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ORIGINAL ARTICLE

Cardiovascular events after elective colorectal cancer surgery in patients with stage I-III disease with no previous cardiovascular disease

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ABSTRACT

Background: The risk of cardiovascular events in patients treated for colorectal cancer is debated due to diverging results in previous studies. Colorectal cancer and cardiovascular disease share several risk factors such as physical inactivity, obesity, and smoking. Information about confounding covariates and follow-up time are therefore essential to address the issue. This study aims to investigate the risk of new-onset cardiovascular events for patients with stage I-III colorectal cancer receiving elective surgery compared to a matched population.

Material and Methods: Using a prospective cohort, we compared cardiovascular events among 876 patients treated with elective surgery for incident stage I-III colorectal cancer diagnosed between January 1st, 2001 and December 31st, 2016 to a cancer-free cohort matched by age, sex, and time since enrollment ($N = 3504$). Regression analyses were adjusted for lifestyle, cardiovascular risk factors, and comorbidity. Multivariable analyses were used to identify risk factors associated with cardiovascular events in the postoperative (<90 days of elective surgery) and long-term phase (>90 days after elective surgery).

Results: After a median follow-up of 3.9 years, the hazard ratio (HR) for incident heart failure was 1.53 (95% CI 1.02–2.28) among patients operated for colorectal cancer. The postoperative risk of myocardial infarction or angina pectoris was associated with the use of lipid-lowering drugs. Long-term risks of cardiovascular events were ASA-score of III+IV and lipid-lowering drugs with HRs ranging from 2.20 to 15.8. Further, the use of antihypertensive drugs was associated with an HR of 2.09 (95% CI 1.06–4.13) for angina pectoris or acute myocardial infarction. Heart failure was associated with being overweight, diabetes, and anastomosis leakage.

Conclusion: We observed an increased hazard of heart failure in patients operated on for stage I-III colorectal cancer compared to cancer-free comparisons. We identified several potential risk factors for cardiovascular events within and beyond 90 days of elective surgery.

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Colorectal cancer; cardiovascular disease; surgery; late effects

Background

Survival after colorectal cancer has increased since the early 2000s due to improved diagnostics, screening, and treatment options [1]. The 5-year relative survival in Denmark is above 70% and consequently, this is the third biggest group of cancer survivors [2]. For long-term survivors of colorectal cancer as with other cancer diagnoses, cancer treatment has been associated with increased disease risk in the survivorship phase [3].

The cornerstone in curing stage I-III colorectal cancer is surgery alone or in combination with radiotherapy and/or chemotherapy. Colorectal cancer surgery induces an immunological stress response, which may be associated with an elevated risk of complications, such as anastomosis leakage and circulatory problems [4,5]. Furthermore, patients with colorectal cancer have a long-term increased risk of cardiovascular disease, possibly associated with the use of cardiotoxic chemotherapy such as fluorouracil (5-FU), oxaliplatin, and capecitabine [6–11].

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Population-based cohort studies show diverging results regarding cardiovascular events in persons with colorectal cancer when compared to populations without cancer [3,12–14]. Discrepancies may be due to differences between studied populations, the definition of key covariates such as treatment and cardiovascular outcomes, and length of follow-up. Moreover, colorectal cancer and cardiovascular disease share several risk factors such as physical inactivity, obesity, smoking, and alcohol consumption [15–18], and only one of the existing studies [12] controls for these potential confounders. We address these gaps by using prospective information on pre-cancer lifestyle along with the use of cardiovascular prescription drugs and clinical factors including treatment. The aim was to analyze new-onset cardiovascular events for persons with stage I-III colorectal cancer receiving elective surgery compared to a matched population. In addition, potential risk factors for cardiovascular events, both long- and short-term, after elective colorectal cancer surgery were identified.

Material and methods

Data sources

The Diet, Cancer, and Health (DCH) cohort was established in 1993–95 and included 56,476 men and women aged 50–64 years at the time of invitation [19]. Blood samples and questionnaires about lifestyle and health status were obtained at enrollment. We used the personal identification number assigned to all Danes at the time of birth or immigration [20] to link the cohort to the Danish Colorectal Cancer Group (DCCG.dk) database which started in 2001. Consequently, cases diagnosed before 1 January 2001 could not be identified in the database. Next, we linked the study population to national health registries for information on outcomes and covariates.

Study population

Case population

Participants from the DCH cohort who were registered in the DCCG.dk database with stage I-III colorectal cancer and underwent elective surgery from 1 January 2001 to 31 December 2016, were eligible for the study. We excluded patients who had no information on stage, a cancer diagnosis before elective surgery, heart failure, or a diagnosis of inflammatory bowel disease due to an increase in the risk of both colorectal cancer and cardiovascular disease [21,22]. To be included in the case population, the participant needed to survive more than 90 days after surgery.

Cancer-free comparisons

For the included persons with colorectal cancer, a 1:4 matched cancer-free comparison population was identified in the DCH cohort among persons free of cancer 90 days after the time of surgery for the case person. We matched cancer-free (except non-melanoma skin cancer) comparisons on age at the date of elective surgery for the case person, sex, and time since entry into the DCH cohort.

Outcome – major cardiovascular events

We used the ICD-10 to identify incident angina pectoris, acute myocardial infarction, heart failure, transitional cerebral ischemia, and ischemic stroke (Supplementary Table 1). In the analyses, acute myocardial infarction and angina pectoris were combined as were transitional cerebral ischemia and ischemic stroke. From the National Patient Registry (NPR) which holds information on all inpatient contacts since 1977 and all outpatient visits since 1995, we retrieved cardiovascular outcomes [23]. In addition, we retrieved information on fatal cardiovascular events from the Cause of Death Registry which holds computerized information on all causes of death since 1970 [24].

Covariates

Education, lifestyle, anthropometry, and cardiovascular risk factors

Educational level, smoking status, alcohol intake, physical activity level (MET-score), Body Mass Index (BMI), diastolic and systolic blood pressure, and serum cholesterol were obtained from questionnaires and measurements made at the time of enrollment into the DCH cohort [19]. Categorical variables were constructed and included educational level (<7 years/7–12 years/>12 years), smoking status (never/former/current), MET-score (in quartiles) and BMI (<25/25–30/>30). Alcohol intake was divided into no use, moderate use (1–14 drinks/week for women and 1–21 drinks/week for men) and excessive use (>14 drinks/week for women and >21 drinks/week for men). Diastolic and systolic blood pressure and serum cholesterol measured at enrollment were included as continuous covariates [25].

Diabetes and prescription drugs related to cardiovascular disease

Information on diabetes, drugs for hypertension and lipid-lowering drugs retrieved from the NPR and the Danish Prescription Registry for the period of two years before the date of elective surgery (Supplementary Table 2).

Cancer characteristics and treatment information

Clinical characteristics of colorectal cancer were obtained from the DCCG.dk database and included information on the site of cancer (colon/rectum), stage of disease (I/II/III), ASA score (I/II/III + IV/unknown), type of surgery (laparotomy/laparoscopy), surgical complications (yes/no) including anastomotic leakage (yes/no). Treatment information was obtained from the NPR and included neo-adjuvant and adjuvant radiotherapy and chemotherapy (registered cytostatic therapy codes BWHA1–2, BOHJ17 or BOHJ19B1). Neoadjuvant chemo- and/or radiotherapy was defined as radiation and chemotherapeutics received up to 100 days before the date of surgery, whereas adjuvant chemotherapy was defined as chemotherapeutics received within 180 days after the date of surgery with less than three months between cycles. For descriptive purposes, we constructed an algorithm to identify

possible relapse using the works of Lash and colleagues [26] and Dobie and colleagues [27]. Palliative radiotherapy was defined as radiation received up to 100 days after the date of surgery. The date of probable relapse was defined as the date of incident chemotherapy more than 180 days after the date of surgery or if the time between chemotherapy cycles was more than three months.

Statistical analysis

Cox Proportional Hazards models were used to compare rates of cardiovascular outcomes for patients operated on for colorectal cancer to cancer-free comparisons from 90 days after surgery. Time since surgery was used as the underlying time scale. Stepwise adjustment for confounders was conducted which included in Model 1 age at entry, sex, and education, in Model 2 + smoking status and alcohol intake at enrollment, and in Model 3 + cardiovascular risk conditions or comorbidity (diabetes, use of anti-hypertensive drugs and use of lipid-lowering drugs). Specifically, Model 3 was analyzed using the information on the cardiovascular risk factors and comorbidity (diastolic/systolic blood pressure and serum cholesterol) obtained at the time of inclusion into the DCH cohort as a proxy for long-term cardiovascular health. All continuous variables were tested for linearity, and none fulfilled the assumption. Thus, age at entry, BMI, blood pressure, serum cholesterol, and MET-score were included in the models as splines. Time since the entry was grouped in quartiles and included in the analysis as strata. In analysis, neoadjuvant and adjuvant chemotherapy was combined to investigate exposure to any chemotherapy. Chemotherapy and the use of lipid-lowering drugs were analyzed as time-varying covariates. Competing events were death, new primary cancer, inflammatory gastrointestinal disease, and migration. The end of follow-up was at the date of a competing risk event or the end of study follow-up on 31 December 2016, whichever came first. Separate analyses for each cancer site showed similar hazard ratios (HRs) for colon and rectum cancer compared to the matched cancer-free comparisons.

In the second part of the analysis, we used Cox models to explore potential lifestyle, clinical, and treatment-related risk factors for cardiovascular disease among colorectal cancer patients. The follow-up time was split into the first 90 days after surgery and from 90 days after surgery until the censoring or end of the study. Covariates analyzed included lifestyle (smoking, alcohol intake, MET-score), BMI, clinical characteristics (stage, surgical complications), and neoadjuvant radiotherapy and adjuvant chemotherapy. The model included adjustment for sex, education, age at diagnosis, and period of diagnosis with the latter two included as splines. As adjuvant chemotherapy is standard treatment only in high-risk stage II and stage III disease, this analysis was further adjusted for the stage. Analyses of risk factors were based on 923 colorectal cancer patients. Cumulative incidence functions were calculated for patients with colorectal cancer for each cardiovascular outcome along with death, with death included as a competing risk. In all analyses, we tested the proportional hazards assumption by inspecting Schoenfeld residual plots in all models. The analyses were conducted in R version 3.3.3 with relevant packages [28–30].

Results

The study population included 923 patients with colorectal cancer of which 876 were at risk of cardiovascular disease 90 days after surgery and thus had four matched cancer-free controls ($N = 3504$) (Supplementary Figure 1). The mean age for patients with colorectal cancer and the matched cancer-free comparisons was 71 years (standard deviation 5.9) (Table 1). Differences in lifestyle, use of cardiovascular prescription drugs and other descriptive characteristics were minor between patients with colorectal cancer and the matched population without cancer.

Clinical characteristics of patients diagnosed with colorectal cancer

Among the 923 persons with colorectal cancer included in the analyses of risk factors for cardiovascular outcomes, men constituted 57% of patients (Table 1). Rectal cancer was more often diagnosed as Stage I disease and the patients had lower ASA-scores. However, more surgical complications were seen after rectal cancer surgery. Laparoscopic access was more common in the colon than rectal surgery (Table 2). In patients with rectal cancer, 21% received neoadjuvant radiotherapy, whereas less than 1% received palliative radiotherapy (results not shown). About 9% of patients with rectal cancer received neoadjuvant chemotherapy while 25% of patients with colon and 15% with rectal cancer received adjuvant chemotherapy. During follow-up, 89 (11%) patients with colorectal cancer received chemotherapy more than 180 days after surgery, interpreted as a relapse of the disease.

Cardiovascular events in patients with colorectal cancer compared to matched cancer-free comparisons

The adjusted HRs of cardiovascular events were similar for colon and rectal cancer when analyzed separately, therefore estimates were reported for patients with colorectal cancer as one group. Acute myocardial infarction, heart failure and transitional cerebral ischemia/ischemic stroke were diagnosed in 5.1%, 4.0%, and 4.5% of the patients with colorectal cancer, respectively, compared to 5.9%, 2.5%, and 5.5% of among the cancer-free comparisons (Supplementary Table 3). The analyses showed a statistically significant higher HR for heart failure in patients with colorectal cancer versus the cancer-free comparisons with an HR of 1.53 (95% CI: 1.02–2.28). Adjustments for education, lifestyle, physical activity, cardiovascular risk factors, and comorbidity did not significantly change the estimates (Figure 1). No statistically significant differences were observed for angina pectoris/acute myocardial infarction and transitional cerebral ischemia/ischemic stroke.

Table 1. Distribution of demographics, lifestyle, anthropometry and gastrointestinal comorbidity for 876 colorectal cancer patients and 3508 matched controls participating in the Diet Cancer and Health study.

		Patients with colorectal cancer		Cancer-free comparisons	
		N	%	*N*	%
Total ($N = 4380$)		876	(20.0)	3504	(80.0)
Demographics					
Sex	Women	375	(43)	1500	(42.8)
	Men	501	(57)	2004	(57.2)
Age at diagnosis (mean, SD)		71	(5.6)	71	(5.9)
Lifestyle					
Alcohol intake	No alcohol intake	66*	(7)	244	(7.0)
	Moderate	651	(74)	2763	(78.9)
	Excessive	159	(18)	486	(13.9)
	Missing	*	(<1)	11	(<1)
Smoking status	Never	274	(31)	1215**	(34.6)
	Former	297	(34)	1141	(32.6)
	Current	305	(35)	1148	(32.8)
	Missing	NA	–	**	(<1)
Physical activity (MET-score)	4th quartile (most active)	221	(25)	934	(26.7)
	3rd quartile	223	(25)	934	(26.7)
	2nd quartile	238	(27)	886	(25.3)
	1st quartile (least active)	194	(22)	744	(21.2)
Anthropometry					
BMI	Normal (<25 kg/m^2)	329	(38)	1568	(44.7)
	Overweight (25–30 kg/m^2)	394	(45)	1461	(41.7)
	Obese (>30 kg/m^2)	152	(17)	473	(13.5)
	Missing	<5	(<1)	<5	(<1)
Cardiovascular comorbidity					
Diabetes		92	(11)	276	(7.9)
Use of hypertensive drugs		511	(58)	1908	(54.5)
Use of lipid-lowering drugs		269	(31)	1052	(30.0)

*missing patients added to "no alcohol intake" due to micro data (<5 patients).
**missing patients added to "never smoked" due to micro data (<5 patients).

Table 2. Clinical and surgical characteristics along with treatment information for 923 persons diagnosed with stage I-III colon or rectum cancer who underwent elective surgery between 2001 and 2015.

		Cancer type				
		Colon		Rectum		
Clinical factors		*N* = 604 (65%)		*N* = 319 (35%)		*p*-value
Stage	I	115	(19.0)	101	(31.7)	<0.001
	II	285	(47.2)	96	(30.1)	
	III	204	(33.8)	122	(38.2)	
ASA score	I	140	(23.2)	101	(31.7)	0.01
	II	367	(60.8)	186	(58.3)	
	III + IV	81	(13.4)	27	(8.4)	
	Unknown	16	(2.6)	5	(1.6)	
Type of surgery	Laparotomy	239	(39.6)	170	(53.3)	<0.001
	Laparoscopy	365	(60.4)	149	(46.7)	
Year of surgery	2001–2005	112	(18.5)	102	(32.0)	<0.01
	2006–2011	213	(35.3)	123	(38.6)	
	2012–2016	279	(46.2)	94	(29.5)	
Complications within 90 days of elective surgery						
Any surgical complications*	Yes	73	(12.1)	70	(21.9)	<0.001
Anastomosis leakage	Yes	25	(4.1)	27	(8.5)	0.01
Radio- and chemotherapy						
Neoadjuvant radiotherapy	Yes	0	0	68	(21.3)	<0.001
Neoadjuvant chemotherapy	Yes	<5	(0.5)	28	(8.8)	<0.001
Adjuvant chemotherapy	Yes	160	(26.5)	40	(15.4)	<0.001
Relapse and deaths						
Relapse	Yes	50	(8.3)	39	(12.2)	0.07
Death	Yes	101	(16.7)	67	(21.0)	0.13

*surgical complications within 90 days of surgery including anastomosis leakage.

Cumulative incidence functions

For the 923 patients with colorectal cancer, the cumulative incidences of angina pectoris/acute myocardial infarction and heart failure were higher than the cumulative incidence of transitional cerebral ischemia/ischemic stroke with the steepest increase seen for angina pectoris/acute myocardial infarction in the first 500 days after elective surgery. The cumulative incidence for all outcomes increased most rapidly within the first 1000 days after elective surgery and then showed a slower increase for the rest of the study period however there were no signs of stagnation (Figure 2). Death from any cause was a strong competing event throughout follow-up.

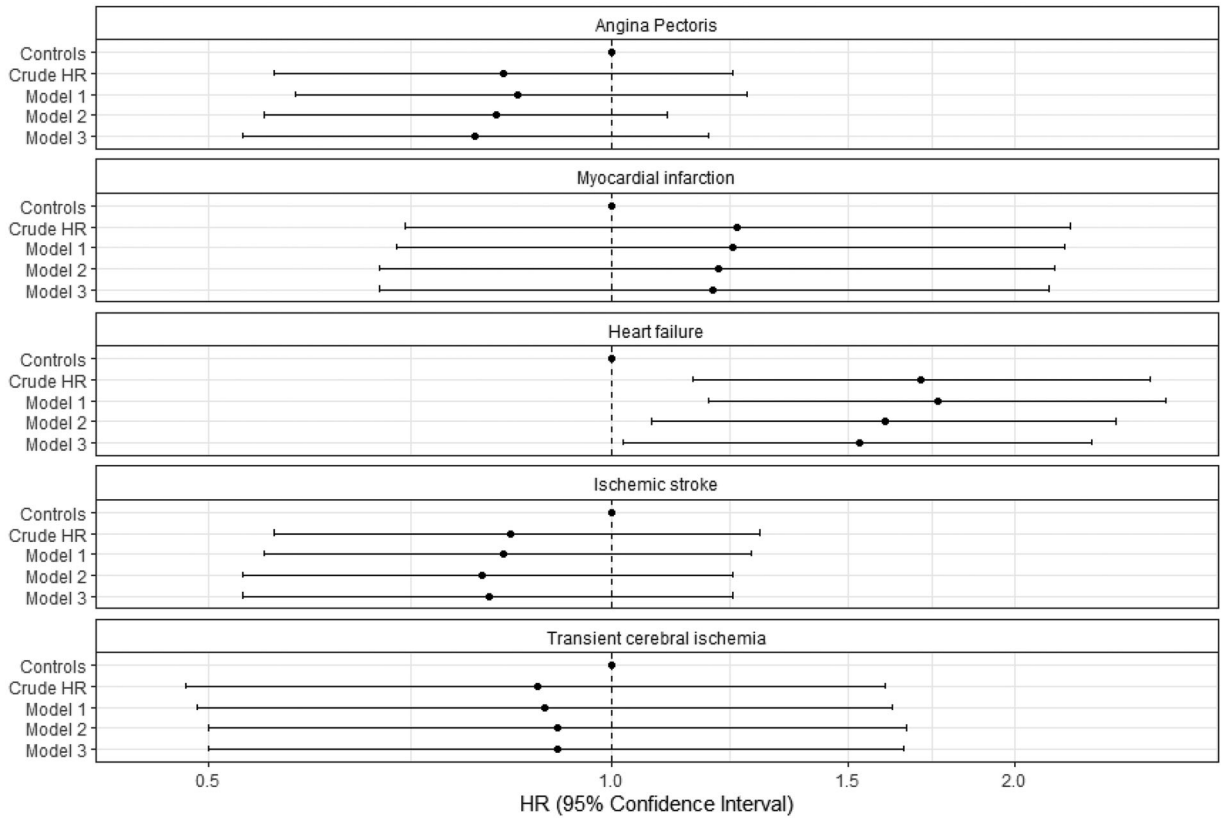

Figure 1. Unadjusted and multivariate-adjusted hazard ratios with 95% confidence intervals for angina pectoris, acute myocardial infarction, heart failure, transitional cerebral ischemia, and ischemic stroke for 876 patients operated for stage I-III colorectal cancer compared to 3504 cancer-free comparisons. HR: hazard ratio; CI: confidence interval. Risk time contributed by controls: 6,896,467 person-years, Risk time contributed by cases: 1,614,340 person-years, Model 1 adjusted for age, sex, time since entry into Diet, Cancer and Health study, and education, Model 2 adjusted for Model 1 + BMI, MET-score, alcohol in g/day and smoking status, Model 3 adjusted for Model 1 + Model 2 + diabetes, use of antihypertensive drugs, and use of lipid-lowering drugs.

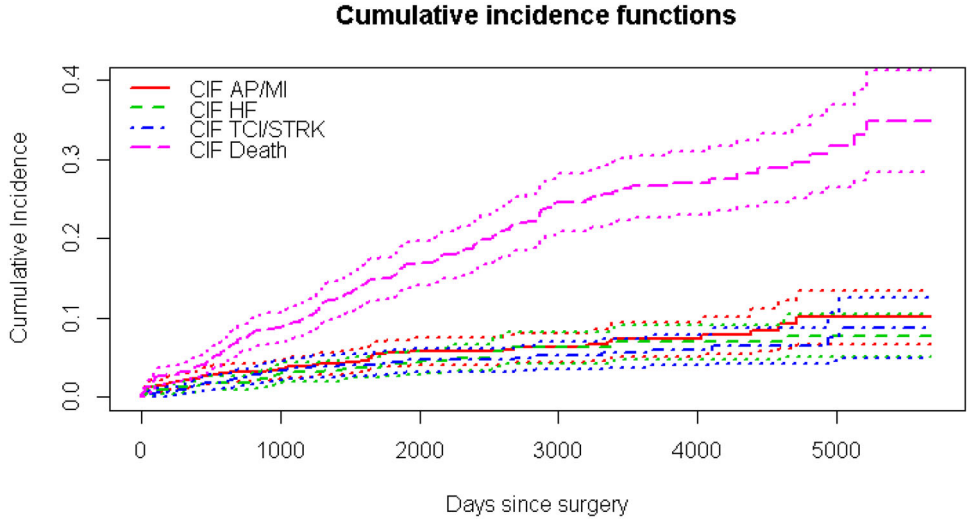

Figure 2. Cumulative incidence functions (CIF) for angina pectoris (AP)/acute myocardial infarction (MI), heart failure (HF), transitional cerebral ischemia (TCI)/ischemic stroke (IS), and deaths in the 908 colorectal cancer patients included in the exploratory analyses of risk factors for cardiovascular events among persons with colorectal cancer.

Risk factors associated with postoperative and long-term risk of cardiovascular events after elective colorectal cancer surgery

Within the first 90 days after elective surgery, patients using lipid-lowering drugs had a higher risk of experiencing angina pectoris/acute myocardial infarction compared to non-users in analysis adjusted for sex, age at diagnosis, period of diagnosis and education (HR: 8.03, 95% CI: 2.14–30.1) (Table 3). Patients with an unknown ASA-score had a higher risk of angina pectoris/acute myocardial infarction (HR: 13.8, 95% CI: 1.92–98.8) compared to patients with ASA score I. Beyond 90 days of elective surgery, the risk of angina pectoris/acute myocardial infarction was increased in patients with an ASA-score of III + IV (HR: 3.26, 95% CI: 1.13–9.43), in patients using antihypertensive drugs (HR: 2.09, 95% CI: 1.06–4.13) and in patients using lipid-lowering

Table 3. Identification of risk factors for cardiovascular events for 923 colorectal cancer patients within the first 90 days and beyond 90 days of elective surgery.

		Within 90 days after surgery			Beyond 90 days of surgery		
		Adjusted* HR (95% CI)			Adjusted* HR (95% CI)		
		Acute myocardial infarction /Angina pectoris	HF	Stroke / Transitional cerebral ischemia	Acute myocardial infarction /Angina pectoris	HF	Stroke / Transitional cerebral ischemia
Lifestyle							
BMI	Normal (< 25)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
	Overweight (25–30)	2.95 (0.49–17.8)	1.20 (0.20-–7.21)	0.84 (0.12–5.97)	1.74 (0.77–3.92)	4.49 (1.52–13.2)	1.59 (0.72–3.48)
	Obese (>30)	2.86 (0.59–13.8)	3.18 (0.53–19.2)	NA	2.37 (0.95–5.95)	7.59 (2.42–23.9)	2.57 (1.07–6.16)
Physical activity (MET-score)	4th quartile (Most active)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
	3rd quartile	0.52 (0.05–5.79)	0.70 (0.12–4.21)	NA	0.75 (0.26–2.19)	1.12 (0.42–2.99)	0.82 (0.34–1.98)
	2nd quartile	2.30 (0.45–11.9)	0.69 (0.11–4.13)	0.98 (0.06–15.6)	1.39 (0.57–3.40)	1.39 (0.56–3.48)	1.02 (0.45–2.32)
	1st quartile	2.05 (0.37–11.2)	0.35 (0.04–3.37)	2.25 (0.20–24.95)	1.49 (0.60–3.73)	1.09 (0.41–2.91)	0.57 (0.21–1.55)
Smoking	Never	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
	Former	1.05 (0.23–4.72)	2.55 (0.26–24.9)	0.38 (0.20–24.9)	0.98 (0.42–2.26)	0.97 (0.43–2.20)	0.86 (0.39–1.87)
	Current	1.32 (0.24–4.80)	3.36 (0.37–30.3)	0.48 (0.04 – 4.48)	1.16 (0.51–2.65)	0.72 (0.31–1.69)	0.74 (0.32–1.71)
Alcohol consumption	Moderate consumption	1.00 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
	Abstaining	NA	7.23 (1.29–40.6)	3.85 (0.39–37.8)	0.81 (0.19–3.47)	2.20 (0.74–6.56)	1.03 (0.44–2.39)
	Excessive consumption	0.36 (0.05–2.77)	1.86 (0.34–10.2)	NA	1.10 (0.49–2.45)	1.50 (0.67–3.39)	1.97 (0.67–5.80)
Clinical factors							
Cancer type	Colon	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
	Rectum	0.53 (0.14–1.97)	1.28 (0.30–5.40)	1.88 (0.26–13.5)	1.19 (0.61–2.31)	0.67 (0.32–1.40)	0.79 (0.40–1.55)
Stage at diagnosis	I	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
	II	0.54 (0.14–2.16)	0.53 (0.07–3.78)	0.51 (0.03–8.16)	1.21 (0.48–3.01)	0.93 (0.41–2.18)	1.10 (0.46–2.62)
	III	2.04 (0.66–6.34)	1.39 (0.25–7.61)	1.40 (0.13–15.4)	2.03 (0.83–4.99)	1.08 (0.44–2.61)	1.08 (0.48–2.44)
Surgical access	Laparotomy	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
	Laparoscopy	1.51 (0.39–5.80)	0.24 (0.03–2.18)	1.77 (0.22–14.3)	1.15 (0.32–4–11)	0.33 (0.04–2.89)	1.37 (0.17–10.8)
ASA-score	I	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
	II	1.02 (0.18–5.63)	NA	NA	1.09 (0.51–2.33)	4.23 (1.24–14.4)	1.87 (0.76–4.59)
	III + IV	5.57 (0.99–31.4)	NA	NA	3.26 (1.13–9.43)	15.8 (4.03–61.8)	8.22 (2.87–23.5)
	Unknown	13.8 (1.92–98.8)	NA	NA	1.31 (0.17–10.3)	5.56 (0.57–54.5)	NA
Complications of surgery							
Any surgical complications	No	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
	Yes	1.69 (0.46–6.25)	3.23 (0.78–13.6)	NA	0.87 (0.34–2.27)	1.41 (0.43–4.65)	1.54 (0.70–3.38)
Anastomosis leakage	No	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
	Yes	3.09 (0.67–14.1)	NA	NA	0.87 (0.21–3.64)	2.31 (1.10–4.84)	0.89 (0.21–3.73)
Diabetes	No	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
	Yes	NA	2.47 (0.50–12.4)	2.60 (0.27–25.3)	1.09 (0.38–3.13)	3.39 (1.61–7.17)	1.61 (0.66–3.91)
Lipid-lowering drugs	No	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
	Yes	8.03 (2.14–30.1)	2.97 (0.71–12.5)	2.07 (0.29–14.9)	2.38 (1.25–4.25)	2.20 (1.04–4.66)	2.39 (1.23–4.62)
Antihypertensive drugs	No	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
	Yes	1.66 (0.49–5.58)	4.64 (0.57–37.9)	0.60 (0.08–4.32)	2.09 (1.06–4.13)	1.34 (0.68–2.65)	1.56 (0.78–3.11)
Treatment							
Chemo-therapy**	No	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
	Yes	1.87 (0.36–9.76)	0.78 (0.09–7.15)	NA	0.32 (0.14–0.74)	0.36 (0.15–0.90)	0.78 (0.36–1.68)

HR: hazard ratio; CI: confidence interval.
*Adjusted for sex, age at diagnosis, period of diagnosis and education.
**further adjusted for the stage at diagnosis.
NA indicates not enough events to conduct an analysis.

drugs (HR: 2.38, 95% CI: 1.25–4.25). The long-term risk of having heart failure was increased in patients being overweight (HR: 4.49, 95% CI: 1.52–13.2) or obese (HR: 7.59, 95% CI: 2.42–23.9) compared to normal-weight patients. Heart failure was also statistically significantly associated with having ASA-scores of II and III + IV (HR: 4.23, 95% CI: 1.24–14.4 and HR: 15.8, 95% CI: 4.03–61.8, respectively), postoperative anastomosis leakage (HR: 2.31, 95% CI: 1.10–4.84), having diabetes (HR: 2.31, 95% CI: 1.10–4.84) and using lipid-lowering drugs (HR: 2.20, 95% CI: 1.04–4.66). Risk factors for transitional cerebral ischemia/ischemic stroke beyond 90 days of surgery were ASA-score III + IV (HR: 8.22, 95% CI: 2.87–23.5), use of lipid-lowering drugs (HR: 2.39 95% CI: 1.23–4.62) and obesity (HR: 2.57, 95% CI: 1.07–6.16). Chemotherapy use was associated with statistically significantly diminished HRs for angina pectoris/acute myocardial infarction and heart failure but not transitional cerebral ischemia/ischemic stroke.

Discussion

We observed an increased hazard for incident heart failure in patients with colorectal cancer who underwent elective surgery compared to cancer-free comparisons. Further, we identified BMI, ASA score, and treatment with anti-hypertensive and lipid-lowering drugs, as potential risk factors for incident cardiovascular events among patients with colorectal cancer.

The observed increased HR for heart failure aligns with the findings from a population-based study in the US including 72,408 persons diagnosed with stage I-III colorectal cancer from 2000–2011 and a 1:1 matched population without cancer [14]. In this study, the HR for heart failure in patients with colorectal cancer was 4.06 (95% CI: 4.06–4.33) while for stroke or acute myocardial infarction, the HR was 3.07 (95% CI: 2.98-3.16). The differences between the results may be explained by the higher median age in the US-based population (78 years at diagnosis), a higher proportion of persons with stage III disease (50%), and the fact that the population were Medicare beneficiaries, who in general may be less healthy than the general population. Not all studies have observed an increased risk of cardiovascular disease in patients with colorectal cancer compared to cancer-free comparisons. A Dutch population-based cohort study including 4826 persons, showed no difference in cardiovascular disease between patients with colorectal cancer surviving a minimum 1 year and matched cancer-free comparisons when adjusting for traditional cardiovascular risk factors and cancer treatment [13]. Similar results were seen in another US population-based cohort study of patients surviving more than two years, with incidence rate ratios (IRR) of 0.93 (95% CI: 0.82–1.06) for patients with colon cancer ($N = 2601$), and IRR of 1.02 (95% CI: 0.84–1.25) for patients with rectum/rectosigmoid cancer ($N = 1299$) compared to matched comparisons. The IRRs were adjusted for age, sex, race/ethnicity, cardiovascular risk factors, overweight/obesity and smoking history but neither stage nor treatment [12].

No significant differences in angina pectoris, acute myocardial infarction, transitional cerebral ischemia, and ischemic stroke rates were found between persons with colorectal cancer and cancer-free comparisons in our study. Thus, we cannot rule out the presence of survivor bias in the study. Death is a competing event in the colorectal cancer setting, and the most vulnerable group of patients may die from the disease before experiencing a cardiovascular event. Another explanation could be that patients at high risk of ischemic heart disease were excluded because they had cardiovascular disease before their colorectal cancer diagnosis. Further, being diagnosed with a life-threatening disease may cause positive behavioral changes in patients with colorectal cancer, which may lower the long-term risk of cardiovascular disease in colorectal cancer survivors [31]. It is surprising that we find an association between colorectal cancer and heart failure but no association with angina pectoris or myocardial infarction since heart failure can be a result of cardiac muscle ischemia induced by the surgical stress response. The lack of association between colorectal cancer and myocardial infarction or angina pectoris could be explained by missed registration due to silent myocardial infarction, which is well described postoperatively [32]. However, other conditions cause heart failures such as rhythm disorder, anaemia and heart muscle defect, all conditions affected by physical stress like surgery [33].

In line with our results on having diabetes, and use of antihypertensive drugs and lipid-lowering drugs, Kenzik et al. found that preexisting cardiovascular comorbidities such as hypertension, hypercholesterolemia, and diabetes, significantly increased the risk of cardiovascular disease with HRs ranging from 1.05 to 1.51 in patients diagnosed with colorectal cancer from 2000–2011 (14). Further, we observed an increased risk of all cardiovascular outcomes beyond 90 days of elective surgery with HRs between 3.26 and 15.8 for patients with an ASA-score of III + IV, and an increased risk of anastomotic leakage within 90 days after surgery. We do not know of any previous studies that have investigated these surgery-related factors in relation to the risk of cardiovascular events among patients with colorectal cancer.

We observed a lower risk for all cardiovascular outcomes with the use of chemotherapy beyond 90 days of surgery. Similar results were observed by Kenzik et al. [14], who compared patients receiving 5-FU only, capecitabine only, or other chemotherapy to patients who had not received chemotherapy and showed significantly lower HRs for both 5-FU (HR: 0.58, 95% CI: 0.55–0.62) and other chemotherapy (HR: 0.84, 95% CI: 0.78–0.90), 2000–2011. These results may indicate that the long-term effect of chemotherapy, if present, is more difficult to document, due to selection bias, that is only the healthiest patients are selected for treatment. The findings appear to suggest that chemotherapy has a protective effect on the risk of cardiovascular events when the opposite is likely the case. Furthermore, the patients with severe cardiovascular comorbidity who do not receive chemotherapy might increase the HR of cardiovascular events in the unexposed group.

Lifestyle factors as predictors were analyzed in a longitudinal Australian study of patients with colorectal cancer ($N = 1966$) aged 20–80 years at diagnosis. Here, obesity predicted de novo hypertension (OR: 2.20, 95% CI: 1.09–4.45) and diabetes (OR: 6.55, 95% CI: 2.19–19.53) three years after colorectal cancer diagnosis [34]. Further, television viewing, a proxy for a sedentary lifestyle, predicted ischemic heart disease at three years post-diagnosis (OR: 5.51, 95% CI: 1.86–16.34) [34]. In line with this, we observed a significantly increased risk of heart failure with overweight and obesity, and an increased risk of transitional cerebral ischemia/ischemic stroke in patients with obesity, which may reflect that this subgroup of patients could benefit from interventions targeting weight loss and increasing physical activity.

Interestingly, anastomotic leakage is significantly associated with heart failure 90 days postoperatively with an HR of 2.31 (95%CI: 1.10–4.84). It may reflect confounding by indication in the sense that patients likely to get anastomotic leakage are also likely to get heart failure due to the same risk factors. In that light, the results are not that surprising. However, anastomotic leakage induces a stress response which increases the risk of endothelial dysfunction and

thromboembolism. This could also explain an increased long-term risk of heart failure [35].

The strengths of our study include the access to individual-level information for both patients with colorectal cancer and the matched cancer-free comparisons on shared risk factors including lifestyle factors that could confound the association between colorectal cancer and cardiovascular events. The information on lifestyle was collected independently of cancer status and is therefore not prone to recall bias caused by the cancer diagnosis. Further, we are the first to include information on prescribed cardiovascular drugs as a proxy for cardiovascular comorbidity and risk conditions before colorectal cancer, which is especially relevant in adult-onset cancer patients where age-related cardiovascular problems are common. We also had information on oncological treatment and included this in a time-dependent manner, thus correctly defining the onset of chemotherapy and avoiding misclassification of time at risk for unexposed and exposed patients. On the other hand, the lack of information on type of chemotherapy and doses received precluded potential dose-response analyses, which is a limitation. Notably, we had a relatively small sample size and few cardiovascular events, which affected the statistical power to detect differences between patients with colorectal cancer and the cancer-free comparisons. However, the findings of our study align with those of larger cohort studies. Death as a competing event is an inevitable challenge in observational cancer studies, and we cannot rule out those patients who are prone to cardiovascular events who die from their cancer or treatment, which would lead to an underestimation of the risk of cardiovascular events in the colorectal cancer population. The observed increased HR for cardiovascular outcomes among patients who underwent laparoscopy may seem counterintuitive in relation to the hypothesis of surgical stress compromising cardiovascular function in laparotomy. However, 27% of those who had a laparotomy died during follow-up which was only the case for 11% in the laparoscopy group (data not shown). Results might also reflect that patients at high risk of complications are not selected for laparotomy. One may wonder if the risk of cardiovascular events is higher with open surgery.

Participants in the DCH cohort experience better survival than the background population in general [36]. Lack of variance may hamper the detection of differences that might have been found in a general population sample. The results should be interpreted with caution, and generalization limited to patients similar to those included in this study.

In conclusion, we found an increased hazard for heart failure in patients with colorectal cancer after 90 days from elective surgery compared to matched cancer-free comparisons. We identified several risk factors for cardiovascular events within 90 days after surgery including high ASA score, overweight/obesity, and the presence of cardiovascular risk conditions or comorbidity at the time of the cancer diagnosis. The findings from our study suggest that focused attention should be given to patients with high cardiac risk and compromised physical status at the time of surgical planning. Prehabilitation efforts have shown promising results in this patient group [37–38]; however, this has yet to be studied with the association of cardiovascular disease, in terms of mediating severity or incidence as the outcome of interest. If the patients at high risk of cardiovascular events are identified postoperatively, it would be interesting to follow this group closely and offer interventions preventive for heart failure. This could be lifestyle changes and treatment of conditions potentially increasing the risk of heart failures such as high blood pressure, rhythm disorders, anemia, and hyperlipidemia [33]. Future research is needed in larger study samples to determine the relative importance of these risk factors and further investigate if and how chemotherapy is associated with an increased long-term risk of cardiovascular events.

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Data availability statement

The data that support the findings of this study are available upon reasonable request from the corresponding author. The data are not publicly available as they contain information that could compromise the privacy of research participations.

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