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ORIGINAL ARTICLE

Risk of heart failure among colon and rectal cancer survivors: a population-based case–control study

Josephina G. Kuiper[1,2*], Myrthe P.P. van Herk-Sukel[3], Valery E.P.P. Lemmens[2,4], Mathijs J. Kuiper[5], Ernst J. Kuipers[6] and Ron M.C. Herings[1,7]

[1]*PHARMO Institute for Drug Outcomes Research, Van Deventerlaan 30-40, Utrecht, 3528 AE, The Netherlands;* [2]*Department of Public Health, Erasmus University Medical Center, Rotterdam, The Netherlands;* [3]*Department of Internal Medicine and Dermatology, University Medical Center Utrecht, Utrecht, The Netherlands;* [4]*Netherlands Comprehensive Cancer Organisation (IKNL), Utrecht, The Netherlands;* [5]*Department of Cardiology, Haga Hospital, The Hague, The Netherlands;* [6]*Department of Gastroenterology and Hepatology, Erasmus University Medical Center, Rotterdam, The Netherlands;* [7]*Department of Epidemiology and Data Science, Amsterdam University Medical Center, Amsterdam, The Netherlands*

Abstract

Aims This population-based case–control study aims to investigate the occurrence of heart failure (HF) among colon and rectal cancer survivors compared with a cancer-free control population taking into account pre-existing cardiovascular risk factors and the influence of treatment.

Methods and results Colon and rectal cancer survivors diagnosed between 2007 and 2014 were selected from a linked cohort of cancer and primary care data in the Netherlands and matched based on gender, birth year, general practitioner (GP) practice, and follow-up period to cancer-free controls. The occurrence of HF was identified based on GP recorded diagnoses after index date (diagnosis date for cases). A Cox proportional hazards model was used to estimate hazard ratios (HRs), adjusted for age, sex, hypertension, diabetes, and hypercholesterolaemia. A total of 5333 colon cancer cases and 2468 rectal cancer cases could be matched to a total of 31 204 cancer-free controls. A statistically significant increased risk of HF was seen among all cases compared with cancer-free controls (HR 1.33; 95% confidence interval: 1.12–1.59). This was also seen when analysing colon cancer and rectal cancer separately. Being diagnosed with stage IV cancer, having hypertension, or having hypercholesterolaemia statistically significantly increased the risk of HF among colon cancer. Hypertension was a statistically significant risk factor for developing HF among rectal cancer cases.

Conclusions Colon and rectal cancer survivors are at increased risk for developing HF. More awareness should be created by treating physicians and GPs for this potential increased risk in order to further improve survival.

Keywords Colorectal cancer; Heart failure; Case–control; Netherlands

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**Correspondence to: Josephina G. Kuiper, PHARMO Institute for Drug Outcomes Research, Van Deventerlaan 30-40, 3528 AE Utrecht, The Netherlands.*
Email: josine.kuiper@pharmo.nl

Introduction

The number of new colorectal cancer cases is increasing globally, but the mortality rates are declining in many developed countries.[1] In the Netherlands, the colorectal cancer death rate declined from 21.1 per 100 000 person-years (PY) in 2010 to 16.3 per 100 000 PY in 2019.[2] The early detection of colorectal cancer and novel developments in treatment approaches are contributing to the improved cancer survival rates.[3] Due to the improved survival, many colorectal cancer survivors are dealing with the late effects of cancer and its treatment, such as physical and psychosocial impairment that negatively influence quality of life.[4] In addition, colorectal cancer survivors have a high risk for developing other chronic diseases, including, for example, cardiovascular disease (CVD). Capecitabine and 5-fluorouracil (5-FU) are key chemotherapeutic agents in the treatment of gastrointestinal cancers, including colorectal cancer.[5] Both agents may potentially induce acute cardiotoxicity with heart failure (HF) being one of the most serious consequences.[6] Furthermore, several clinical trials showed an increased risk of HF among rectal patients receiving radiation therapy.[7] Population-based studies

determining this association are scarce and are mainly determined among breast cancer patients who are receiving radiotherapy in the area of the heart.

Although CVD has many different manifestations, only few studies examined the association between cancer and the risk of specific CVD outcomes. Specifically, the relationship between colorectal cancer and the occurrence of HF is limited and the current evidence shows conflicting results. In a study among patients age older than 65 years with colorectal cancer not yet spread to other organs or parts of the body, the 10 year cumulative incidence of HF was 54.5% among colorectal cancer patients compared with 18% among controls.[8] A higher risk was observed among older patients and those with pre-existing multimorbidity, such as diabetes and hypertension. However, in a study among 14 216 colorectal cancer survivors in the UK, no increased risk for HF was found.[9] The latter study did not control for pre-existing or concurrent multimorbidity. This information is particularly valuable for survivorship care in order to improve the long-term outcomes of high-risk populations.

The aim of this study is to investigate the occurrence of HF among colon and rectal cancer survivors compared with a cancer-free control population. Furthermore, we aim to assess whether the occurrence of HF differ by received cancer treatment and pre-existing cardiovascular risk factors.

Methods

Data sources

Data for this population-based case–control study were obtained from a cohort of patients with linked data from the GP Database of the PHARMO Database Network and the Netherlands Cancer Registry (NCR): the PHARMO GP-NCR cohort. Details on the formation of this cohort can be found elsewhere.[10]

In short, the PHARMO GP Database comprises data from electronic patient records registered by general practitioners (GPs). The records include information on diagnoses and symptoms, laboratory test results, referrals to specialists, and healthcare product/drug prescriptions. The prescription records include information on type of product, prescription date, strength, dosage regimen, quantity, and route of administration. At the moment of conducting this study, the PHARMO GP Database included all electronic healthcare dossiers of 1157 GPs from 754 different GP practices across the Netherlands with a defined catchment area of 2.5 million inhabitants. Information regarding the incidence and detailed diagnoses of colorectal cancer in the PHARMO GP Database, especially with respect to the incidence and details on tumour characteristics, is limited. This information was obtained from the NCR, which is a national population-based registry maintained by the Comprehensive Cancer Centre of the Netherlands (IKNL) and comprises information on newly diagnosed cancer patients in the Netherlands. As all citizens are registered with a GP in the Netherlands, except those living in a nursing home or hospice, primary care information of patients included in the PHARMO GP-NCR cohort can be considered complete.

Colorectal cancer survivors and cancer-free controls selection

From the linked PHARMO GP-NCR cohort, all patients who were diagnosed with a primary tumour of colon cancer {included the caecum and appendix [International Classification of Diseases (ICD) 10-CM code C18.0 and C18.1], right colon [ICD 10-CM C18.2 and C18.3], the transverse colon [ICD 10-CM C18.4], the left colon [ICD 10-CM C18.5, C18.6, and C18.7], and other [ICD 10-CM C18.8 and C18.9] or rectal cancer [ICD 10-CM code C20]} between 2007 and 2014 were selected. The first diagnosis date was defined as index date. Population controls were selected from the PHARMO GP Database. Each patient with a manifestation of colon or rectal cancer was matched to up to four controls based on gender, birth year, GP practice, and follow-up period in the PHARMO Database Network. Matched controls received the same index date as their matched case with cancer. Controls could not be matched more than once.

Heart failure outcome

The outcome of the study was HF and identified based on a recording of a diagnostic code for HF [International Code for Primary Care (ICPC) code K77] and free-text searches (i.e. HF recorded as note, but not accompanied with an ICPC code) within the PHARMO GP Database. It is possible that a GP records HF without a confirmation of the diagnoses by a cardiologist, which results in false-positive cases.[11] In order to limit the number of false-positive cases, the text accompanied with the diagnostic code as entered by the GP was reviewed. If any denials were present such as words as 'probably', 'possible', 'maybe', or question marks, the diagnosis was not taken into account. Furthermore, a sensitivity analysis was performed in which a lag time of 12 months was applied between index date and the start of follow-up for identifying HF. HF identified in the first year may not be related to the treatment received given the fact that patients usually finish their treatment after 1 year. A second sensitivity analysis was performed in which only patients with a prescription (ever) for a drug indicated for HF and commonly prescribed to patients with confirmed HF in the Netherlands during the study period were taken into account.[12–15] These drugs included angiotensin-converting enzyme (ACE) inhibitors (ATC code

C09), diuretics [ATC code C03, including loop diuretics (ATC code C03CA02 and C03CA01) and spironolactone (ATC code C03DA01)], and digoxin (ATC code C01AA05).

Risk factors for heart failure

The following risk factors for HF were identified based on prescribed drugs or a diagnostic code recorded by a GP in the 12 months before index date: hypertension, diabetes, and hypercholesterolaemia. Patients with a diagnostic code for elevated blood pressure, uncomplicated hypertension, or hypertension with involvement of target organs (ICPC code K85, K86, or K87, respectively) and/or who had a prescription of antihypertensives, diuretics, or beta-blockers (ATC code C02, C03, C07, C08, and C09, respectively) were defined as having hypertension. Patients were classified as having diabetes when a GP recorded diagnosis of diabetes mellitus was present (ICPC code T90) and/or were prescribed insulin or oral blood glucose lowering drugs (ATC code A10A and A10B). Patients with hypercholesterolaemia were identified based on a diagnostic code for lipid disorders (ICPC code T93) and/or having a prescription for a lipid-lowering drug (ATC code C10).

Demographics and clinical information

Information on age and gender at index date were extracted from the PHARMO GP Database. Tumour staging information [according to the TNM classification developed and maintained by the Union for International Cancer Control (UICC[16])], tumour location, and type of treatment received (chemotherapy, radiotherapy, and surgery) were obtained from the NCR.

Statistical analyses

Baseline characteristics of colon and rectal cancer cases and their matched cancer-free controls were reported descriptively.

Unadjusted incidence rates (IRs) were determined by dividing the total number of events by the total number of PY at risk. A Cox proportional hazards model was used to estimate hazard ratios (HRs) and their corresponding 95% confidence interval (CI). Crude HRs as well as HRs adjusted for age, sex, and risk factors for HF (hypertension, diabetes, and hypercholesterolaemia) were determined. Analyses were performed among colon and rectal cancer combined compared with their matched cancer-free controls and separately for each tumour location. Furthermore, analyses were restricted to colon and rectal cancer cases only in order to identify potential additional risk factors for HF. In all analyses, cases or cancer-free controls with a diagnosis of HF prior to the index date were excluded.

All data were analysed using SAS programs organized within SAS Enterprise Guide Version 7.1 (SAS Institute Inc., Cary, NC, USA) and conducted under Windows using SAS Version 9.4.

Results

Included in the study were 5333 colon cancer cases and 2468 rectal cancer cases matched to a total of 31 204 cancer-free controls (*Table 1*). Rectal cancer cases were slightly younger than colon cancer cases (67.1 years vs. 69.8 years, respectively). Both rectal cancer and colon cancer were more often diagnosed in males (53% and 62%). No differences were seen in the proportion of patients having hypertension, diabetes, or hypercholesterolaemia between colon and rectal cancer cases and their matched cancer-free controls. At the time of initial diagnosis, the majority of all tumours had grown into the outermost layers of the colon or rectal but had not spread to distant sites (stage II and stage III disease both account for more than half of all tumours). More than 80% of the colon and rectal cancer cases underwent surgery. More than one-third of the colon cancer cases received chemotherapy (with or without surgery) and $<$2% received radiotherapy. Radiotherapy alone or in combination with chemotherapy was seen in 71% of the rectal cancer cases.

Table 2 shows the IR of HF among both colon cancer and rectal cancer cases combined as well as for colon cancer and rectal cancer separately compared with cancer-free controls stratified by gender and age. Overall, the incidence of HF was 6.14 per 1000 PY (95% CI: 5.21–7.19) among all cases and 5.09 per 1000 PY (95% CI: 4.70–5.51) among cancer-free controls. After adjustment for potential confounders, a statistically significant increased risk of HF was seen among all cases compared with cancer-free controls (HR 1.33; 95% CI: 1.12–1.59). When stratifying by gender, a statistically significant increased risk of HF was seen in both men and women, but there was a higher risk of HF seen in women than in men (HR 1.42; 95% CI: 1.09–1.84 vs. HR 1.27; 95% CI: 1.00–1.62).

Results were similar when stratifying by colon cancer and rectal cancer with the highest risk of HF found among rectal cancer cases (HR 1.43; 95% CI: 1.05–1.95).

The risk of HF among colon cancer cases and rectal cancer was stratified by characteristics (*Figure 1*). Characteristics with $<$10 events in any of the categories were not presented in the figures as this results in imprecise estimates (see Supporting Information, *Tables S1* and *S2*). Factors that statistically significantly increased the risk of HF among colon cancer cases included being diagnosed with stage IV colon cancer, having hypertension, and having hypercholesterolaemia. Being 70 years or older and having diabetes also increased the risk

Table 1 Baseline characteristics of colorectal cancer cases and their matched cancer-free controls

Characteristics	Colon cases *N* = 5333	Cancer-free controls *N* = 21 332	Rectal cases *N* = 2468	Cancer-free controls *N* = 9872
Sex, *n* (%)				
Male	2821 (53)	11 284 (53)	1519 (62)	6076 (62)
Female	2512 (47)	10 048 (47)	949 (39)	3796 (39)
Age at index date (years)				
40–49	191 (4)	764 (4)	131 (5)	524 (5)
50–59	626 (12)	2504 (12)	431 (18)	1724 (18)
60–69	1665 (31)	6660 (31)	846 (34)	3384 (34)
70–79	1914 (36)	7656 (36)	792 (32)	3168 (32)
≥80	937 (18)	3748 (18)	268 (11)	1072 (11)
Mean (±SD)	69.8 ± 10.0	69.8 ± 10.0	67.1 ± 10.2	67.1 ± 10.1
Observation time period[a] (years)				
Mean (±SD)	3.2 ± 2.3	4.0 ± 2.3	3.5 ± 2.3	4.1 ± 2.3
Precancer conditions, *n* (%)				
Hypertension	2470 (46)	9879 (46)	1037 (42)	4191 (43)
Diabetes	652 (12)	2446 (12)	273 (11)	1012 (10)
Hypercholesterolaemia	1552 (29)	6451 (30)	668 (27)	2808 (28)
Tumour stage, *n* (%)				
I	999 (19)	N/A	512 (21)	N/A
II	1647 (31)	N/A	457 (19)	N/A
III	1391 (26)	N/A	996 (40)	N/A
IV	1135 (21)	N/A	452 (18)	N/A
Unknown	161 (3)	N/A	51 (2)	N/A
Type of initial treatment received, *n* (%)				
Chemotherapy alone[b]	1876 (35)	N/A	186 (8)	N/A
Radiotherapy alone[b]	25 (<0.5)	N/A	824 (33)	N/A
Chemotherapy and radiotherapy	35 (1)	N/A	927 (38)	N/A
Surgery	4599 (86)	N/A	2018 (82)	N/A

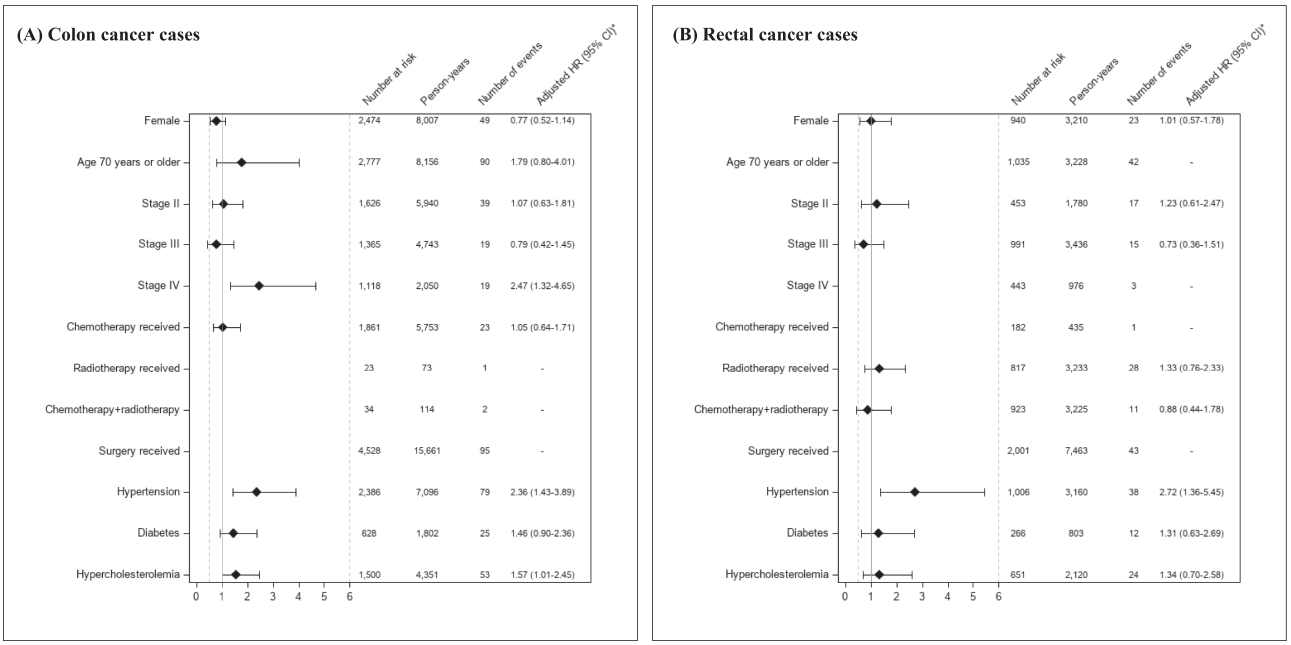
N/A, not applicable; SD, standard deviation.
[a]Defined as the time between date of colorectal cancer diagnosis until the end of data collection in the PHARMO Database Network (i.e. the patient moves out of the PHARMO Database Network catchment area), death, or end of the study period (31 December 2015), whichever occurred first.
[b]With or without surgery.

Table 2 Risk of heart failure among colorectal cancer cases and their matched cancer-free controls, stratified by sex, age, and tumour site

	N Event	PY of follow-up	Incidence rate (95% CI) (per 1000 PY)	*N* Event	PY of follow-up	Incidence rate (95% CI) (per 1000 PY)	Crude HR (95% CI)	Adjusted HR (95% CI)[a]
All	155	25 246	6.14 (5.21–7.19)	629	123 474	5.09 (4.70–5.51)	1.23 (1.03–1.46)	1.33 (1.12–1.59)
Sex								
Male	83	13 875	5.98 (4.76–7.42)	353	67 279	5.25 (4.71–5.82)	1.16 (0.91–1.47)	1.27 (1.00–1.62)
Female	72	11 370	6.33 (4.95–7.97)	276	56 195	4.91 (4.35–5.53)	1.31 (1.01–1.70)	1.42 (1.09–1.84)
Age at index date								
Age < 70	25	14 108	1.77 (1.15–2.62)	89	65 990	1.35 (1.08–1.66)	1.34 (0.86–2.08)	1.39 (0.89–2.16)
Age ≥ 70	140	11 968	11.70 (9.84–13.80)	576	62 252	9.25 (8.51–10.04)	1.29 (1.07–1.56)	1.34 (1.11–1.61)
Colon	104	16 874	6.16 (5.04–7.47)	440	83 706	5.26 (4.78–5.77)	1.19 (0.96–1.48)	1.29 (1.04–1.60)
Sex								
Male	55	8757	6.28 (4.73–8.18)	243	43 119	5.64 (4.95–6.39)	1.13 (0.84–1.51)	1.24 (0.92–1.66)
Female	49	8117	6.04 (4.47–7.98)	197	40 587	4.85 (4.20–5.58)	1.27 (0.93–1.74)	1.35 (0.99–1.85)
Age at index date								
Age < 70	14	8607	1.63 (0.89–2.73)	52	40 671	1.28 (0.95–1.68)	1.27 (0.70–2.30)	1.31 (0.73–2.37)
Age ≥ 70	90	8267	10.89 (8.75–13.38)	388	43 035	9.02 (8.14–9.96)	1.24 (0.98–1.56)	1.29 (1.02–1.62)
Rectal	51	8371	6.09 (4.54–8.01)	189	39 768	4.75 (4.10–5.48)	1.31 (0.96–1.78)	1.43 (1.05–1.95)
Sex								
Male	28	5118	5.47 (3.63–7.91)	110	24 160	4.55 (3.74–5.49)	1.22 (0.81–1.85)	1.34 (0.89–2.04)
Female	23	3254	7.07 (4.48–10.61)	79	15 608	5.06 (4.01–6.31)	1.41 (0.89–2.25)	1.55 (0.97–2.47)
Age at index date								
Age < 70	9	5099	1.76 (0.81–3.35)	35	23 215	1.51 (1.05–2.10)	1.22 (0.58–2.53)	1.33 (0.64–2.77)
Age ≥ 70	42	3272	12.84 (9.25–17.35)	154	16 553	9.30 (7.89–10.89)	1.41 (1.00–1.98)	1.46 (1.04–2.06)

CI, confidence interval; HR, hazard ratio; PY, person-years.
[a]Adjusted for age, sex, hypertension, diabetes, and hypercholesterolaemia.

Figure 1 Risk of heart failure among (A) colon cancer cases and (B) rectal cancer cases stratified by characteristics. CI, confidence interval; HR, hazard ratio.



of HF, but this was not statistically significant. Among rectal cancer cases, having hypertension was statistically significantly associated with an increased risk of HF. An increased risk was also seen among those diagnosed with stage II, receiving radiotherapy, and having diabetes or hypercholesterolaemia, although this did not reach statistically significance.

Results were in the same direction when applying a lag time of 12 months between index date and the start of follow-up for identifying HF, although the HRs were slightly lower compared with the primary analysis. An overall HR of 1.21 was seen (95% CI: 0.98–1.49), which was 1.14 (95% CI: 0.88–1.47) for colon cancer and 1.35 (95% CI: 0.95–1.93) for rectal cancer.

Restricting the analyses to HF cases with a prescription for a drug indicated for HF and often used in common practice resulted in a loss of a total of 21 HF cases. Among those treated for HF, almost all received a diuretic (94%) of which the majority received a loop diuretic (90%). The use of an ACE inhibitor was seen in 80% of the HF cases. About a quarter received digoxin (24%) and spironolactone was used among 36% of the HF cases. Restricting the analyses to those receiving a drug commonly used for treating HF did not alter the results.

Discussion

This population-based case–control study showed a statistically significant increased risk of HF in both colon and rectal cancer cases compared with a population without cancer. This risk was higher among females compared with males. Having hypertension significantly increased the risk of HF among both colon and rectal cancer cases. Additional risk factors in our study that significantly increased the risk of HF among colon cancer cases were stage IV cancer and having hypercholesterolaemia before index date.

Previous studies mainly focused on composite CVD instead of analysing the different types of CVD separately or investigated the risk of HF among cancer patients overall and no specific site of cancer.[17–20] Only a few investigated the risk of HF among colorectal cancer patients specifically. Similar to our study, a previous study among individuals with incident stage I to III colorectal cancer of 65 years or older also found an increased risk of HF.[8] More than a three-fold increased hazard of HF was found in this study, which is much higher than in ours. Our study included a younger population, and as HF is predominantly a disorder of the elderly, this might partially explain the lower rate found in our study. Furthermore, we might have underestimated the number of cases with an HF diagnosis resulting in a lower, but increased, risk. They found that hazards were significantly greater among colorectal cancer cases receiving radiotherapy. We also found a higher risk of HF among rectal cancer receiving radiotherapy, although not statistically significant. In previous randomized control trials, rectal cancer patients receiving radiotherapy had an increased risk of HF compared with rectal cancer patients not receiving radiotherapy.[7] Population-based studies determining the association

between non-chest radiotherapy-induced HF among rectal cancer patients specifically are scarce. Present knowledge of the underlying biological mechanisms is insufficient and differs per type of CVD and dose of radiation.[21,22] In a study among Japanese atomic bomb survivors, HF was showed to be associated with exposure to low dose of radiation, while no increased risk was seen for myocardial infarction.[23] Although this was not specifically determined among rectal cancer patients, it might explain the increased risk we are seeing among stage II rectal cancer, who are usually treated with a lower dose of radiation compared with stage III and stage IV.

Although 5-FU and capecitabine, the key chemotherapeutic agents in the treatment of colon and rectal cancer, have been shown to potentially induce cardiotoxicity,[6] we however did not find a higher risk of HF among those treated with chemotherapy and lacked detailed information about type of systemic therapy. In the study by Kenzik *et al*.,[8] type of chemotherapy was available and they showed that receiving 5-FU alone or capecitabine alone did not increase the risk of HF compared with those not receiving chemotherapy. Surprisingly, receiving 5-FU alone even lowered the risk of HF. Other studies that determined the association between colorectal cancer and the risk of HF found no evidence of a relationship.[9,17,18]

We did found an increased risk of developing HF among cases diagnosed with stage IV colon cancer. A higher risk of HF among patients with advanced cancer has been seen in other studies assessing the association between cancer and risk of HF as well.[24] There are several explanations for this finding. For example, the enzymes and proteins released by tumours may activate blood clotting and this mechanism may be more prominent in patients with advanced disease stage resulting in a higher risk of HF.[25] Furthermore, the PY of follow-up among patients with stage IV colon cancer was lower compared with patients with stage I–III colon cancer in our study. This can be explained by the fact that patients with stage IV colon cancer often do not receive surgery and are therefore more likely to die from their cancer than from heart disease.

There is a synergistic link between CVD, including HF, and cancer through shared modifiable risk factors and underlying pathophysiological mechanisms.[26,27] In our study, no differences were seen in the prevalence of precancer conditions such as hypertension, diabetes, and hypercholesterolaemia between colorectal cancer cases and cancer-free controls. However, these individual cardiovascular risk factors, and especially hypertension, in a cancer survivor appear to carry greater risk than hypertension in an individual without a history of cancer. This is likely the result of receiving adjuvant therapies that can cause or worsen hypertension and thereby increases the risk of HF.[28] Also, hypertension and cancer have a number of common risk factors, including smoking and obesity. We unfortunately did not have information on smoking and obesity and were unable to correct for these confounders. The prevalence of smokers and obese patients is probably higher among those with hypertension and having more risk factors will even enhance the risk of HF.

Some limitations should be considered. First, a diagnosis of HF was based on a GP recorded diagnosis only. This might have resulted in some false-positive classifications of HF. We did not have information on echocardiography to confirm the diagnosis. To minimize the inclusion of false-positive cases, the free-text notes of the GP were reviewed and denials as well as uncertain diagnosis were excluded. Furthermore, we performed a sensitivity analysis excluding those cases not receiving treatment indicated for HF and commonly used in practice. The treatment pattern we saw among the included cases was in line to what is seen among the group of HF patients treated by a cardiologist.[12] It can therefore be speculated that the majority of the HF cases included in this study population have a confirmed HF diagnosis by a cardiologist. However, some false-positive classifications of HF may still exist. Second, we missed information from patients in nursing homes or hospices. The risk of HF found in the current population might therefore be underestimated. Third, we missed information on physical activity, body mass index, and smoking status, which are important risk factors for developing HF. We did had this information recorded for ~30% of the patients, but as this information is more frequently assessed among high-risk populations like diabetic patients, we did not want to limit our study population to a specific group of patients having this information available and thereby overestimate the risk of HF. Fourth, we did not have information on cancer recurrence and potential treatment received for recurrence, which can subsequently increase the risk of HF. Thereby, the NCR records treatment received during the first 6 months after diagnosis and no information after this period is available or specifics about the type of chemotherapy received. At last, according to the information registered in the NCR, some colon cancer cases received radiotherapy, which is not standard treatment for this group. Because the NCR is a population-based database, there are always a number of special cases that receive a different treatment than you would expect based on the guideline. It could be, for example, that patients are diagnosed in the hospital as rectal cancer (and therefore received radiotherapy), but who are registered as a colon cancer case in the NCR on the basis of definitions.

One of the major strengths of our study is the inclusion of a large population of colon and rectal cancer patients. To the best of our knowledge, this is the first study assessing the risk of HF separately for colon and rectal cancer patients. It is important to treat those cancers separately given the different treatment strategies and thereby differences in the risk of developing HF. By using data from the NCR, we had detailed information on tumour characteristics such as tumour stage and the power to stratify by important cardiovascular risk

factors. This is also one of the few studies that specifically looked at HF instead of the risk of CVD as a whole.

In conclusion, patients with colon and rectal cancer have an increased risk of HF compared with those without cancer. Among rectal cancer cases, the risk of HF statistically significantly increases when having hypertension. This was also the case for colon cancer in addition to having hypercholesterolaemia or being diagnosed with stage IV colon cancer. Although these findings might not have an impact on the treatment of colorectal cancer given the far-reaching consequences of leaving colorectal cancer untreated, more awareness of this potential risk should be created on the long term. In current guidelines for the primary prevention of CVD, the risk in the general population and among those with specific comorbidities is discussed, but cancer patients are not specifically mentioned. Especially GPs play an important role in the early prevention and detection of HF among cancer survivors, and more awareness of this potential risk should be created in order to further improve survival and eliminate the risk of dying from other diseases than cancer.

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Conflict of interest

Josephina G. Kuiper and Ron M.C. Herings are employees of the PHARMO Institute for Drug Outcomes Research. This independent research institute performs financially supported studies for government and related healthcare authorities and several pharmaceutical companies.

Myrthe P.P. van Herk-Sukel, Valery E.P.P. Lemmens, Ernst J. Kuipers, and Mathijs J. Kuiper declare that they have no conflict of interest.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Risk of heart failure among colon cancer cases stratified by characteristics.
Table S2. Risk of heart failure among rectal cancer cases stratified by characteristics.

References

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