Adjusting for education we could not detect any increased risk of cardiovascular death following SBA, NET or GIST. However, patients with adenoma were at a 56% increased risk of dying form cardiovascular disease. One reason for the association with cardiovascular death may be shared risk factors including smoking [18]. While all small bowel neoplasia subtypes saw an increased risk of cancer-specific death, we also observed a 2-fold increased risk of death by suicide in SBA and NET patients but in none of the two groups did the risk estimates reach statistical significance. Adenoma patients were also at increased risk of dying from respiratory disease, suicide (non-significant) and other diseases. We urge caution when interpreting these findings.

This paper has some strengths and limitations. The nationwide approach means that we are likely to have identified average patients, not only those with most severe disease.

While we are unaware of any validation of SBC subtypes in Sweden, mortality rates in the two previously presented subgroups of patients (SBA, NET) were similar for the years 2000–2017, the two most recent calendar periods of the study by Landerholm [10] based on the Swedish Cancer Register. Consistent with earlier studies a majority of participants in our study were men [2, 8, 19]. The validity of our cases is further strengthened by the similar distribution of subtypes [2,19], and age at diagnosis as in earlier literature. In a recent study by Bouvier et al. [19], lymphoma and non-specified cancers represented some 18% of SBC. The mean age at cancer diagnosis was almost identical in our study and that of Bouvier (e.g. adenocarcinoma: 70.3 years vs. 69.7 in their study [19] and 68 years in a Danish study [9]). Mean age at first diagnosis of GIST was 65.1 years in our study compared with 64.3 years among sarcoma cases in France [19].

With the exception of the Landerholm study where the majority of follow-up took place before year 2000, [10] our study is one of the largest studies with modern data. We also adjusted for education as proxy for socioeconomic status. Socioeconomic status has been linked to mortality risk [11], and adjusting for this variable made a substantial difference especially with regards to the risk of death among SBA patients (HRs dropped from 9.87 to 7.60), while we saw almost no risk reduction for NET, GIST or for the cancer precursor adenoma (Table 3). Still we acknowledge that any firm conclusions on socioeconomic status and SBC mortality will need a more detailed examination. When Shack et al. reviewed SBC, they found no association between socioeconomic status and cancer survival in data available from Wales [7]. Finally, linkage through the personal identity number with the TPR [20] and the Cause of Death Register [14] virtually guarantees complete follow-up [13]. Both data on incident small bowel neoplasia and mortality were prospectively recorded without risk of recall bias.

Among the limitations is the risk that some moribund individuals underwent extensive investigation and an incidental small bowel neoplasia was detected. This may have contributed to the high HRs during the first year after SBC. We lacked data on smoking, body mass index, and diet (consumption of alcohol, sugar and red meat) [5], but also had limited information on comorbidity. When Aparicio et al. reviewed 347 patients with SBA, 19.7% had at least one predisposing disease [21]. Neither did we have any information on treatment modality, and it was beyond the scoop of this study to evaluate the role of surgery and chemotherapy in SBA or the management of small bowel neoplasia. We did not consider race or ethnicity in our study since such variables are not registered in Swedish national healthcare registers in order to protect the integrity of citizens. Of note, for instance NET may be overrepresented in certain ethnic groups [22]. However, it should also be noted that Sweden's healthcare system is universal, publicly funded and almost free of charge [23]. This allows residents seek healthcare independently of their ethnicity, and should also minimize the influence of socioeconomic status on survival. Finally, we lacked important tumour data including stage, localization across the 3 segments of small bowel, and tumor grade.

Small bowel NET survival has been linked to higher mitotic count [24]. Swedish pathology data did not allow the distinction between Grade I, II, and III tumours and we cannot rule out that early NET as well as late NET have death rates other than that in our study (where we found an average mortality rate of 80/1000 person-years as compared with 33/1000 in age-matched comparators). It is difficult to explain the increased risk of death from cardiovascular disease in adenoma, and we cannot rule out that individuals with increased cardiovascular comorbidity (such as chest pain) were at increased risk of undergoing gastrointestinal investigation (upper endoscopy) with a subsequent detection of an adenoma. We did not have data on GIST size or mitotic count, which have been linked to cancer mortality [25].

Finally, our biopsy data did not allow us to rule out syndromic types of SBC such as FAP of the lynch syndrome. Although SBC has been linked to both inflammatory bowel disease (IBD) [26] and celiac disease [27] (per se associated with increased mortality [28,29]), this is highly unlikely to impact on our mortality rates since IBD and celiac disease occur in at the most 2–3% of the Swedish population.

In conclusion, this nationwide study confirms earlier findings of increased death rates in patients with SBA and NET but now in a modern population. However, we also demonstrate a more than 2-fold increased risk of death in both GIST and the cancer precursor adenoma. While absolute death rates were highest in older people, the relative risk of death was highest in SBC and adenoma diagnosed in early age.

Disclosure statement

JFL coordinates a study on behalf of the Swedish IBD quality register (SWIBREG). This study has received funding from the Janssen corporation. JFL has also received financial support from MSD developing a paper reviewing national healthcare registers in China.

Ethics

The study was approved by the Regional Ethics Review Board, Stockholm, Sweden (2014/1287-31/4 and 2018/972-32).

Funding

The Swedish Cancer Foundation (JFL).

CRediT authorship contribution statement

LE and JFL wrote the first draft of the paper, and JMO helped revise it. All authors conceived and designed the study. JFL funded the study and collected the data. LE carried out the statistics. LE takes responsibility for the integrity of the data and the accuracy of the data analyses. LE is the guarantor of the data.

Declaration of Competing Interest

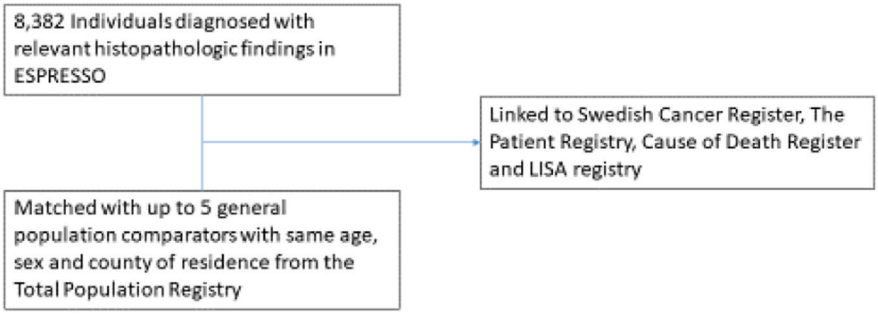
The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability

Other researchers can apply for our data through the Swedish National Board of Health and Welfare.

Appendix

Characteristics	SnoMed code	Topography
Adenoma	M82632, M82112, M82611, M81400, M81400, M72040, M82612, M82630, M82100, M82102	T64 and T65
Adenocarcinoma	M81403	T64 and T65
Gastrointestinal Stromal Tumor	M89363, M89361, M88001, M88003	T64 and T65
Neuroendocrine tumor	M82403, M82463, M82493	T64 and T65



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