Colorectal cancer patients: what do they die of?

Matias Riihimäki,^{1,2} Hauke Thomsen,¹ Kristina Sundquist,^{2,3}
Kari Hemminki^{1,2}

¹Division of Molecular Genetic Epidemiology, German Cancer Research Center (DKFZ), Heidelberg, Germany

²Center for Primary Care Research, Lund University, Malmö, Sweden

³Stanford Prevention Research Center, Stanford University School of Medicine, Stanford, California, USA

Correspondence to

Dr Hauke Thomsen, Division of Molecular Genetic Epidemiology, German Cancer Research Center (DKFZ), C050, Im Neuenheimer Feld 580, Heidelberg, Baden-Württemberg 69120, Germany; h.thomsen@dkfz-heidelberg.de

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Introduction

The 5-year relative survival rate after colorectal cancer (CRC) diagnosis has increased from around 40% in the 1960s to approximately 60% in Sweden.^{1–4} Some probable reasons for the increased survival may be earlier diagnosis, improved treatment and better health status.² Survival is worse among men^{1,2,4} and older patients.^{1,5} In the western countries, around 80% of the patients are diagnosed at ages over 60 years.⁴ Because the older population frequently suffers from comorbidities, a majority of CRC patients are affected by one or several comorbidities at diagnosis.^{6,7} Further improvements in the outcome of CRC patients motivate increased knowledge of these comorbidities. The influence of specific comorbidities on CRC mortality has been well covered in previous studies, and results have suggested that several chronic disorders (eg, cardiovascular diseases, diabetes and chronic pulmonary obstructive disease) and the number of comorbidities may affect survival and life expectancy negatively.^{6–12} However, little is known whether CRC patients are at an increased risk to die from specific causes; higher death rates have been described among CRC patients from cardiovascular causes, gastrointestinal causes, injuries¹³ and suicide.^{13,14} Furthermore, knowledge of the actual death causes mentioned in death certificates of CRC patients is incomplete. A recent study has shown though, that among deceased CRC patients, 75% had died from CRC itself.¹⁵ However, estimates of the actual proportion of cancer patients dying from their primary cancer may vary greatly. For example, in breast cancer, these estimations have varied between 50% and 76%.¹⁶ The use of nationwide healthcare registers with complete coverage could help to further

clarify the proportions of specific death causes among CRC patients.

The present retrospective cohort study used a nationwide database, the Swedish Family-Cancer Database, and aimed to investigate whether a diagnosis of CRC is associated with an increased risk to die from any specific condition. Data relating to both, accompanying and underlying causes of death were used. The underlying cause of death is, as defined by the WHO, ‘the disease or injury which initiated the train of morbid events leading directly to death’, whereas the multiple causes comprise complications and contributing causes.¹⁷ Inclusion of data accompanying causes of death enables a more complete understanding of the causes of death.^{16,18–20} We also performed separate analyses depending on time since diagnosis and anatomical location of CRC.

Methods

Study population

The Swedish Family-Cancer Database was created by linking data from several databases.²¹ Data on cancers is from the Swedish Cancer Registry, death causes from the Swedish Cause of Death Register, and data on the familial relationships from the Swedish Multigenerational Register. In addition, the database includes socioeconomic information from national census data. The 2010 update includes Swedish residents born after 1931, together with their biological parents, totalling around 12 million individuals, with over one million cancer diagnoses made until 2008. During the set study time, 1987–2008, death causes were coded using International Classification of Diseases 9 (ICD-9) (1987–1996) or ICD-10 (since 1997). The study population was defined as all individuals born before 1967 and residing in Sweden, totalling 6.13 million

individuals, of which 95 000 were CRC patients. CRC patients were defined as those with a diagnosis of CRC as the first invasive cancer, and were identified by ICD-7 codes 153 and 154.0. All other individuals were allocated to the non-CRC cohort. The database includes information on both the underlying cause of death and up to five accompanying causes. Causes of death were assigned into several disease categories. The ICD-codes included in the different categories are discussed below.

Statistical method

A Cox regression model with age as the underlying time scale was used to estimate cause-specific HR, comparing CRC patients with individuals without CRC. Calculations were performed using SAS software (PROC PHREG; SAS V. 9.2). Entry time was January 1987, immigration, or presence at census, whichever occurred first. Censoring events included: December 2008, emigration, absence at census, or death from a cause not included in the chosen disease categories. Individuals who initially were part of the reference group were assigned to the CRC group upon CRC diagnosis. First, HRs were estimated for the underlying causes, the event of interest being dying with a specific condition listed as the underlying cause. Next, the multiple causes of death were also considered. Here, the event of interest was defined as dying with any mention of a specific cause in the death certificate. Thus, calculations on the multiple causes always included the underlying cause. Diseases may have a higher incidence shortly after diagnosis.⁹ In order to investigate whether the risk to die from a specific cause was higher shortly after or long after diagnosis, time-dependent analyses were conducted. Separate HRs were calculated for the first 5 years and subsequent years after diagnosis. Furthermore, analyses depending on the anatomical location of the tumour were performed, wherein tumours were classified to proximal (ICD-7 codes 153.0, 153.1), distal (153.2, 153.3) or rectal (154.0). Finally, separate HRs were estimated for men and women. The socioeconomic index (categories 'blue-collar', 'white-collar', 'agriculture', 'professional', 'private', 'other/unknown'), sex, and the geographical region of residence (north, south, big city, unknown) were included as covariates, with individuals grouped according to data from the latest census.

Definitions of disease categories

ICD-codes used in the disease categories were the following (ICD-10; -9): myocardial infarction (I21-I22; 410), other coronary heart disease (I20, I23-I25; 411-414), cerebrovascular event (I60-I69; 430-438), arterial disease (I70-I79; 440-448), heart failure (I50; 428), pneumonia (J10-J18; 480-487), chronic lower respiratory disease (J40-J49; 490-496), external causes including subgroups (S00-T98, V01-Y98; 800-900, e800-e999), complications of diagnostic or surgical procedures (Y60-Y84; e870-e879), complications

of therapeutic drug or vaccine usage (Y40-Y59; e930-e949), suicide (X60-X84; e950-e959), traffic accident (V01-V99; e800-e848), falls (W00-W19; e880-e888), other heart disease (I30-I49, I52; 420-427), gastrointestinal disease (K00-K93; 520-579), dementia (F00-F03, G30; 290, 331.0), diabetes (E10-E14; 250), complications of heart disease (I51; 429), urinary system disease (N00-N39; 580-599), certain symptoms (R00-R99; 780-799), pulmonary circulation disease (I26-I28, J81; 415-417, 514), nervous system disease (G00-G99, except G30; 320-359, except 331.0), hypertensive disease (I10-I19; 401-405), other bacterial disease (A30-A49; 030-041), psychiatric disease (F04-F99; 291-319), anaemia (D50-D64; 280-285), tumours other than CRC (C00-D48, excluding C18-C20, C77-C80 and C97; 140-239, excluding 153, 154.0, 154.1), CRC (C18-C20; 153, 154.0, 154.1).

Results

Out of 6.13 million individuals included, 1.49 million died during the study period. Of the 95 000 included CRC patients, 61 000 died. CRC was the most common underlying cause, accounting for 55.9% of deaths among CRC patients; 62.9% of deceased CRC patients had CRC mentioned in their death certificate, as either the underlying or one of the multiple causes of death.

First, HRs were calculated for the underlying causes (table 1). CRC patients were found to be at a higher risk to die from, for example, 'other bacterial disease' (HR=1.40, see 95% CI in table 1), 'gastrointestinal disease' (1.20), and 'diseases of pulmonary circulation' (1.19). By contrast, some causes of death featured decreased risks, for example, dementia (0.75), 'diseases of the nervous system' (0.77) and 'pneumonia' (0.87).

Next, the multiple causes were included in the analyses (table 1). CRC patients were found to be at a higher risk to die with 'gastrointestinal disease' (3.22) or 'external causes' (2.53) listed among the multiple causes of death. High HRs were found for some subcategories of external causes: iatrogenic causes and suicide, whereas falls and traffic accidents featured no increased risk. The only death cause to feature a significantly decreased risk was 'dementia' (0.86), whereas other causes with decreased risks as underlying causes now featured either increased or similar risks.

In further analyses, separate HRs were estimated with regard to the time since diagnosis of CRC (table 2, only significant differences are shown). Notable differences were found between the two defined time periods: <5 and >5 years since diagnosis. For example, the HRs for 'diseases of pulmonary circulation' and 'gastrointestinal diseases' were substantially higher during the first 5 years. By contrast, 'dementia' and 'nervous system disease' featured significantly lower HRs during the first 5 years. These findings were similar both when regarding underlying causes only, and also when considering accompanying death causes (data not shown).

Table 1 Cox regression models were used to determine HRs for dying from selected conditions when individuals were diagnosed with CRC as first cancer (n=95 468) compared with all other individuals (n=6 034 288)

Event (death due to)	As the underlying cause of death				As one of the multiple causes of death			
	No. of dead with CRC	No. of dead without CRC	HR	95% CI	No. of dead with CRC	No. of dead without CRC	HR	95% CI
Myocardial infarction	3780	205 097	0.95	0.91	4769	234 423	1.02	0.99
Cerebrovascular event	2975	147 712	0.96	0.93	5188	228 825	1.06	1.03
Other CHD	2847	134 224	0.97	0.93	6229	274 373	1.07	1.04
Heart failure	1215	43 937	1.06	1.00	7956	270 395	1.23	1.20
Gastrointestinal disease	1069	47 127	1.20	1.12	6297	99 370	3.22	3.14
Other heart disease	1038	43 969	1.08	1.01	4866	175 547	1.28	1.25
Arterial disease	1050	51 924	0.90	0.84	3976	174 417	1.01	0.98
Pneumonia	1011	47 679	0.87	0.82	4215	162 235	1.14	1.10
Dementia	998	54 333	0.75	0.71	2497	117 096	0.86	0.83
External causes	869	71 901	1.06	0.99	6233	154 486	2.53	2.47
Complication of diagnostic or surgical procedures	24	1036	1.05	0.70	4415	52 259	4.65	4.50
Complication of therapeutic drug or vaccine usage	1	95	0.66	0.09	246	9437	1.58	1.39
Suicides	190	21 254	1.56	1.34	190	21 332	1.56	1.33
Traffic accidents	57	9260	0.97	0.74	61	9499	0.98	0.76
Falls	256	12 420	1.01	0.89	427	19042	1.05	0.95
Chronic lower respiratory disease	753	39 762	0.99	0.92	2025	84 453	1.19	1.14
Symptoms	586	26112	0.98	0.90	9922	280 250	1.61	1.57
Diabetes	534	27 322	1.07	0.98	3200	119 129	1.38	1.33
Urinary system disease	451	17 485	1.15	1.04	2565	83 213	1.45	1.39
Pulmonary circulation disease	313	12 456	1.19	1.05	2623	73 042	1.66	1.59
Complications of heart disease	313	13 512	1.08	0.96	1686	69 898	1.16	1.10
Hypertensive disease	269	11 826	1.00	0.88	2025	84 401	1.15	1.10
Nervous system disease	209	19 453	0.77	0.67	1181	66 594	1.03	0.98
Other bacterial disease	205	7239	1.40	1.22	1138	29 311	2.00	1.88
Psychiatric disease	77	11 273	0.77	0.61	567	51 188	1.02	0.94
Anaemia	57	2606	0.92	0.70	653	16 877	1.55	1.43
Tumour other than CRC	4853	322 449	1.03	1.00	6463	369 059	1.12	1.09
CRC	34103	9033	295.00	288.00	38342	10 954	247.3	242.00
								252.80

Boldface entries indicate significant HRs.

CHD, coronary heart disease; CRC, colorectal cancer.

Table 2 Cox regression models were used to determine HRs for dying from selected conditions when individuals were diagnosed with CRC as first cancer (n=95 468) compared to all other individuals (n=6 034 288), depending on time since diagnosis

	< 5 years after diagnosis (n=40 513)				> 5 years after diagnosis (n=20 447)				
Event (death due to)	No.	HR	95% CI		No.	HR	95% CI		p Value
Cerebrovascular event	989	0.91	0.85	0.97	1986	0.99	0.94	1.03	0.04
Gastrointestinal disease	497	1.33	1.20	1.47	572	1.13	1.04	1.22	0.01
External causes	371	1.13	1.01	1.26	498	1.02	0.94	1.12	0.17
Complication of diagnostic or surgical procedures	13	1.71	0.99	2.96	11	0.72	0.40	1.31	0.04
Suicide	114	1.83	1.48	2.26	76	1.36	1.09	1.69	0.06
Dementia	166	0.40	0.34	0.46	832	0.91	0.85	0.97	<0.01
Symptoms	183	1.14	0.98	1.32	403	0.92	0.83	1.01	0.02
Pulmonary circulation disease	167	1.40	1.16	1.69	146	1.07	0.91	1.26	0.03
Nervous system disease	68	0.60	0.47	0.77	141	0.88	0.74	1.04	0.01
Psychiatric disease	26	0.50	0.32	0.79	51	0.93	0.72	1.22	0.02
Tumour other than CRC	1927	0.98	0.93	1.02	2926	1.06	1.02	1.10	<0.01
CRC	30311	595.70	581.70	609.90	3792	54.20	52.20	56.40	<0.01

Boldface entries indicate significant HRs.
CRC, colorectal cancer.

Finally, a distinction between the anatomical locations (proximal, distal and rectal) was made (table 3). When considering the underlying causes only, risks of death from anaemia, CRC and diseases of pulmonary circulation varied substantially depending on tumour localisation. The latter two featured a higher HR among CRC patients with a rectal tumour compared with proximal and distal tumours. By contrast, those CRC patients with a proximal tumour were at the highest risk to die from anaemia.

Discussion

We used a Cox regression model to investigate causes of death in CRC patients. To our knowledge, this is the first study that estimates cause-specific HRs for several causes of death among CRC patients. We observed that CRC patients are at an increased risk to die from several disease categories, including diseases of pulmonary circulation, gastrointestinal disease and other bacterial disease. Sepsis is the major cause of death in the latter category and has been estimated to occur postoperatively in 7.4% of performed emergency surgeries in CRC patients.²²

We also found that CRC patients have a decreased risk to die from, for example, 'dementia' and 'nervous system diseases', although only 'dementia' featured decreased HRs when analysing multiple causes of death. These findings are similar to recent studies. Decedents with a diagnosis of Parkinson's disease, one major disease in the category 'nervous system diseases', have been found to have a decreased risk to develop cancer²³ and also have fewer mentions of cancer in their death certificates compared with a control group.²⁴ Similarly, demented patients have been found to be less likely to have malignancies as the underlying cause of death.²⁵ A possible explanation to the

results is that physicians issuing a death certificate for demented CRC patients might not include dementia as a cause of death. Earlier trials have suggested that if deceased individuals have a main diagnosis of an acute or 'dramatic' condition, such as CRC, it is more likely to be the underlying cause of death.²⁶ By contrast, more benign and chronic conditions may be less actively chosen by physicians as the cause of death in the case of concomitant malignancies. Therefore, we believe that several more benign causes of death might be underrepresented in death certificates.

Some limitations to the data need to be considered. Because we do not have access to outpatient data regarding time of onset of the comorbidities, we cannot conclude whether specific comorbidities precede CRC, or if CRC precedes the comorbidities. For example, Parkinson's disease might decrease the risk of CRC, as discussed above, whereas anaemia may often be caused by CRC. Furthermore, we did not have access to data on what treatment CRC patients had received. In addition, the accuracy of death certificates may have an impact on our results. In an earlier study, the accuracy of Swedish death certificates has been discussed: the highest accuracy has been found for death certificates with a malignant disease as the underlying cause.²⁶ The authors themselves point out, that some of the 'inaccuracy' may be attributed to different definitions of the underlying cause of death and main condition from the hospital discharge register.²⁷ This also further motivates inclusion of accompanying death causes in our analyses.

Our study on cause-specific mortality differs from many previous CRC comorbidity studies,^{6–8 10–12} which have assessed the influence of comorbidities on survival. Our approach has several advantages. We have

Table 3 Cox regression models were used to determine HRs for dying from selected conditions when individuals were diagnosed with CRC as first cancer compared to all other individuals, depending on anatomical location of malignancy

Event (death due to)	Proximal colon (n=29 160)			Distal colon (n=22 219)			Rectum (n=33 702)			p Value			
	No.	HR	95% CI	No.	HR	95% CI	No.	HR	95% CI				
Myocardial infarction	1149	0.91	0.86	0.97	909	0.95	0.89	1.01	1295	0.97	0.92	1.03	0.28
Other CHD	939	0.97	0.91	1.04	677	0.96	0.89	1.04	922	0.99	0.92	1.05	0.90
Cerebrovascular event	987	0.97	0.91	1.03	726	0.98	0.91	1.05	922	0.93	0.88	1.00	0.60
Arterial disease	330	0.89	0.80	1.00	240	0.86	0.76	0.98	354	0.95	0.85	1.06	0.52
Heart failure	388	0.98	0.89	1.09	305	1.12	1.00	1.25	384	1.11	1.01	1.22	0.13
Pneumonia	344	0.87	0.78	0.97	219	0.80	0.70	0.91	326	0.92	0.82	1.02	0.29
Chronic lower respiratory disease	261	1.08	0.95	1.22	162	0.88	0.75	1.03	255	1.01	0.89	1.14	0.14
External causes	274	1.09	0.96	1.23	196	1.01	0.87	1.17	282	1.03	0.92	1.17	0.70
Complication of diagnostic or surgical procedures	7	0.94	0.45	1.98	4	0.73	0.27	1.95	11	1.51	0.83	2.73	0.39
Complication of therapeutic drug or vaccine usage	0	0.00	0.00	0.00	1	2.74	0.38	19.74	0	0.00	0.00	0.00	1.00
Suicides	56	1.73	1.32	2.27	38	1.36	0.97	1.90	61	1.38	1.05	1.80	0.41
Traffic accidents	12	0.73	0.41	1.28	14	1.02	0.60	1.72	22	1.00	0.65	1.53	0.62
Falls	76	0.94	0.74	1.17	64	1.07	0.84	1.38	76	0.91	0.72	1.15	0.58
Other heart disease	346	1.08	0.97	1.20	243	1.07	0.94	1.21	331	1.10	0.98	1.22	0.95
Gastrointestinal disease	335	1.14	1.02	1.29	264	1.21	1.06	1.37	329	1.23	1.10	1.37	0.68
Dementia	330	0.71	0.64	0.80	233	0.74	0.65	0.84	304	0.76	0.68	0.85	0.73
Diabetes	189	1.11	0.99	1.32	112	0.95	0.79	1.14	179	1.11	0.96	1.29	0.27
Complications of heart disease	90	0.92	0.74	1.15	73	1.08	0.85	1.36	113	1.24	1.02	1.50	0.14
Urinary system disease	148	1.16	0.99	1.36	111	1.15	0.96	1.39	140	1.12	0.99	1.32	0.94
Symptoms	183	0.86	0.74	1.00	143	1.01	0.86	1.19	191	1.13	0.98	1.30	0.03
Pulmonary circulation disease	96	1.05	0.86	1.33	61	1.03	0.79	1.35	114	1.36	1.11	1.67	0.14
Nervous system disease	62	0.76	0.59	0.97	47	0.68	0.51	0.92	74	0.81	0.64	1.02	0.67
Hypertensive disease	85	0.93	0.75	1.15	61	0.95	0.73	1.22	98	1.19	0.98	1.46	0.19
Other bacterial disease	69	1.48	1.16	1.88	51	1.39	1.04	1.85	59	1.29	1.00	1.67	0.76
Psychiatric disease	14	0.45	0.26	0.77	24	1.04	0.69	1.55	30	0.87	0.61	1.26	0.04
Anaemia	27	1.33	0.91	1.94	7	0.49	0.23	1.03	16	0.88	0.54	1.43	0.05
Tumour other than CRC	1473	1.01	0.96	1.07	1119	0.98	0.93	1.04	1571	0.98	0.93	1.03	0.60
CRC	10171	290.80	282.40	299.50	7459	265.80	257.60	274.40	12672	322.30	313.50	331.20	<0.01

Boldface entries indicate significant HRs and significant p values.
CHD, coronary heart disease; CRC, colorectal cancer.

used a large nationwide database on over 95 000 CRC cases, and performed analyses on 27 non-CRC causes of death, and also included accompanying death causes. In agreement with previous reports,^{16–18–20} we believe that restricting mortality analyses to underlying causes only may lead to underrepresentation of some death causes, and that the true risks therefore might be underestimated. For example, in the present study, the risk of death from ‘pneumonia’ as the underlying cause was decreased in CRC patients. By contrast, CRC patients were at a slightly increased risk to die with a mention of ‘pneumonia’ as an accompanying death cause. Similarly, in a recent study, men with prostate cancer have been identified to have a decreased risk to die from categories ‘urinary system disease’ and ‘anaemia’ as the underlying cause (0.69 (95% CI 0.62 to 0.77) and 0.74 (95% CI 0.56 to 0.98) respectively), but an increased risk to die with these two causes mentioned anywhere in the death certificate (1.90 (95% CI 1.84 to 1.96) and 2.28 (95% CI 2.14 to 2.42), respectively).¹⁹ Inclusion of accompanying causes of death enables the assessment of the whole spectrum of comorbidities.

Venous thromboembolism (VTE) is the dominant disease in the category ‘diseases of pulmonary circulation’, which our CRC patients were at an increased risk to die from. The relationship between malignancy and VTE, eponymously known as Trousseau’s syndrome, is well known. Thrombosis in cancer is multi-factorial, for example, cancer-related mechanisms causing a procoagulative state are endothelial damage and release or activation of procoagulative substances.²⁸ Treatment modalities in CRC have also been associated with CRC. Surgery is a widely acknowledged risk factor for VTE. Application of the recently introduced biological Bevacizumab may also be associated with an increased risk of developing VTE.²⁹ Chemotherapy has been associated with a twofold VTE risk increase among cancer patients.³⁰ Similar to our results, the risk of VTE has been recognised to be highest shortly after CRC diagnosis, reaching an incidence of 5% in the first 6 months following CRC diagnosis, and conferring an overall negative impact on survival among CRC patients.^{8–9}

Several gastrointestinal diseases can be linked to CRC. At diagnosis of CRC, 20–25% of patients present with hepatic metastases, which may cause hepatic failure and have long been associated with a poor prognosis in CRC patients.³¹ Previous comorbidity studies have associated concurrent liver diseases with increased risk of death among CRC patients.^{6–8–10} However, 5-year survival after resection of colorectal liver metastases has in recent years improved, approaching 50%.³¹ Ileus is a well-known postoperative complication, possibly due to postoperative alterations in autonomic nerve activity and due to opioid use.³²

The category ‘external causes’ also featured high HRs, especially for iatrogenic causes. A Danish study

What is already known on this subject

- ▶ Survival from cancer has increased during the past decades.
- ▶ In only about 50% of, for example, prostate and breast cancer patients, the cancer is the underlying cause of death.
- ▶ Comorbidities have a substantial effect on colorectal cancer (CRC) survival.

What this study adds

- ▶ CRC patients have an increased risk to die from several causes.
- ▶ Time since cancer diagnosis and anatomical location of tumour may alter the hazard of death from several causes.
- ▶ Including of all death causes mentioned in the death certificate is essential for death cause statistics.

How might this study impact on clinical practice in the foreseeable future?

To further improve survival, this study may increase awareness of comorbidities in clinicians handling CRC patients.

found that during the first 30 days after an emergency surgery, 20.4% of CRC patients suffer from a surgical complication, for example, anastomosis leakage or obstruction.²² Surgical complications have been associated with an increased risk of death (OR 2.3 (1.2 to 4.4)). Suicide also presented high HRs, similar to several cancer types.^{14–19–33} The increased risk may be associated with the psychological reactions when a malignancy is diagnosed. Recently, the standardised death rate for suicide has been estimated at 1.90 (1.74 to 2.07) for individuals with CRC.¹⁴ The increased risk was especially high among male CRC patients.

In conclusion, although the majority of CRC patients are dying from the CRC itself, we have found that affected individuals are at an increased risk to die from several other causes, notably external causes, diseases of pulmonary circulation and gastrointestinal diseases. The decreased risk of death from dementia and nervous system diseases remains intriguing. In the light of the present results, considering the prevention of non-CRC causes of death and comorbidities is therefore of interest in CRC patients.

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