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Risk of second primary malignancies and causes of death in patients with adenocarcinoma and carcinoid of the small intestine

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ABSTRACT

We studied risk of second malignancies and causes of death in 1829 cases of adenocarcinoma and 3055 cases of carcinoid tumours in the small bowel reported to the Swedish Cancer Registry from 1960 through to 2000. Data on causes of death were analysed as from 1966 whereas data on second tumours was available during the whole registry-period. Follow-up was available until 2001.

Standard mortality ratio (SMR) and standard incidence ratio (SIR) were calculated.

Female patients with adenocarcinoma had increased risk of acquiring cancer in the female genital organs (SIR 3.2; 95% confidence intervals (CI) 1.9–5.0) and breasts (SIR 2.7; 95% CI 1.1–5.4). Both sexes combined had increased risk of second tumours in the gastrointestinal tract (SIR 1.5; 95% CI 1.1–2.1) and skin (SIR 4.6; 95% CI 1.2–12). Men with carcinoid tumour had increased risk of prostate cancer (SIR 2.8; 95% CI 1.6–4.6). Increased risk was seen for both sexes with carcinoid for malignant melanoma (SIR 6.3; 95% CI 2.7–12), malignant skin tumours (SIR 3.6; 95% CI 1.7–6.7) and malignancies of endocrine organs (SIR 2.3 95% CI 1.3–3.8). Patients with adenocarcinoma had increased risk of dying from malignant diseases other than the primary cancer (SMR 9.5; 95% CI 8.6–10) and gastrointestinal disease (SMR 2.6 95% CI 1.6–4.2). The cohort with carcinoid had higher than expected risk of dying from malignant disease (SMR 4.3; 95% CI 4.0–4.6), gastrointestinal disease (SMR 2.8; 95% CI 2.1–3.6) and cardiovascular disease (SMR 1.1; 95% CI 1.0–1.3).

The increased risk of second malignant tumours is an indication of common aetiology, or possibly, a general vulnerability to malignant disease for these patients. A detailed analysis of causes of death in a population-based cohort of small intestinal malignancies has not been presented before in the literature.

1. Introduction

Second malignant neoplasms associated with tumours of the small intestine have been recognised in autopsy studies[1] and numerous relatively small case series.[2–7] Few population-based studies have investigated the incidence of second primary cancers in patients with small intestinal malignancies. Analyses of cases from the Danish Cancer Registry revealed

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statistically significant excess risks of cancer of the liver and biliary tract and statistically non-significant excess risks of colorectal and pancreatic cancers.[8] A similar analysis of the Connecticut tumour registry cases found statistically significantly increased risks of acquiring cancers of the digestive system and the prostate gland.[9] These studies were not stratified for histolopathologic subtype of the small bowel neoplasms. In a recent report of data from the SEER database it was noted that 29% of patients with small intestinal carcinoid had associated malignancies.[10] Earlier analyses of data from the same registry have described increased risk of colorectal cancer following small intestinal adenocarcinoma and increased risk of prostate cancer following carcinoid tumour in the small intestine.[11] A recent population-based study including cases from 13 national cancer registries showed increased incidence of cancers of the oropharynx, colon, rectum, ampulla of Vater, pancreas, corpus uteri, ovary, prostate, kidney, thyroid gland, skin and soft tissue sarcomas after primary diagnosis of small intestinal malignancies.[12]

Increased incidence of a second primary tumour could indicate shared etiologic factors between the index cancer and the second malignancy or that agents used in the treatment are oncogenic. Furthermore, the demonstration of reciprocally excessive occurrences supports the plausibility of a common pathogenesis.[13] Excess risk of small intestinal malignancies has been reported following colorectal cancer .[11,14,15] Increased incidence rates of small intestinal carcinoid have been reported following prostate cancer[16] and after thyroid and other endocrine gland tumours.[17]

Knowledge of causes of death of patients with small intestinal carcinoid mainly comes from small series from specialist centres. Heart-valve disease with heart failure is often stated as a common cause of death in these patients whereas other causes of death not directly related to the malignancy are described as uncommon.[18] There are no population-based descriptions of causes of death of patients with small intestinal adenocarcinoma in the literature although prognosis is described as poor and most patients die of their malignancy.[19]

The aim of this study was to estimate the excess risk of second primary malignancies and causes of death following adenocarcinoma or carcinoid tumours in the small intestine using data from the Swedish Cancer Registry.

2. Patients and methods

2.1. The National Causes of Death Registry and Cancer Registry

Data on causes of deaths in Sweden have been systematically collected and classified according to the International classification of Diseases (ICD) in the National Causes of Death Registry since 1951. Obligatory death certificates, including the date and cause of death, are issued by the physician who has examined the dead body (clinical examination, autopsy or forensic necropsy).[20]

The Swedish Cancer Registry was established in 1958. Physicians, pathologists and cytologists must report all cases of diagnosed malignant tumours to the registry, whereby most cases are reported twice. The information from death certificates is supplied from the causes of death registry and merged into the files of the Cancer Registry supplying date, underlying and contributory causes of death.[21]

2.2. Patients

We have studied all cases of primary adenocarcinoma and carcinoid in the small intestine (histological type 096 and 084, ICD-7 152.0–152.9, WHO/HS/CANC/24.1 Histology Code), diagnosed during 1960–2000 and reported to the Swedish Cancer Registry. A total number of 1982 cases of adenocarcinoma and 3741 cases of carcinoid were recruited from the registry. Cases where date of death was the same as date of diagnosis of the primary small intestinal tumour were excluded (Table 1). Tumours of the ampulla of Vater (ICD 155.3) were disregarded. The definitive cohorts included 1829 patients with adenocarcinoma and 3055 patients with carcinoid.

The main second primary tumour-groups of interest were as follows (ICD-7): the gastrointestinal system (140–151,153–158), the female genital tract and breasts (170–176), the respiratory system (160–164), the prostate gland (177), urinary tract (180–181), brain (193), skin (190–191), and endocrine organs (1940–1959). We only included tumours occurring after diagnosis of the small bowel malignancy. The correctness of the diagnoses in individuals reported to suffer from multiple malignancies in the Swedish Cancer Registry has been analysed earlier; in conclusion, the registry data are reliable enough to be used for adequate analyses aiming at studying the epidemiology of multiple malignant tumours in a large unselected population.[22]

Causes of death according to the Swedish Causes of Death Registry were pooled into subgroups. Corresponding ICD-codes in relation to different time-periods are shown in Table 2. In the analysis of causes of death, cases who succumbed 30 days or less after diagnosis of the primary malignancy were excluded leaving 1586 patients with adenocarcinoma and 2531 patients with carcinoid.

2.3. Statistical method

Computation of person-years (pyr) at risk started at the date of diagnosis of small intestinal adenocarcinoma or carcinoid, and ended at the diagnosis of the second primary cancer, the date of death, or the end of the follow-up period. The expected number of second tumours was calculated by multiplication of pyr at risk by the corresponding age-, sex- and period-specific incidence rates. Incidence rates for all cancer sites for the Swedish population were obtained from the Swedish Cancer Registry, as was information on the observed incidence of second tumours in the cohort. The standard inci-

Table 1 – Cases recruited from the Swedish Cancer Registry and exclusions due to lack of diagnosis in vivo

	Adenocarcinoma	Carcinoid
Total number reported	1982	3741
Date of diagnosis same as date of death	153	686
Included	1829	3055

Table 2 – Causes of death grouped according to ICD in relation to time-periods

	ICD7 (1958–68)	ICD8 (1969–86)	ICD9 (1987–96)	ICD10 (1997–)
Infectious diseases	001–138	000–136	000–139	A00–B99
Neoplasms, except 152	140–151, 153–239	140–151, 153–239	140–151, 153–239	C00–C16, C18–D46
Haematological diseases	290–299	280–289	279–289	D50–D89
Endocrine, nutritional and metabolic diseases	250–289	240–279	240–279	E00–E79
Diseases of the nervous system	340–369	320–358	320–359	G00–G99
Cardiovascular diseases	400–468	390–429, 440–458	390–429, 440–459	I00–I52, I70–I99
Diseases of the respiratory system	470–520	460–519	460–519	J00–J99
Gastrointestinal diseases	530–588	520–577	520–579	K00–K93
Urogenital diseases	590–638	580–629	580–629	N00–N99
Cerebrovascular diseases	330–334	430–438	430–438	I60–I69
Pancreatic cancer	157	157	157	C25
Colorectal cancer	153–154	153–154	153–154	C18–C20
Heart valve disease	410–413, 421	395–398, 424	394–397, 424	I05–I08, I34–I39
Other causes	–	–	–	–

dence ratio (SIR) was defined as the ratio of observed numbers of a second malignancy to the expected numbers. Analyses were made by sex, period of diagnosis and time from diagnosis of the small bowel malignancy.

Correspondingly, the standard mortality ratio (SMR) was calculated using data from the Swedish Causes of Death Registry. Detailed analyses of SMR by gender, age, period of diagnosis and follow-up were made only for causes of death with enough data to permit stable calculations.

The 95% confidence intervals (CI) for the SIRs and SMRs were established by assuming that the observed cases have a Poisson distribution using Byar's normal approximation.[23] All the statistical analyses were carried out using the SAS version 8.2.

3. Results

3.1. *Second tumours after adenocarcinoma*

Patients with adenocarcinoma had increased risk of acquiring other gastrointestinal malignancies (Table 3). For both sexes combined, 36 cases were seen compared with 24 expected (SIR 1.5; 95% CI 1.1–2.1, for the whole study period). Statistically significantly increased risks were only seen for men. For all patients with small intestinal adenocarcinoma the most common second gastrointestinal tumours were cancers of the pancreas and lower gastrointestinal tract. SIRs for these tumours were statistically significantly raised although increased incidence of pancreatic cancer was seen only for cases diagnosed from 1960 to 1980 (Table 3). Again, statistically significant increase in SIR was only seen for male gender. For women, tumours of the female genital system and breasts were seen more frequently than anticipated (Table 3). The SIR for cancer in the female genital organs was 3.1 (95% CI 1.9–5) for the whole study period. The gynaecological site most commonly affected was the ovaries. The SIR for ovarian cancer was 3.9 (95% CI 2.0–7.0) for the whole study period and an increased risk of breast cancer was seen in the early study period (SIR 2.7; 95% CI 1.1–5.4) but not in recent years (Table 3). No increase in male breast cancer was seen. For both sexes combined, an increased risk of skin cancer was seen but the excess risk was only confined to the earlier study period and only related to non-melanoma tumours (Table 3). The SIR for prostate cancer and malignancies of the respiratory system and brain did not differ statistically significantly from unity (Table 3).

3.2. *Second tumours after carcinoids*

The incidence of prostate cancer subsequent to carcinoid tumour was higher than expected. Seventeen cases were seen versus six expected during the earlier study period (SIR 2.8; 95% CI, 1.6–4.6, Table 3). During the later study period there was no increase in the incidence of prostate cancer. For men and women combined, the incidence of malignant melanoma and other skin malignancies was statistically significantly increased for patients with carcinoid but only when analysing cases diagnosed from 1960–1980 (SIR 6.3 and 3.6 respectively, Table 3). The risk of acquiring malignancies in other endocrine organs was statistically significantly increased during the whole study period (SIR 2.2; 95% CI 1.1–3.8). Twenty percent of these malignancies were thyroid cancers and 40 percent were adrenal malignancies.

3.3. *Causes of death after adenocarcinoma*

In the cohort with adenocarcinoma, 1754 patients (88% of the cohort with adenocarcinoma) died during the study period and in 899 patients, the cause of death was the primary small bowel malignancy. 396 patients died within 30 days from diagnosis of the primary malignancy and 153 had the same death date as date of diagnosis.

The patients with small bowel adenocarcinoma had increased risk to die from other malignant diseases (Table 4). The overall standard mortality ratio (SMR) was 9.5 (95% CI 8.6–10). Such lethal malignancies were largely dominated by colon and pancreatic cancer (34% and 17% respectively of all deaths from malignant diseases). The SMRs for pancreatic cancer and colorectal cancer were 24 and 26 respectively and the increased incidence was most pronounced during the first year of follow-up (Table 5). The SMR for gastrointestinal diseases was statistically significantly raised (Table 4). It mainly related to duodenal ulcer (29% of deaths from gastrointestinal disease).

Endocrine disorders were overrepresented as cause of death for patients with adenocarcinoma of the small bowel

Table 3 – Standard incidence ratios (SIR) with 95% confidence interval (CI) for the second primary tumours studied (analyses by period of diagnosis of small intestinal tumour)

Second tumour	Period	Adenocarcinoma				Carcinoid			
(ICD-7)		O/E	PYR	SIR	(95% CI)	O/E	PYR	SIR	(95% CI)
Gastrointestinal (1500–1549)	1960–80	13/5.3	1205	2.4	(1.3–4.2)	17/17	4089	1.0	(0.0–1.6)
	1981–00	23/13	2640	1.7	(1.1–2.6)	24/40	7739	0.6	(0.4–0.9)
Colorectal (1530–1549)	1960–80	10/3.3	1205	3.0	(1.4–5.6)	7/10	4097	0.7	(0.3–1.3)
	1981–00	21/9.9	2658	2.1	(1.3–3.2)	23/29	7764	0.8	(0.5–1.2)
Pancreas (1579)	1960–80	4/0.5	1257	7.3	(1.9–19)	2/1.7	4273	1.7	(0.1–4.1)
	1981–00	3/1.2	3014	2.5	(0.5–7.3)	1/3.4	8378	0.3	(0.0–1.7)
Biliary tract (1551–1552)	1960–80	–/0.3	1258	–	–	–/8.0	4270	–	–
	1981–00	2/0.5	3007		(0.4–14)	–/0.5	8386	–	–
Esophagus (1509)	1960–80	–/0	1258	–	–	–/0.1	4273	–	–
	1981–00	–/0.2	3017	–	–	1/0.6	8385	–	–
Respiratory system (1600–1649)	1960–80	3/1.9	1253	1.6	(0.3–4.5)	7/7.2	4271	1.0	(0.4–2.0)
	1981–00	2/6.4	3005	0.3	(0.1–1.1)	8/20	8366	0.4	(0.2–0.8)
Breast (1700–1709)	1960–80	7/2.6	1233	2.7	(1.1–5.4)	10/7.7	4251	1.3	(0.6–2.4)
	1981–00	4/8.8	2963	0.4	(0.1–1.1)	8/20	8250	0.4	(0.2–0.8)
Gynaecologic (1710–1760)	1960–80	9/1.4	1241	6.6	(3.0–12)	6/4.0	1983	1.5	(0.5–3.3)
	1981–00	9/3.2	2898	2.8	(1.3–5.4)	4/7.2	3444	0.6	(0.1–1.4)
Ovary (1750–1759)	1960–80	5/0.7	683	7.2	(2.3–17)	3/2.0	2003	1.5	(0.3–4.3)
	1981–00	6/1.5	1567	4.0	(1.4–8.7)	1/3.6	3747	0.3	(0.0–1.6)
Skin (1910–1919)	1960–80	4/0.9	1256	4.6	(1.2–11)	10/2.7	4266	3.6	(1.7–6.7)
	1981–00	6/5.1	2977	1.2	(0.4–2.5)	17/15	8264	1.1	(0.6–1.7)
Melanoma (1900–1909)	1960–80	1/0.4	1258	2.7	(0.1–15)	8/1.3	4265	6.3	(2.7–12)
	1981–00	3/2.2	2998	1.4	(0.2–4.0)	5/6.3	8316	0.8	(0.2–1.8)
Urinary tract (1800–1819)	1960–80	5/2.5	1133	2.0	(0.6–5.4)	8/7.3	4226	1.1	(0.5–2.2)
	1981–00	5/6.9	2970	0.7	(0.2–1.7)	13/21	8468	0.6	(0.3–1.0)
Prostate (177)	1960–80	3/1.6	2385	1.2	(0.6–2.1)	17/6.0	2233	2.8	(1.6–4.6)
	1981–00	10/6.8	1360	1.5	(0.7–2.7)	21/24	4458	0.9	(0.5–1.4)
Endocrine (1940–1959)	1960–80	–/0.4	1252	–	–	6/1.3	4264	4.8	(1.7–10)
	1981–00	2/1.4	2989	1.4	(0.2–5.1)	9/3.6	8251	2.5	(1.1–4.7)
Thyroid (1940–1949)	1960–80	–/0.1	1259	–	–	1/0.3	4270	3.1	(0.1–17)
	1981–00	1/0.2	3013	4.8	(0.1–27)	2/0.5	8332	3.7	(0.4–13.0)

Table 4 – Standard mortality ratios (SMR) with 95% confidence interval (CI) for the causes of deaths studied for patients with adenocarcinoma and carcinoid in the small intestine

Cause of death	Adenocarcinoma			Carcinoid		
	O/E	SMR	95%CI	O/E	SMR	95%CI
Infectious diseases	2/1.5	1.3	(0.3–5.2)	4/4.6	0.9	(0.3–2.3)
Neoplasms, except 152	403/42	9.5	(8.6–10)	569/133	4.3	(4.0–4.6)
Haematological diseases	2/0.5	3.8	(0.9–15)	2/1.6	1.3	(0.3–5.2)
Endocrine, nutritional and metabolic diseases	8/3.9	2.0	(1.0–4.1)	167/12	14	(12–17)
Diseases of the nervous system	1.0/2.3	0.4	(0.1–3.1)	7/6.9	1.0	(0.5–2.1)
Cardiovascular diseases	100/88	1.3	(0.9–1.3)	306/269	1.1	(1.0–1.3)
Diseases of the respiratory system	12/15	0.7	(0.4–1.2)	56/47	1.2	(0.9–1.5)
Gastrointestinal diseases	17/6.5	2.6	(1.6–4.2)	54/19	2.8	(2.1–3.6)
Urogenital diseases	4/3	1.3	(0.5–3.4)	9/10	0.9	(0.5–1.7)
Cerebrovascular diseases	26/24	1.1	(0.7–1.5)	64/70	0.9	(0.7–1.2)
Pancreatic cancer	68/2.9	24	(19–30)	18/8.8	2.0	(1.3–3.2)
Colorectal cancer	137/5.4	26	(22–30)	130/16	7.9	(6.7–9.4)
Heart valve disease	2/2.2	0.9	(0.2–3.7)	20/6.4	3.1	(2.0–4.8)
Other causes	10/15	0.8	(04–1.2)	48/45	1.1	(0.8 –1.4)
Endocrine, nutritional and metabolic diseases except ICD8 = 258	6/3.9	1.5	(0.7–3.4)	9/11	0.8	(0.4–1.5)

(Table 4). The increased SMR was most pronounced for men, and during the early study period. Furthermore, a significant increase in SMR was only seen during the first year of follow-up and not for patients older than 68 years. Diabetes was stated as cause of death in 50% of deaths related to endocrine disease.

Table 5 – Standard mortality ratios for some causes of death for patients with adenocarcinoma and carcinoid (analyses by sex, age, period of diagnosis and follow-up)

Cause of death		Adenocarcinoma					Carcinoid				
		O	E	SMR	95% CI	Pyr	O	E	SMR	95% CI	Pyr
Neoplasms, except 152											
Sex	Male	197	22	9.0	(7.8–10)	2441	311	82	3.8	(3.4–4.2)	8847
	Female	206	20	10	(8.8–11)	2927	258	51	5.1	(4.5–5.8)	7592
Age at diagnosis	<68	196	19	10	(9.1–12)	3534	290	64	4.5	(4.0–5.1)	11587
	>68	207	24	8.7	(7.6–10)	1833	279	69	4.1	(3.6–4.6)	4852
Period	1960–1980	134	9	15	(12–18)	1258	275	29	9.4	(8.4–10)	4280
	1981-2000	269	24	11	(9.9–13)	3032	294	71	4.2	(3.7–4.7)	8456
Follow-up	0–1 year	228	8.5	27	(24–30)	1178	168	16	10	(8.9–12)	2247
	>1 year	175	36	4.8	(4.2–5.6)	4190	401	124	3.2	(2.9–3.6)	14192
Cardiovascular diseases											
Sex	Male	49	41	1.2	(0.9–1.6)	2441	173	163	1.1	(0.9–1.2)	8847
	Female	51	47	1.1	(0.8–1.4)	2927	133	106	1.3	(1.1–1.5)	7592
Age at diagnosis	<68	26	27	1.0	(0.6–1.4)	3534	107	93	1.2	(1.0–1.4)	11587
	>68	74	61	1.2	(1.0–1.5)	1833	199	176	1.1	(1.0–1.3)	4852
Period	1960–1980	42	21	2.0	(1.4–2.7)	1257	161	62	2.6	(2.2–3.0)	4280
	1981-2000	58	44	1.3	(1.0–1.7)	3032	145	132	1.1	(0.9–1.3)	8456
Follow-up	0–1 year	25	16	1.5	(1.0–2.3)	1177	59	31	1.9	(1.5–2.5)	2247
	>1 year	75	76	1.0	(0.8–1.2)	4190	247	251	1.0	(0.9–1.1)	14191
Pancreatic cancer											
Sex	Male	34	1.3	26	(18–36)	2409	11	4.9	2.2	(1.2–4.0)	8788
	Female	34	1.6	22	(16–31)	2914	7	3.9	1.8	(0.9–3.8)	7547
Age at diagnosis	<68	30	1.3	24	(16–34)	3489	7	4.4	1.6	(0.8–3.3)	11486
	>68	38	1.6	24	(17–32)	1833	11	4.4	2.5	(1.4–4.5)	4850
Period	1960–1980	16	0.6	27	(16–43)	1238	6	1.9	3.1	(1.4–6.9)	4229
	1981-2001	52	1.6	32	(24–41)	3010	12	4.6	2.6	(1.5–4.6)	8409
Follow-up	0–1 year	44	0.6	77	(57–103)	1177	8	1.1	7.3	(3.7–15)	2247
	>1 year	24	2.5	9.8	(6.6–15)	4145	10	8.1	1.2	(0.7–2.3)	14087
Colorectal cancer											
Sex	Male	73	2.5	29	(23–36)	2432	75	9.6	7.8	(6.2–9.8)	8831
	Female	64	2.8	23	(18–29)	2924	55	6.8	8.0	(6.2–10)	
Age at diagnosis	<68	59	2.1	28	(21–36)	3523	58	7.4	7.8	(6.1–10)	11559
	>68	78	3.2	24	(19–30)	1833	72	9.0	8.0	(6.3–10)	4852
Period	1960–1980	63	1.3	50	(39–64)	1255	66	3.9	17.0	(13–22)	4272
	1981-2000	74	2.9	25	(20–32)	3024	64	8.4	7.6	(6.0–9.8)	8439
Follow-up	0–1 year	69	1.1	66	(52–83)	1177	55	2.0	27.4	(21–36)	2247
	>1 year	68	4.6	15	(12–19)	4179	75	15	4.9	(3.9–6.2)	14163
Heart valve disease											
Sex	Male	2	0.9	2.2	0.6–9.0)	2421	13	3.3	3.9	(2.3–6.7)	8797
	Female	0.0	1.3	0.0	(0 -)	2859	7	3.1	2.3	(1.1–4.8)	7400
Age at diagnosis	<68	1	0.7	1.4	(0.2–10)	3447	9	2.4	3.7	(1.9–7.1)	11345
	>68	1.0	1.5	0.7	(0.1–4.9)	1833	11	4.0	2.8	(1.5–5.0)	4852
Period	1960–1980	0.0	0.4	0.0	(0 -)	1230	8	1.3	6.4	(3.2– 3)	4212
	1981-2000	2	1.2	1.6	(0.4–6.6)	2983	12	3.4	3.6	(2.0–6.3)	8301
Follow-up	0–1 year	1	0.4	2.5	(0.4–18)	1177	4	0.8	5.4	(2.0–14)	2247
	>1 year	1	1.9	0.5	(0.1–3.8)	4102	16	6.0	2.7	(1.6–4.4)	13950

3.4. *Causes of death after carcinoids*

In the cohort with carcinoid tumours, 3011 (80% of the cohort with carcinoid) died during the study period and 613 patients died of their primary malignancy.1210 died within 30 days from diagnosis of the primary malignancy and 686 had the same death date as date of diagnosis.

Patients with carcinoid had increased overall risk to die from malignant diseases (SMR 4.3; 95% CI 4.0–4.6) (Table 4). These neoplasms were dominated by colorectal cancer (23%), although in 44% the cause of death was stated as 'disseminated malignant tumour'. The increase in risk of dying from malignant disease was most pronounced during the early study period and during the first year of follow-up (Table 5). The risk of dying from cardiovascular disease was slightly increased (SMR = 1.1; 95% CI 1.0–1.3). It mainly related to ischemic heart disease (62%) and was most pronounced during the early study period and during the first year of follow-up. Seven percent of deaths from cardiovascular disease were related to heart failure whereas 9% were registered as

caused by heart valve disease. The SMR for heart valve disease was 3.1 (Table 4). Thirty percent were registered as mitral valve disease, 25% as aortic valve disease and 35% as 'unspecified heart valve disease'. The SMR for gastrointestinal disorders was statistically significant increased (Table 4). The overall risk was 2.8 (95% CI 2.1–3.6). Twenty-four percent of the deaths from gastrointestinal disorders were duodenal or gastric ulcer and 12% were caused by intestinal obstruction. The risk of dying from endocrinological disorders was increased during the whole study period (overall SMR 14; 95% CI 12–17, Table 4). In 97% of these cases, the endocrinological disorder in question was not specified in the National Causes of Death Registry.

4. Discussion

Our findings pertain to increased risks of acquiring gastrointestinal malignancy and genital or breast malignancy for patients with histologically verified small bowel adenocarcinoma, while carcinoid tumour of the small intestine couple to increased risk of prostate cancer, melanoma and malignancies of other endocrine organs. Malignant disorders, cardiovascular and gastrointestinal diseases were overrepresented as causes of death for both study cohorts. The lethal malignancies were dominated by cancers of the lower gastrointestinal tract and pancreas in the cohort with adenocarcinoma, and colorectal in the cohort with carcinoid tumours. Notably, in the latter cohort, a substantial amount of cases was registered with the diagnosis 'disseminated malignant tumour' as the cause of death. It is thus unknown if this diagnosis represents a second malignancy or a late manifestation of the original disease, that has been misclassified in the National Causes of Death Registry.

For the patients with carcinoid tumours, endocrine disorders were also overrepresented as causes of death, although the majority (97%) were registered as 'non-specified endocrine disorder', and may potentially represent misclassifications of the carcinoid syndrome. Most of these cases were coded according to ICD 8 as 258. When excluding this diagnosis there remained no increase in SMR for endocrine disorders (Table 4).

The expected age and year specific incidence rates of malignant tumours during the study period were calculated using data from the Swedish Cancer Registry, which covers the whole Swedish population. The observed cases in the cohort of patients with adenocarcinoma and carcinoid in the small intestine were derived from the same source. Information on causes of death was obtained by computerised record linkage between the National Causes of Death Registry and the Cancer Registry. Accuracy and completeness of the registry have been carefully evaluated in earlier studies and the degree of misclassification is below 10%.[24,25]

Adenocarcinomas and carcinoids were analysed separately because of the differences in clinical presentation between these tumours and their probable divergence in histogenic origin[26] as well as, most likely, different etiological pathways. However, because of the relatively small number of observed cases, second tumours and causes of death were pooled into larger groups, although attempts to perform a detailed analysis were made even though this includes lower number of cases and more difficulties to identify relevant associations.

Generally, second malignancies were diagnosed within the first year after diagnosis of the small bowel tumour, possibly due to increased activity in the clinical workup. The increased risk of acquiring other gastrointestinal malignancies noted in men with adenocarcinoma could be due to misclassification of metastatic disease or local recurrences, at least during the first observation years. Tumours of the small intestine generally cause vague symptoms and are difficult to diagnose. Thus, before correct localisation of the disease, patients have often undergone extensive clinical and laboratory investigations.[27] Earlier studies have also indicated an increased risk of acquiring cancers of the liver and biliary tract as well as the digestive system.[8,9,11]It is, however, unclear why this increase should be isolated to men and thus a chance finding cannot be excluded. One study has indicated a possible mutual etiological trait between colon cancer and small intestinal malignancy, namely high consumption of red meat.[28]

Previously, an association between small intestinal malignancy, especially for carcinoids, and cancer of the prostate has been noted.[9,16] These findings induce a need for further exploration of the pathogenetic pathways for prostate cancer and carcinoid tumours, including the role of vitamin D deficiency.[29] The association between genital and breast cancer in females and adenocarcinoma of the small intestine has not been noted before. Detection bias cannot be ruled out and the excess risk was mostly confined to the earlier study period. Breast cancer cases and female genital cancers may largely be represented by *in situ* cancers as they have become part of screening programmes. Although we did not formally exclude *in situ* cancers, less than 4% of all tumours diagnosed after the index small intestinal malignancy were registered as *in situ*. No breast cancers or gynaecologic cancers diagnosed after the primary small bowel tumour were non-invasive. Breast cancer and prostate cancer have with time lost their association to small bowel malignancy, possibly due to more found cases due to screening, at least in the case of breast cancer. Formally, there are no regular screening programmes in Sweden for prostate cancer, although in later years there has been a tendency for 'wild screening' initiated by patients as well as physicians. If, hypothetically, the study population with small bowel malignancies, are less prone to attend screening programmes than the general population, changes in the relation between the number of observed versus expected cases could affect the result due to the relatively small number of observed second malignancies.

The increased risk of second tumours in this study could possibly be explained by the misinterpretation of a recurrence from the small intestinal malignancy as a new gastrointestinal cancer. A more plausible explanation is that basal genetic disturbances including microsatellite instability or defect DNA repair mechanisms may be present in these patients[30] generating a true increase in second malignancies and possibly a more adverse course of the disease. For carcinoids, the risk of dying from colorectal cancer was statistically significantly increased although the risk of acquiring this cancer was not. A plausible explanation may be that the treatment for the carcinoid tumour affects the course of this type of malignancy. Interferon

may be one possible factor. However, interferon may also be an explanation to why the incidence of melanoma is reduced as second malignancy from 1980–2000 compared to 1960–1980 for patients with carcinoid tumours.[31]

The marked difference between the number of pancreatic and colorectal cancers recorded respectively as incident cases and deaths in Tables 3 and 5 is striking. The file acquired from the Cancer Registry for the present study contains all patients with small intestinal adenocarcinoma and carcinoid from 1960 to 2000. Furthermore, the file contains all registered malignant tumours for these patients during the study period; before as well as after diagnosis of the small intestinal malignancy. Thus, an explanation for the discrepancy between incident cases in the analysis of risk of colorectal cancer as second malignancy, and the number of deaths caused by colorectal cancer, could be that most cases of colorectal cancer associated with small intestinal carcinoid as well as adenocarcinoma were diagnosed before diagnosis of the small intestinal malignancy. These cases are obviously not included in the analysis of standardised incidence ratio.

For pancreatic cancer, data should be interpreted with caution. In the case of primary adenocarcinoma 80% of index tumours were situated in the duodenum. The physician responsible for issuing the death certificate could have misdiagnosed these cases as pancreatic cancers at the time of death. On the other hand it is well known from the Causes of Death Register that a substantial amount of patients are registered with pancreatic cancer as cause of death without previous records in the Cancer Register.

The increased risk of cardiovascular deaths could possibly be accounted for if exposure to smoking is more common in patients with small intestinal malignancies, as previously noted in an epidemiological study .[32] However, this possibility is partly contradicted by the fact that we could not find any increased risk for cancers of the respiratory system and another investigation of small bowel malignancy does not implicate smoking as a risk factor.[28] Other known cardiovascular risk factors such as hyperlipidemia and hypertension have not been thoroughly investigated in these patients. To date, there is only a vague or even absent hereditary factor in adenocarcinoma as well as midgut carcinoid disease, arguing against a common genetic ethiology between cardiovascular disease and either of the small bowel malignancies. A detailed analysis of valve disturbances reveals that not only right-sided, but also defect left-sided valves – mitral and aortic valves – are present in high frequency.

The association to increased risk of dying in gastrointestinal disorders gives further arguments to speculations that other gastrointestinal diseases could be on the etiologic pathway for small bowel malignancy, such as celiac disease, inflammatory bowel disease, conditions giving stasis or decreased intestinal motility, all forms of gastrointestinal adenomas and polyps, disorders of bile secretion and cholecystectomy as well as peptic ulcer.[28,33,34]

Our results support an increased risk of other second malignancies after diagnosis of small bowel tumour, and clearly demonstrate differences between adenocarcinoma and midgut carcinoid disease in this respect. Moreover, a detailed analysis of causes of death in a population based cohort of small intestinal malignancies has not been presented before in the literature. Cause of death in malignancy is high in both histological types studied. This is not surprising, as patients with small bowel adenocarcinoma as well as carcinoid frequently had a history of malignant disease before diagnosis of the small bowel malignancy. In fact, compared to cancers registered after the index small bowel tumour, there are twice as many malignancies registered before the small bowel malignancy. Although not analysed in the present study, this indicates that patients with small bowel adenocarcinomas and carcinoid may have an increased life-time risk of developing malignant diseases of any kind. There is also an increased risk to die of cardiovascular disease, and similarly to the analysis of second malignancies, there are differences between the two tumour types. Association between prostate cancer and carcinoids as well as the novel finding of increased risk of cause of death in colorectal cancer and pancreatic cancer in these patients mandates further investigations.

Conflict of interest statement

None declared.

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