Incident Cardiovascular Diseases Among Survivors of High-Risk Stage II–III Colorectal Cancer: A Cluster-Wide Cohort Study

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ABSTRACT

Background: The incidence and survival of colorectal cancer (CRC) are increasing. There is an increasing number of long-term survivors, many of whom are elderly and have comorbidities. We conducted a population-based study in Hong Kong to assess the long-term cardiovascular disease (CVD) incidence associated with adjuvant fluoropyrimidine-based chemotherapy among CRC survivors. **Patients and Methods:** Using the population-based electronic medical database of Hong Kong, we identified adults who were diagnosed with high-risk stage II–III CRC and treated with radical surgery followed by adjuvant fluoropyrimidine-based chemotherapy between 2010 and 2019. We evaluated the cause-specific cumulative incidence of CVD (including ischemic heart disease, heart failure, cardiomyopathy, and stroke) using the flexible parametric competing risk modeling framework. The control group without a history of CVD was selected from among a noncancer random sample from primary care clinics in the same geographic area. **Results:** We analyzed 1,037 treated patients with CRC and 5,078 noncancer controls. The adjusted cause-specific hazard ratio (HR) for CVD in the cancer cohort compared with the control group was 2.11 (95% CI, 1.39–3.20). The 1-, 5-, and 10-year cause-specific cumulative incidences were 2.0%, 4.5%, and 5.4% in the cancer cohort versus 1.2%, 3.0%, and 3.8% in the control group, respectively. Age at cancer diagnosis (HR per 5-year increase, 1.16; 95% CI, 1.08–1.24), male sex (HR, 1.40; 95% CI, 1.06–1.86), comorbidity (HR, 1.88; 95% CI, 1.36–2.61 for 1 comorbidity vs none, and HR, 6.61; 95% CI, 4.55–9.60 for ≥2 comorbidities vs none), diabetes (HR, 1.38; 95% CI, 1.04–1.84), hypertension (HR, 3.27; 95% CI, 2.39–4.50), and dyslipidemia/hyperlipidemia (HR, 2.53; 95% CI, 1.68–3.81) were associated with incident CVD. **Conclusions:** Exposure to adjuvant fluoropyrimidine-based chemotherapy was associated with an increased risk of CVD among survivors of high-risk stage II–III CRC. Cardiovascular risk monitoring of this group throughout cancer survivorship is advisable.

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Background

A general decline in mortality in colorectal cancer (CRC) in recent decades is attributed to improvements in treatment, changing patterns in CRC risk factors, and screening.[1,2] CRC is the one of the most common cancers among cancer survivors in the United States, where there are >1.2 million CRC survivors,[3,4] most of whom are aged >60 years.[5] Although surgery is the mainstay of treatment for early-stage disease, fluoropyrimidines, which include 5-FU and its oral prodrug capecitabine, are commonly used in adjuvant or neoadjuvant chemotherapy.[6]

Among conventional cytotoxic agents, 5-FU is the most common one that causes cardiotoxicity, second only to anthracyclines.[7] Symptomatic acute cardiotoxicity occurs in up to 20% of patients treated with 5-FU and in

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up to 35% of patients treated with capecitabine.[8] However, there is limited evidence regarding the magnitude of long-term cardiovascular disease (CVD) risk related to adjuvant chemotherapy for CRC.

Further compounding these risks, most CRC survivors are elderly and have comorbidities.[9,10] In particular, the presence of factors such as obesity, tobacco exposure, and hypertension may increase the overall risk of CVD.[4,11,12] Therefore, we conducted a population-based study in the New Territories West region of Hong Kong to assess the adjuvant fluoropyrimidine-based chemotherapy–related long-term CVD incidence among CRC survivors, adjusting for treatment regimens and doses, comorbidities, sociodemographic information, and their interactions.

Patients and Methods

Data Source, and Case and Outcome Definitions

Data were retrieved from the Clinical Data Analysis and Reporting System (supplemental eAppendix 1, available with this article at JNCCN.org). We identified patients diagnosed with high-risk stage II–III colorectal adenocarcinoma treated with curative surgical operations followed by adjuvant chemotherapy between January 1, 2010, and December 31, 2019, in the New Territories West region of Hong Kong. Figure 1 shows study criteria and the final number of patients in the study cohort.[13] The composite primary outcome was incident CVD after CRC diagnosis index date, including ischemic heart disease, heart failure, cardiomyopathy, and stroke clinically diagnosed during inpatient hospital visits or as the cause of death after cancer diagnosis (ICD-9-CM codes in supplemental eTable 1). The validity of ICD-9-CM codes has been compared with that of ICD-10 codes, showing strong consistency.[14] Prior studies from Hong Kong also showed high accuracy of ICD-9-CM codes in capturing various clinical conditions.[15–18] Although Hong Kong has been transitioning to ICD-10 in the past few years, ICD-9-CM codes were used more frequently than ICD-10 for clinical records and administrative data during the study period; therefore, we used ICD-9-CM for data abstraction. Patients were excluded if they (1) had unknown demographic data or were aged <18 years, (2) developed CVD before the CRC diagnosis, or (3) had not received adjuvant chemotherapy for CRC.

Treatment Information

Generally, adjuvant chemotherapy is offered to patients who have stage II disease with risk factors or stage III disease. The possible adjuvant chemotherapy regimens are capecitabine alone, 5-FU alone, CAPOX (capecitabine/oxaliplatin), and FOLFOX (leucovorin/5-FU/oxaliplatin). Other treatment data included the number of cycles and any dose reduction.

Preexisting Cardiovascular Risk Factors, Comorbidities, and Other Variables

We retrieved data on the preexisting cardiovascular risk factors, including hypertension, dyslipidemia, diabetes, comorbidities, chronic obstructive pulmonary disease (COPD) or smoking, and alcohol-related diseases, using a combination of ICD-9-CM codes and the prescription of medications as appropriate (supplemental eTable 2 and

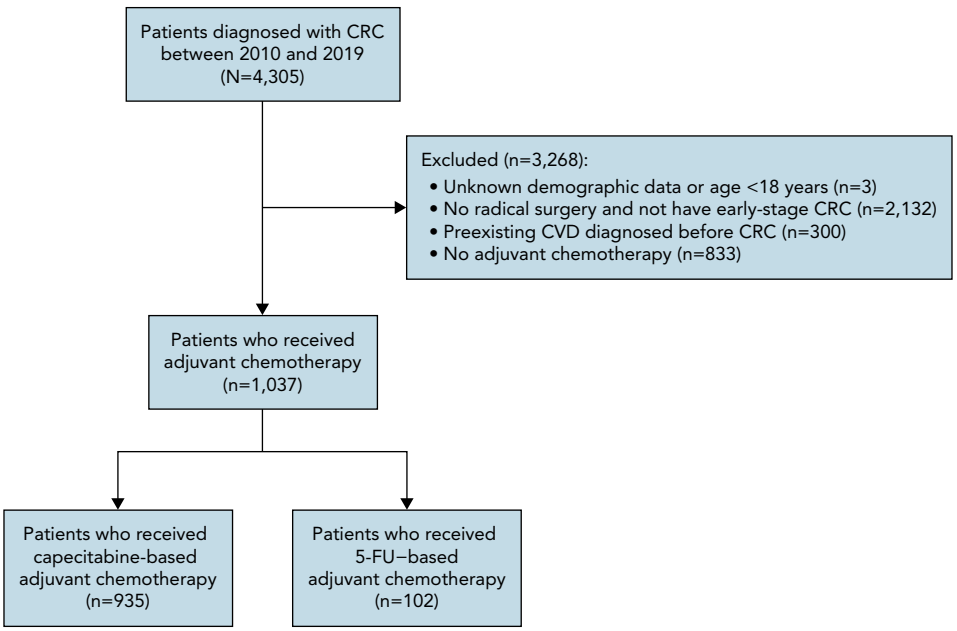

Figure 1. Flowchart outlining inclusion and exclusion criteria for final study cohort of patients with CRC who received adjuvant chemotherapy.
Abbreviations: CRC, colorectal cancer; CVD, cardiovascular disease.

eAppendix 2).[19–21] We regarded the need for medical fee waiver as a surrogate for lower socioeconomic status.

Control Group

The external comparison control group was selected from among a noncancer random sample from primary care clinic registries. The external control group might represent the CVD risk in the overall population. From among 50,782 eligible adult patients in primary care, we selected a random sample of 10%, so that the case/control ratio was 1:5 (supplemental eFigure 1). The external comparison group had no history of cancer or CVD at baseline (ie, January 1, 2010) verified using ICD-9-CM codes (ie, 140–239 for cancer; CVD codes are detailed in supplemental eTable 1). Both the CRC and control groups were retrieved from the same geographic district of Hong Kong.

Statistical Analysis

We describe statistics for demographics, follow-up duration, and prevalence of characteristics. Continuous variables are presented as medians with interquartile ranges (IQRs), and differences in patient and control status were assessed using rank-sum tests. Categorical variables are presented as percentages, and differences in patient and control status were assessed using chi-square tests.

We hypothesized that exposure to fluoropyrimidine in the adjuvant setting determines the differences in CVD outcomes between patient and external control groups. We dealt with the competing risks of death and derived cause-specific hazard ratios (HRs) based on a cause-specific hazard framework (ie, censoring death when assessing CVD risk by cancer treatment).[22–27] Details of the competing risk analysis are provided in supplemental eAppendix 3. Statistical analyses were performed using Stata, version 16.1 (StataCorp LLC).[28,29]

Results

The characteristics of the cancer cohort (n=1,037) and the control group (n=5,078) are detailed in Table 1. Median age at diagnosis for the cancer cohort was 62 years (IQR, 56–68 years); 63.6% were male. As of October 31, 2021, the median follow-up from the index date for the entire cancer survivor cohort was 5.7 years (IQR, 3.5–8.2 years), providing 5,135 person-years of follow-up. Beyond 2 months from diagnosis, 41 (3.9%) of the patients with CRC developed CVD, with a median interval to CVD of 2.3 years (IQR, 0.2–4.4 years). The incidence rate was 9.7 per 1,000 person-years (95% CI, 7.4–12.8 per 1,000 person-years). Among cancer survivors, most deaths were a result of CRC (67.4%). Supplemental eTable 3 provides the characteristics of patients with cancer who received different adjuvant chemotherapy regimens.

Within the cancer cohort, there was a higher proportion of men (63.6% vs 51.6%; $P<.001$), alcohol-related disease (2.6% vs 0.7%; $P<.001$), fewer comorbidities (Royal College of Surgeons [RCS] score 0, 77.6% vs 50.5%; $P<.001$), lower medical fee waiver requirement (13.3% vs 23.2%; $P<.001$), fewer smokers or individuals with COPD (1.8% vs 3.3%; $P=.011$), less diabetes (12.9% vs 32.3%; $P<.001$), and less dyslipidemia or hyperlipidemia (32.6% vs 70.3%; $P<.001$) (Table 1).

Univariable and multivariable analyses are shown in Table 2. Multivariable analysis showed that the use of fluoropyrimidine-based adjuvant chemotherapy among patients with CRC was associated with an approximately 2-fold increase in the risk of CVD compared with the control group (adjusted cause-specific HR, 2.11; 95% CI, 1.39–3.20; $P<.001$). The patients with CRC who had received adjuvant chemotherapy had 1-, 5-, and 10-year cause-specific cumulative incidences (csCIs) of CVD of 2.0% (95% CI, 1.4%–3.0%), 4.5% (95% CI, 3.2%–6.3%), and 5.4% (95% CI, 3.8%–7.5%), respectively. The corresponding csCI estimates for the control group were 1.2% (95% CI, 0.9%–1.5%), 3.0% (95% CI, 2.6%–3.5%), and 3.8% (95% CI, 3.3%–4.4%), respectively (Figure 2).

In the main analysis, we also found that age at cancer diagnosis (HR per 5-year increase, 1.16; 95% CI, 1.08–1.24; $P<.001$), sex (HR for male vs female, 1.40; 95% CI, 1.06–1.86; $P=.020$), RCS comorbidity score (HR for 1 comorbidity vs none, 1.88; 95% CI, 1.36–2.61; $P<.001$; HR for ≥2 comorbidities vs none, 6.61; 95% CI, 4.55–9.60; $P<.001$), diabetes (HR, 1.38; 95% CI, 1.04–1.84; $P=.025$), hypertension (HR, 3.27; 95% CI, 2.39–4.50; $P<.001$), and dyslipidemia/hyperlipidemia (HR, 2.53; 95% CI, 1.68–3.81; $P<.001$) were associated with incident CVD.

The csCI plots of individual CVD endpoints (ischemic heart disease, heart failure, cardiomyopathy, and stroke) adjusted for the same covariates (age, sex, need for medical fee waiver, preexisting cardiovascular risk factors, and RCS comorbidity score) showed a markedly higher csCI of stroke in patients with CRC than in the control group (supplemental eFigures 2–4).

Within the cancer group, the 1-, 5-, and 10-year csCIs of cancer death were 9.1% (95% CI, 6.8%–12.1%), 55.4% (95% CI, 50.5%–60.7%), and 62.5% (95% CI, 57.5%–68.0%), respectively, whereas the 1-, 5-, and 10-year csCIs of other causes of death were 3.8% (95% CI, 2.4%–5.9%), 21.1% (95% CI, 17.3%–25.7%), and 26.0% (95% CI, 21.6%–31.1%), respectively. The ratios of predicted csCI of cancer death and CVD among the cancer cohort at 1, 5, and 10 years were 3.91 (95% CI, 3.72–4.10; $P<.001$), 6.67 (95% CI, 6.64–6.69; $P<.001$), and 5.67 (95% CI, 5.66–5.67; $P<.001$), respectively. The corresponding ratios of other causes of death and CVD in the group at 1, 5, and 10 years were 1.59 (95% CI, 1.54–1.64; $P<.001$), 2.55 (95% CI, 2.54–2.55; $P<.001$), and 2.35 (95% CI, 2.35–2.36; $P<.001$), respectively (Figure 3). The

Table 1. Patient Cohort Characteristics

Characteristic	Total (N=6,115)			Patients With CRC Categorized by CVD (N=1,037)		
	All Patients With CRC n (%)	Control Group[a] n (%)	*P* Value	CVD n (%)	No CVD n (%)	*P* Value
Total, n	1,037	5,078		50	987	
Patient factors						
Age at cancer diagnosis			<.001			<.001
Median (IQR), y	62 (56–68)	59 (53–68)		67 (62–73)	62 (56–68)	
Sex			<.001			.593
Male	659 (63.6)	2,620 (51.6)		30 (60.0)	629 (63.7)	
Female	378 (36.4)	2,458 (48.4)		20 (40.0)	358 (36.3)	
RCS comorbidity score			<.001			<.001
0	805 (77.6)	2,565 (50.5)		25 (50.0)	780 (79.0)	
1 comorbidity	200 (19.3)	2,151 (42.4)		16 (32.0)	184 (18.7)	
≥2 comorbidities	32 (3.1)	362 (7.1)		9 (18.0)	23 (2.3)	
Follow-up time for alive patients			<.001			<.001
Median (IQR), y	5.7 (3.5–8.2)	8.9 (6.8–10.6)		2.8 (0.6–5.9)	5.8 (3.5–8.2)	
Fee waiver recipients (surrogate for lower SES)	138 (13.3)	1,178 (23.2)	<.001	6 (12.0)	132 (13.4)	.780
COPD or smoker	19 (1.8)	169 (3.3)	.011	3 (6.0)	16 (1.6)	.024
Alcohol-related diseases	27 (2.6)	35 (0.7)	<.001	1 (2.0)	26 (2.6)	.786
Diabetes mellitus	134 (12.9)	1,641 (32.3)	<.001	16 (32.0)	118 (12.0)	<.001
Hypertension	219 (21.1)	1,119 (22.0)	.515	26 (52.0)	193 (19.6)	<.001
Dyslipidemia/Hyperlipidemia	338 (32.6)	3,570 (70.3)	<.001	36 (72.0)	302 (30.6)	<.001
Aspirin use	118 (11.4)	1,903 (37.5)	<.001	9 (18.0)	108 (11.0)	.131
β-blocker use	202 (19.5)	927 (18.3)	.355	15 (30.0)	187 (19.0)	.054
Calcium channel blocker use	343 (33.1)	2,089 (41.1)	<.001	19 (38.0)	324 (32.8)	.448
ACE inhibitor use	218 (21.0)	924 (18.2)	.033	22 (44.0)	196 (19.9)	<.001
ARB use	39 (3.8)	131 (2.6)	.035	4 (8.0)	35 (3.6)	.106
Diuretic use	717 (69.1)	715 (14.1)	<.001	35 (70.0)	682 (69.1)	.893
Statin use	333 (32.1)	2,322 (45.7)	<.001	36 (72.0)	297 (30.1)	<.001
Treatment factors						
Chemotherapy			—			.004
Capecitabine alone	537 (51.8)	—		37 (74.0)	500 (50.7)	
5-FU alone	78 (7.5)	—		5 (10.0)	73 (7.4)	
CAPOX	398 (38.4)	—		7 (14.0)	391 (39.6)	
FOLFOX	24 (2.3)	—		1 (2.0)	23 (2.3)	
Chemotherapy cycles, median (IQR), n	8 (5–8)	—		8 (6–8)	8 (5–8)	.398
Chemotherapy dose reduction	163 (15.7)	—		5 (10.0)	158 (16.0)	.255

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CAPOX, capecitabine/oxaliplatin; COPD, chronic obstructive pulmonary disease; CRC, colorectal cancer; CVD, cardiovascular disease; FOLFOX, 5-FU/leucovorin/oxaliplatin; IQR, interquartile range; RCS, Royal College of Surgeons; SES, socioeconomic status.
[a]Participants in the control group were selected from among a noncancer random sample without replacement from primary care clinics in the same geographic region of the patients with CRC.

control group showed a similar pattern of csCI of CVD and death, which increased with time (supplemental eFigure 5).

Subgroup analysis comparing patients with CRC who received capecitabine-based versus 5-FU–based regimens revealed weak evidence of difference between

Table 2. Cause-Specific HRs for New-Onset CVDs

Characteristic[a]	Univariable HR (95% CI)[b]	*P* Value	Multivariable HR (95% CI)[b]	*P* Value
Adjuvant chemotherapy for CRC (vs control)	1.45 (1.03–2.05)	.034	2.11 (1.39–3.20)	<.001
Age at cancer diagnosis (per 5-y increase)	1.27 (1.19–1.35)	<.001	1.16 (1.08–1.24)	<.001
Sex (male vs female)	1.48 (1.12–1.95)	.006	1.40 (1.06–1.86)	.020
RCS comorbidity score[c]				
1 comorbidity vs 0	1.16 (0.88–1.52)	.282	1.88 (1.36–2.61)	<.001
≥2 comorbidities vs 0	7.67 (5.67–10.38)	<.001	6.61 (4.55–9.60)	<.001
Fee waiver recipients (surrogate for lower SES)	1.58 (1.17–2.12)	.002	1.34 (0.99–1.81)	.060
Diabetes mellitus	2.16 (1.65–2.83)	<.001	1.38 (1.04–1.84)	.025
Hypertension	6.13 (4.65–8.06)	<.001	3.27 (2.39–4.50)	<.001
Dyslipidemia/Hyperlipidemia	3.20 (2.17–4.70)	<.001	2.53 (1.68–3.81)	<.001
Aspirin use	1.22 (0.93–1.61)	.157	0.92 (0.69–1.24)	.601
β-blocker use	2.27 (1.70–3.02)	<.001	1.30 (0.94–1.81)	.112
Calcium channel blocker use	2.53 (1.92–3.33)	<.001	1.02 (0.73–1.45)	.888
ACE inhibitor use	2.69 (2.03–3.56)	<.001	1.09 (0.80–1.50)	.575
ARB use	1.33 (0.62–2.82)	.461	0.76 (0.35–1.65)	.486
Diuretic use	1.87 (1.40–2.50)	<.001	0.97 (0.68–1.37)	.849
Statin use	4.23 (3.06–5.83)	<.001	—	—

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; COPD, chronic obstructive pulmonary disease; CRC, colorectal cancer; CVD, cardiovascular disease; HR, hazard ratio; RCS, Royal College of Surgeons; SES, socioeconomic status.
[a]Alcohol-related disease and COPD or smokers were not included in this analysis because of data scarcity. Because of the collinearity between dyslipidemia/hyperlipidemia and statin use, only dyslipidemia/hyperlipidemia was included in the multivariable analysis.
[b]Cause-specific HRs by competing risk analyses (ie, censoring death).
[c]Included peripheral vascular disease, cerebrovascular disease, dementia, COPD, rheumatic disease, liver disease, hemiplegia/paraplegia, renal disease, AIDS/HIV infection.

the regimens (HR, 1.66; 95% CI, 0.56–4.91; *P*=.356), number of cycles (HR, 1.00; 95% CI, 0.86–1.16; *P*=.980), and chemotherapy dose reductions (HR, 0.42; 95% CI, 0.14–1.31; *P*=.136) in terms of incident CVD risks (Table 3).

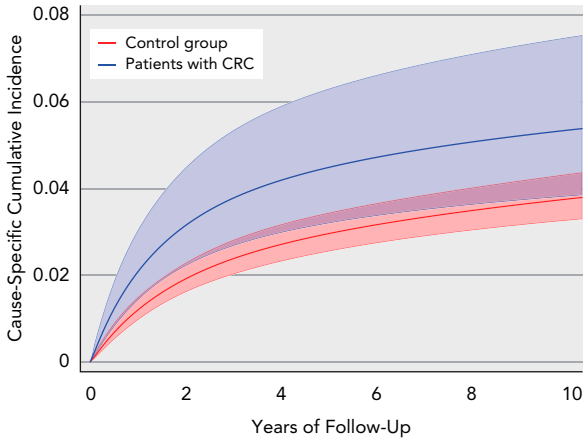

Figure 2. Cause-specific cumulative incidence of cardiovascular diseases in patients with CRC who received adjuvant chemotherapy (n=1,037) versus the control group (n=5,078), with death as a competing risk. Bands represent 95% confidence intervals.
Abbreviation: CRC, colorectal cancer.

However, we found that capecitabine-based chemotherapy was associated with a higher risk of CVD when compared with the control group (supplemental eTable 4 and eFigure 6). Sensitivity analyses including additional variables or without landmark periods produced largely consistent results (supplemental eTables 5 and 6).

Discussion

We evaluated the long-term CVD risk among patients with high-risk stage II–III CRC in the clinically relevant time period from 2 months after surgery to 10 years, both in additive (ie, csCI) and multiplicative scales (ie, HR). We show evidence of an association between exposure to fluoropyrimidine-based adjuvant chemotherapy and higher risk of CVD in the long run among patients with high-risk stage II–III CRC when compared with the control group. The difference in CVD incidence over time between the cancer cohort and control group persisted and continued to increase.

The csCI increased the most within the first 2 years after chemotherapy. We also found that all individual CVD diagnoses were more common in patients who received chemotherapy. In particular, patients within the cancer cohort had the greatest increase in the relative risk of stroke.

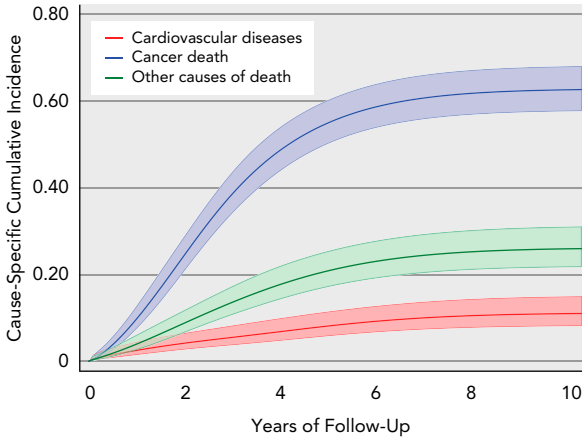

Figure 3. Cause-specific cumulative incidence of cardiovascular diseases versus other causes of death among patients with colorectal cancer. Bands represent 95% confidence intervals.

To our knowledge, this study is one of the first contemporary comprehensive analyses reporting long-term incident CVD events in patients with CRC after initiation of fluoropyrimidine-based chemotherapy versus control subjects.

A previous study reported that among CRC survivors, 1.6% and 0% had new-onset self-reported myocardial infarction and heart failure, respectively, at 3 years after diagnosis.[30] Another study that assessed an older group (80% were aged ≥70 y) of patients with stages I–III CRC (most without adjuvant chemotherapy) detected a higher cumulative incidence of CVD of 23% at 3 years and 57% at 10 years after the cancer diagnosis.[31] In a recent study that assessed the risk for myocardial infarction in patients with gastrointestinal cancer treated with 5-FU compared with age- and sex-matched noncancer control subjects, the 6-month and 1-year cumulative incidences of myocardial infarction were 0.7% and 0.9% versus 0.3% and 0.6% in the control group, respectively.[32] The discrepancies among these studies are likely related to the differences in the study populations, endpoint definitions, and methodologies.

Our study is unique because we assessed well-defined CVD endpoints from patients who were diagnosed with high-risk stage II–III CRC treated with adjuvant chemotherapy. We provided cumulative incidence estimates of clinically relevant time points up to 10 years based on

Table 3. Cause-Specific HRs for New-Onset CVDs Among Patients With CRC

Characteristic[a]	Unadjusted HR (95% CI)[b]	*P* Value	Adjusted HR (95% CI)[b]	*P* Value
Capecitabine-based vs 5-FU–based chemotherapy	1.10 (0.43–2.83)	.846	1.66 (0.56–4.91)	.356
Number of chemotherapy cycles (per 1 increase)	1.02 (0.89–1.17)	.749	1.00 (0.86–1.16)	.980
Chemotherapy dose reduction (yes vs no)	0.55 (0.19–1.53)	.251	0.42 (0.14–1.31)	.136
Age at cancer diagnosis (per 5-y increase)	1.53 (1.26–1.85)	<.001	1.40 (1.13–1.73)	.002
Sex (male vs female)	0.89 (0.48–1.67)	.719	0.70 (0.35–1.40)	.319
RCS comorbidity score[c]				
1 comorbidity vs 0	1.99 (1.03–3.84)	.040	1.82 (0.86–3.85)	.120
≥2 comorbidities vs 0	9.75 (4.50–21.12)	<.001	9.10 (3.76–22.00)	<.001
Fee waiver recipients (surrogate for lower SES)	1.15 (0.48–2.73)	.757	0.58 (0.22–1.51)	.263
Diabetes mellitus	3.30 (1.71–6.36)	<.001	1.60 (0.72–3.52)	.247
Hypertension	4.07 (2.20–7.50)	<.001	1.79 (0.81–3.95)	.149
Dyslipidemia/Hyperlipidemia	5.13 (2.57–10.25)	<.001	2.49 (1.12–5.52)	.025
Aspirin use	1.81 (0.83–3.92)	.133	2.42 (1.07–5.47)	.034
β-blocker use	1.62 (0.81–3.24)	.169	0.92 (0.42–2.01)	.827
Calcium channel blocker use	1.99 (1.08–3.69)	.028	0.57 (0.24–1.38)	.213
ACE inhibitor use	3.81 (2.06–7.05)	<.001	1.80 (0.80–4.06)	.156
ARB use	4.00 (1.41–11.38)	.009	1.61 (0.49–5.23)	.432
Diuretic use	1.25 (0.64–2.46)	.513	0.94 (0.41–2.18)	.885
Statin use	5.20 (2.60–10.39)	<.001	—	—

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; COPD, chronic obstructive pulmonary disease; CRC, colorectal cancer; CVD, cardiovascular disease; HR, hazard ratio; RCS, Royal College of Surgeons; SES, socioeconomic status.
[a]Alcohol-related disease and COPD or smokers were not included in this analysis because of data scarcity. Because of the collinearity between dyslipidemia/hyperlipidemia and statin use, only dyslipidemia/hyperlipidemia was included in the multivariable analysis.
[b]Cause-specific HRs by competing risk analyses (ie, censoring death).
[c]Included peripheral vascular disease, cerebrovascular disease, dementia, COPD, rheumatic disease, liver disease, hemiplegia/paraplegia, renal disease, AIDS/HIV infection.

the flexible parametric competing risk analysis, which allowed us to evaluate the trajectory and competing risks of cancer death and noncancer death and the influence of various patient characteristics. Importantly, a population-based study using SEER-Medicare data revealed that the occurrence of comorbid conditions before CRC diagnosis was common and contributed to increased death in patients.[33] However, it remains unclear how established cardiovascular risk factors influence fluoropyrimidine cardiotoxicity. Our study built on the previous work by adjusting for comorbidities and common cardiovascular risk factors, including tobacco and alcohol use.

There remains uncertainty about the role of cardioprotective medications (eg, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, β-blockers, and diuretics) for patients treated with fluoropyrimidine in terms of their subsequent risk of CVD.[34,35] Our study assessed the baseline use of these medications and found that none were associated with a reduced risk of CVD. This is a finding supplementary to the main results largely because of lack of information about indications of the prescriptions, dosages, and adherence to medications.

Some studies found that cardiovascular risk is increased with continuous infusions compared with bolus regimens, suggesting that cardiotoxicity might be influenced by plasma exposure over time (ie, the administration schedule).[36–38] However, we detected no statistically significant difference between capecitabine-based and 5-FU–based chemotherapy in their association with CVD risk. This is consistent with results of another study assessing patients with gastrointestinal cancers, in which capecitabine and 5-FU were largely similar in terms of the timing and type of cardiotoxicity.[39]

Our analysis detected that CVD was more common among older patients and patients with more comorbidities. Intuitively, elderly patients tend to have more comorbidities and reduced cardiovascular reserve. This could lead to a higher chance of cardiac decompensation after receipt of chemotherapy. This may explain why most CVD cases are detected within the first 2 years, when the physiologic (related to the postoperative recovery and adjuvant chemotherapy) and emotional stress is high.

Mechanisms responsible for fluoropyrimidine-related cardiotoxicity are multifactorial.[7,40] Fluoropyrimidine treatment can lead to endothelial damage, which can increase secretion of vasoconstrictors,[41,42] disturb production of nitric oxide,[43] activate apoptosis in endothelial cells and myocytes,[44,45] and trigger thrombosis due to platelet clumps and fibrin formations.[46] Endothelial dysfunction and primary smooth muscle dysfunction result in coronary artery spasm, which is an important mechanism implicated in myocardial ischemia and damage.[47,48] Fluoropyrimidine treatment is also associated with enhanced oxidative stress due to the formation of reactive oxygen species, lipid peroxidation, and the decrease in glutathione level, with myocytes being especially susceptible to cellular damage due to their numerous mitochondria.[44] Furthermore, fluoropyrimidine can lead to disruption of erythrocyte metabolism, with a subsequent change in the cellular structures, integrity, and functioning.[49] The ability of erythrocytes to deliver and transport oxygen is decreased.[50] Insufficient oxygen supply and associated ischemic injury to metabolically active organs such as the heart can occur as a result.

Stroke was found to be the CVD that had the greatest relative difference between patients with cancer and the control subjects. This suggests that some other mechanisms may play a role in CVD incidence in at least some patients. Ischemia in particular may be related to the underlying hypercoagulable state of malignancy, causing small-vessel thrombosis.[51,52] In addition, anemia secondary to chemotherapy-related bone marrow suppression or nutritional deficiency may contribute to the ischemic state.[53–55] Risk factors for CRC, such as obesity and sedentary lifestyle, may also contribute to CVD.[56] Moreover, cancer survivors may experience chronic fatigue and have reduced exercise capacity, further contributing to CVD.[57]

The American Cancer Society and ESMO guidelines, along with the European Society of Cardiology position paper, are not very specific regarding the screening methods and frequencies.[4,40,58] Generally, it was suggested that patients with cancer with preexisting CVD should have optimal control of cardiovascular risk factors and close monitoring during and after fluoropyrimidine treatment. Our study found that the risk for incident CVD is highest within 5 years after diagnosis, especially in the first 2 years, and the events continue to occur along the survivorship, albeit at a slower rate. Long-term risk-adapted surveillance of CRC survivors that accounts for their baseline CVD risk factors and exposure to chemotherapy is advisable.

Our study has several strengths. First, we identified that active cancer itself may increase the CVD risk, which can confound the association between cancer treatment and CVD. Therefore, we only included patients who had undergone a radical resection and were being treated with adjuvant chemotherapy. Second, we compared the incident CVD risk of our cohort with that of a control group without cancer and not against a group with CRC treated with radical resection alone. This reduces the risk of confounding by indication. Third, because of the heavily subsidized healthcare system in Hong Kong, patients with chronic diseases and serious conditions (eg, myocardial infarction) are mostly treated in the public healthcare system.[59] Therefore, the Hong Kong Hospital Authority data should have captured nearly all the hospital-managed CVD outcomes, together with the corresponding dates.

Our study's limitations include the lack of details regarding chemotherapy dosing and whether particular drugs were omitted from the regimen. As such, it is difficult to draw strong conclusions on the dose–response relationship between drug exposure and CVD incidence and the CVD risks associated with different regimens. To mitigate this, we adjusted for chemotherapy dose reduction and the number of chemotherapy cycles, which were surrogates for dosages. Information such as level of physical exercise and performance status was not readily available in our database, and we acknowledge that these may be contributing factors to CVD. Additionally, some ICD-9-CM codes, such as those for medical conditions, alcoholism, and smoking, may be undercoded, leading to the problems of underdiagnosis or misclassification. However, when possible, we used medication prescriptions to supplement diagnoses (eg, antidiabetic medications for diabetes). Finally, our study was based on an Asian cohort, and one should be careful when generalizing our findings to other populations, which can have different demographics, cardiovascular risk factor profiles, and susceptibilities to cancer treatment toxicities.

Conclusions

In this Asian population-based study, we detected a 2-fold increase in the risk of incident CVD among survivors of high-risk stage II–III CRC without preexisting CVD with exposure to adjuvant fluoropyrimidine-based chemotherapy. We also found that most CVD events occurred soon after diagnosis and treatment. Together, these findings highlight the importance of pretreatment screening for CVD risk factors, periodic monitoring of cardiac function, and timely intervention to minimize the risk of CVD during and after cancer treatment and throughout cancer survivorship.

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Supplemental online content for:

Incident Cardiovascular Diseases Among Survivors of High-Risk Stage II–III Colorectal Cancer: A Cluster-Wide Cohort Study

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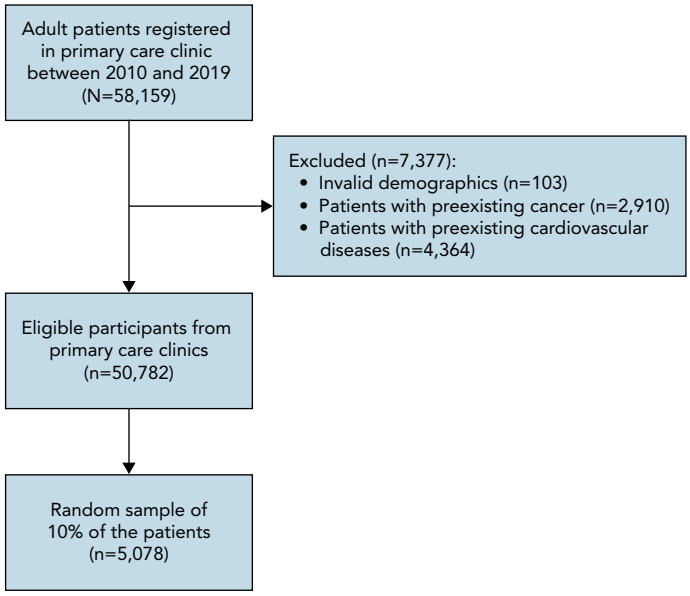
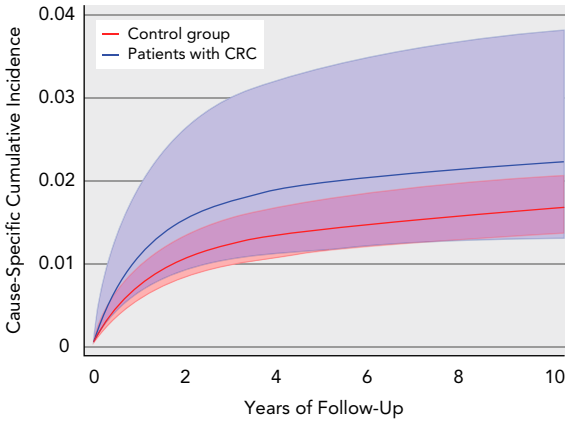
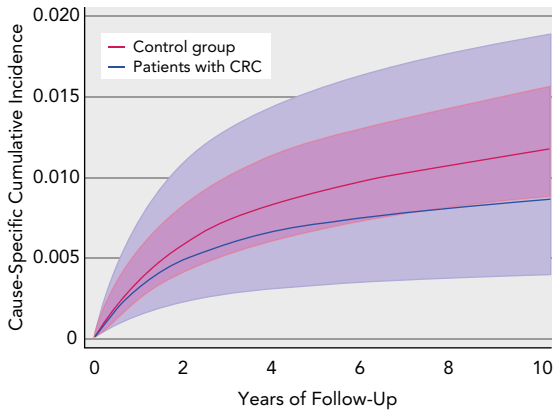


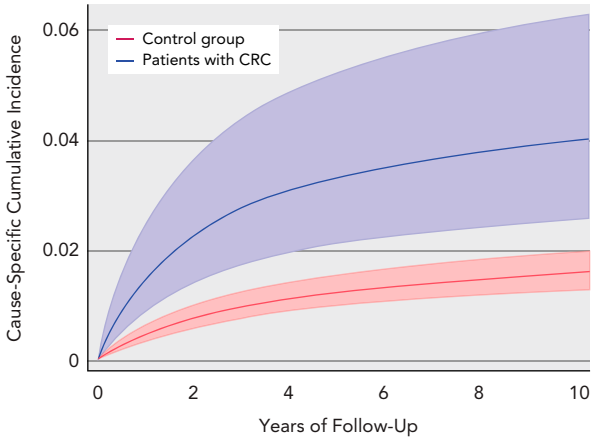
eFigure 1. Flowchart outlining the inclusion and exclusion criteria for the control group (n=5,078).



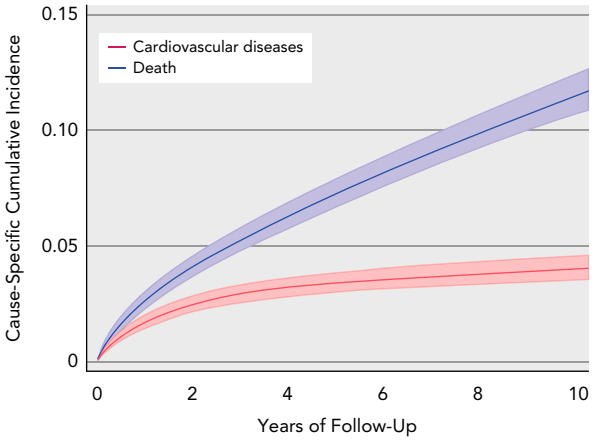
eFigure 2. Cause-specific cumulative incidences of ischemic heart disease, with death as competing risk. Bands represent 95% confidence intervals.
Abbreviation: CRC, colorectal cancer.



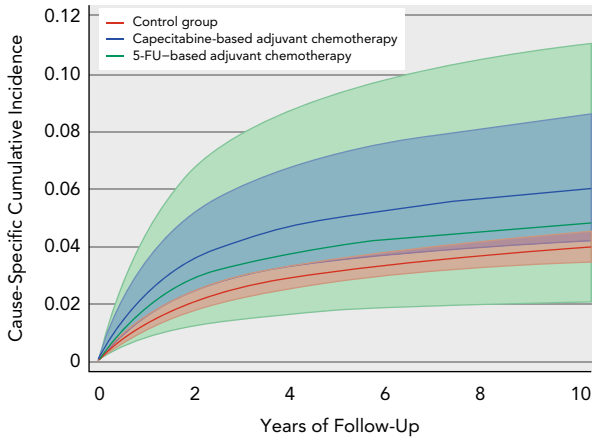
eFigure 3. Cause-specific cumulative incidences of heart failure and cardiomyopathy, with death as competing risk. Bands represent 95% confidence intervals.
Abbreviation: CRC, colorectal cancer.



eFigure 4. Cause-specific cumulative incidences of stroke, with death as competing risk. Bands represent 95% confidence intervals.
Abbreviation: CRC, colorectal cancer.



eFigure 5. Cause-specific cumulative incidence of cardiovascular diseases among the control group, with death as competing risk. Bands represent 95% confidence intervals.



eFigure 6. Cause-specific cumulative incidence of cardiovascular diseases with different adjuvant chemotherapy regimens and in control group, with death as competing risk. Bands represent 95% confidence intervals.

eTable 1. ICD-9-CM Codes of the Outcomes (Cardiovascular Diseases)

Cardiovascular Disease	ICD-9-CM Codes
Ischemic heart disease	410–413, 414.0, 414.8, 414.9, 429.7, V45.81, V45.82
Cardiomyopathy and heart failure	425, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 428, V42.1
Stroke	430–432, 433.01, 433.11, 433.21, 433.31, 433.81, 433.91, 434.01, 434.11, 434.91, 435, 436, 437.0, 437.1

eTable 2. ICD-9-CM Codes of the Medical Conditions and Associated Medications

Medical Condition	ICD-9-CM	Medications
Hypertension	401.×, 402.×, 403.×, 404.×, 405.×	Amlodipine, Diltiazem, Felodipine, Nifedipine, Verapamil, Atenolol, Bisoprolol Carvedilol, Labetalol, Metoprolol, Propranolol, Clonidine, Hydralazine, Losartan, Telmisartan, Valsartan, Bumetanide, Frusemide, Amiloride, Eplerenone, Spironolactone, Hydrochlorothiazide, Indapamide, Moduretic, Dyazide, Methyldopa, Doxazosin, Prazosin, Terazosin, Captopril, Enalapril, Lisinopril, Perindopril
Dyslipidemia	272.0, 272.1, 272.2, 272.3, 272.4	Atorvastatin, Rosuvastatin, Simvastatin, Fenofibrate, Gemfibrozil, Ezetimibe
Diabetes	249, 250.xx, 357.2, 362.0, 366.41, 648.0	Insulin Neutral, Insulin Lispro, Insulin Aspart, Insulin Human, Insulin Lispro Human, Insulin Aspart Human Analog, Insulin Detemir, Insulin Isophane Human, Insulin Degludec, Insulin Glargine, Gliclazide, Glimepiride, Glipizide, Metformin, Alogliptin, Linagliptin, Sitagliptin, Dulaglutide, Exenatide, Liraglutide, Lixisenatide, Pioglitazone, Dapagliflozin, Empagliflozin, Acarbose
Chronic obstructive pulmonary disease	491, 492, 496	Beclomethasone, Budesonide ± Formoterol, Fluticasone, Flutiform or equivalent, Relvar or equivalent, Seretide or equivalent, Trelegy or equivalent, Anoro or equivalent, Ultibro or equivalent, Spiolto or equivalent, Combivent or equivalent, Tiotropium, Ipratropium, Glycopyrronium, Indacaterol, Salbutamol, Montelukast, Roflumilast, Theophylline, Terbutaline
Smoking	V15.82	—
Alcohol-related diseases	291, 303, 305.0, 571.0, 571.1, 571.2, 571.3, 980.8, 980.9	—

eTable 3. Characteristics of CRC Survivors Who Received Different Adjuvant Chemotherapy Regimens (N=1,037)

Characteristic	Capecitabine-Based Chemotherapy n (%)	5-FU–Based Chemotherapy n (%)	*P* Value
Total, n	935	102	
Patient factors			
Age at cancer diagnosis,			.385
Median (IQR), y	62 (56–68)	61 (55–67)	
Sex			.047
Male	585 (62.6)	74 (72.6)	
Female	350 (37.4)	28 (27.4)	
RCS comorbidity score			.001
None	740 (79.1)	65 (63.7)	
1 comorbidity	170 (18.2)	30 (29.4)	
≥2 comorbidities	25 (2.7)	7 (6.9)	
Follow-up time for alive patients			.001
Median (IQR), y	5.4 (3.3–7.6)	9.0 (7.4–10.8)	
Fee waiver recipients (surrogate for lower SES)	115 (12.3)	23 (22.6)	.004
COPD or smoker	17 (1.8)	2 (2.0)	.919
Alcohol-related diseases	24 (2.6)	3 (2.9)	.822
Diabetes mellitus	112 (12.0)	22 (21.6)	.006
Hypertension	199 (21.3)	20 (19.6)	.694
Dyslipidemia/Hyperlipidemia	300 (32.1)	38 (37.3)	.290
Aspirin use	106 (11.3)	12 (11.8)	.897
β-blocker use	181 (19.4)	21 (20.6)	.766
Calcium channel blocker use	323 (34.6)	20 (19.6)	.002
ACE inhibitor use	198 (12.2)	20 (19.6)	.712
ARB use	36 (3.9)	3 (2.9)	.647
Diuretics use	657 (70.3)	60 (58.8)	.018
Statins use	295 (31.6)	38 (37.3)	.241
Treatment factors			
Chemotherapy			—
Capecitabine alone	537 (57.4)	—	
5-FU alone	—	78 (76.5)	
CAPOX	398 (42.6)	—	
FOLFOX	—	24 (23.5)	
Chemotherapy cycles, median (IQR), n	8 (5–8)	6 (2–6)	<.001
Chemotherapy dose reduction	148 (15.8)	15 (14.7)	.767

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CAPOX, capecitabine and oxaliplatin; COPD, chronic obstructive pulmonary disease; CRC, colorectal cancer; FOLFOX, 5-FU/leucovorin/oxaliplatin; IQR, interquartile range; RCS, Royal College of Surgeons; SES, socioeconomic status.

eTable 4. Cause-Specific HRs for New-Onset CVDs by Different Adjuvant Chemotherapy Regimens With the 2-Month Landmark Period

Characteristic[a]	Unadjusted HR (95% CI)[b]	*P* Value	Adjusted HR (95% CI)[b]	*P* Value
Capecitabine-based chemotherapy vs control	1.41 (0.99–2.03)	.060	2.22 (1.42–3.45)	<.001
5-FU–based chemotherapy vs control	1.53 (0.63–3.71)	.349	1.62 (0.65–4.05)	.301
Age at cancer diagnosis (per 5-y increase)	1.27 (1.19–1.35)	<.001	1.13 (1.06–1.21)	<.001
Sex (male vs female)	1.48 (1.12–1.95)	.006	1.40 (1.06–1.86)	.019
RCS comorbidity score[c]				
1 comorbidity vs 0	1.16 (0.88–1.52)	.282	1.89 (1.37–2.62)	<.001
≥2 comorbidities vs 0	7.67 (5.67–10.38)	<.001	6.67 (4.59–9.70)	<.001
Fee waiver recipients (surrogate for lower SES)	1.58 (1.17–2.12)	.002	1.34 (0.99–1.81)	.059
Diabetes mellitus	2.16 (1.65–2.83)	<.001	1.40 (1.05–1.86)	.021
Hypertension	6.13 (4.65–8.06)	<.001	3.42 (2.48–4.70)	<.001
Dyslipidemia/Hyperlipidemia	3.20 (2.17–4.70)	<.001	2.53 (1.68–3.81)	<.001
Aspirin use	1.22 (0.93–1.61)	.157	0.92 (0.68–1.24)	.596
β-blocker use	2.27 (1.70–3.02)	<.001	1.31 (0.94–1.81)	.111
Calcium channel blocker use	2.53 (1.92–3.33)	<.001	1.02 (0.73–1.45)	.892
ACE inhibitor use	2.69 (2.03–3.56)	<.001	1.10 (0.80–1.50)	.553
ARB use	1.33 (0.62–2.82)	.461	0.76 (0.35–1.64)	.484
Diuretics use	1.87 (1.40–2.50)	<.001	0.96 (0.67–1.36)	.815
Statin use	4.23 (3.06–5.83)	<.001	—	—

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; COPD, chronic obstructive pulmonary disease; CRC, colorectal cancer; CVD, cardiovascular disease; HR, hazard ratio; RCS, Royal College of Surgeons; SES, socioeconomic status.
[a]Alcohol-related disease and COPD or smoker were not included in this analysis due to data scarcity. Due to the collinearity between dyslipidemia/hyperlipidemia and statins use, only dyslipidemia/hyperlipidemia was included in the multivariable analysis.
[b]Cause-specific HRs by competing risk analyses (ie, censoring death).
[c]Included peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, rheumatic disease, liver disease, hemiplegia/paraplegia, renal disease, AIDS/HIV infection.

eTable 5. Sensitivity Analysis by Adding CKD, PVD, and Anemia in Analysis of Cause-Specific HRs for New-Onset CVDs

Characteristic[a]	Univariable HR (95% CI)[b]	*P* Value	Multivariable HR (95% CI)[b]	*P* Value
Adjuvant chemotherapy for CRC (vs control)	1.45 (1.03–2.05)	.034	2.02 (1.33–3.08)	.001
Age at cancer diagnosis (per 5-y increase)	1.27 (1.19–1.35)	<.001	1.15 (1.08–1.23)	<.001
Sex (male vs female)	1.48 (1.12–1.95)	.006	1.40 (1.05–1.86)	.021
RCS comorbidity score[c]				
1 comorbidity vs 0	1.16 (0.88–1.52)	.282	1.82 (1.31–2.54)	<.001
≥2 comorbidities vs 0	7.67 (5.67–10.38)	<.001	5.52 (3.55–8.57)	<.001
Fee waiver recipients (surrogate for lower SES)	1.58 (1.17–2.12)	.002	1.34 (0.99–1.81)	.060
Diabetes mellitus	2.16 (1.65–2.83)	<.001	1.34 (1.01–1.78)	.045
Hypertension	6.13 (4.65–8.06)	<.001	3.14 (2.28–4.32)	<.001
Dyslipidemia/Hyperlipidemia	3.20 (2.17–4.70)	<.001	2.58 (1.71–3.90)	<.001
CKD	7.87 (5.57–11.12)	<.001	1.17 (0.76–1.80)	.487
PVD	6.15 (3.35–11.28)	<.001	1.36 (0.71–2.59)	.350
Anemia	4.08 (3.00–5.54)	<.001	1.69 (1.20–2.40)	.003
Aspirin use	1.22 (0.93–1.61)	.157	0.90 (0.66–1.21)	.475
β-blocker use	2.27 (1.70–3.02)	<.001	1.34 (0.97–1.86)	.079
Calcium channel blocker use	2.53 (1.92–3.33)	<.001	1.00 (0.70–1.41)	.982
ACE inhibitor use	2.69 (2.03–3.56)	<.001	1.02 (0.74–1.41)	.884
ARB use	1.33 (0.62–2.82)	.461	0.75 (0.35–1.63)	.470
Diuretics use	1.87 (1.40–2.50)	<.001	0.93 (0.66–1.33)	.705
Statin use	4.23 (3.06–5.83)	<.001	—	—

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CRC, colorectal cancer; CVD, cardiovascular disease; HR, hazard ratio; PVD, peripheral vascular disease; RCS, Royal College of Surgeons; SES, socioeconomic status.

[a]Alcohol-related disease and COPD or smoker were not included in this analysis due to data scarcity. Due to the collinearity between dyslipidemia/hyperlipidemia and statins use, only dyslipidemia/hyperlipidemia was included in the multivariable analysis.

[b]Cause-specific HRs by competing risk analyses (ie, censoring death).

[c]Included peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, rheumatic disease, liver disease, hemiplegia/paraplegia, renal disease, AIDS/HIV infection.

eTable 6. Sensitivity Analysis by Adding CKD, PVD, and Anemia in Analysis of Cause-Specific HRs for New-Onset CVDs Among Patients With CRC

Characteristic[a]	Unadjusted HR (95% CI)[b]	*P* Value	Adjusted HR (95% CI)[b]	*P* Value
Capecitabine-based vs 5-FU–based chemotherapy	1.10 (0.43–2.83)	.846	1.76 (0.58–5.35)	.316
Number of chemotherapy cycles (per 1 increase)	1.02 (0.89–1.17)	.749	1.00 (0.86–1.17)	.981
Chemotherapy dose reduction (yes vs no)	0.55 (0.19–1.53)	.251	0.40 (0.12–1.29)	.124
Age at cancer diagnosis (per 5-y increase)	1.53 (1.26–1.85)	<.001	1.43 (1.14–1.78)	.002
Sex (male vs female)	0.89 (0.48–1.67)	.719	0.71 (0.36–1.42)	.338
RCS comorbidity score[c]				
1 comorbidity vs 0	1.99 (1.03–3.84)	.040	1.80 (0.1–3.98)	.148
≥2 comorbidities vs 0	9.75 (4.50–21.12)	<.001	9.87 (3.27–29.77)	<.001
Fee waiver recipients (surrogate for lower SES)	1.15 (0.48–2.73)	.757	0.61 (0.22–1.67)	.339
Diabetes mellitus	3.30 (1.71–6.36)	<.001	1.53 (0.68–3.43)	.300
Hypertension	4.07 (2.20–7.50)	<.001	1.81 (0.82–4.01)	.145
Dyslipidemia/Hyperlipidemia	5.13 (2.57–10.25)	<.001	2.57 (1.15–5.75)	.022
CKD	3.75 (1.79–7.86)	<.001	1.09 (0.40–3.00)	.860
PVD	5.44 (1.68–17.66)	.005	0.60 (0.14–2.64)	.497
Anemia	1.42 (0.71–2.83)	.324	0.97 (0.46–2.08)	.947
Aspirin use	1.81 (0.83–3.92)	.133	2.64 (1.12–6.24)	.026
β-blocker use	1.62 (0.81–3.24)	.169	0.94 (0.43–2.08)	.887
Calcium channel blocker use	1.99 (1.08–3.69)	.028	0.56 (0.23–1.35)	.197
ACE inhibitor use	3.81 (2.06–7.05)	<.001	1.83 (0.81–4.12)	.146
ARB use	4.00 (1.41–11.38)	.009	1.61 (0.49–5.28)	.430
Diuretics use	1.25 (0.64–2.46)	.513	0.91 (0.39–2.12)	.826
Statin use	5.20 (2.60–10.39)	<.001	—	—

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CRC, colorectal cancer; CVD, cardiovascular disease; HR, hazard ratio; PVD, peripheral vascular disease; RCS, Royal College of Surgeons; SES, socioeconomic status.

[a]Alcohol-related disease and COPD or smoker were not included in this analysis due to data scarcity. Due to the collinearity between dyslipidemia/hyperlipidemia and statins use, only dyslipidemia/hyperlipidemia was included in the multivariable analysis.

[b]Cause-specific HRs by competing risk analyses (ie, censoring death).

[c]Included peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, rheumatic disease, liver disease, hemiplegia/paraplegia, renal disease, AIDS/HIV infection.

eAppendix 1. Clinical Data Analysis and Reporting System

Clinical Data Analysis and Reporting System (CDARS) is an electronic healthcare database operated by the Hospital Authority of Hong Kong, which is the sole public healthcare provider in Hong Kong. It covers approximately 90% of all secondary and tertiary care and serves a population of 7.5 million.[1,2] Patient data, including demographics, diagnoses, hospital admission and clinic attendance, treatments, laboratory results, and causes and dates of death, are recorded in the CDARS. Clinicians provide the ICD-9-CM codes for each episode of clinic attendance and hospital admission, respectively.[3,4] These codes have showed a high accuracy in diagnosing myocardial infarction and stroke with positive predictive values of 85% and 91%, respectively, in a previous study.[5] Another study also demonstrated the reliability of the CDARS in capturing the demographics and the use of antidiabetic medications with a near-perfect level of data completeness exceeding 99%.[4] High-quality population-based studies on cardiovascular diseases, oncology, and medications have been published based on information retrieved from the CDARS.[6–10]

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eAppendix 2. Royal College of Surgeons Adaptation of the Charlson Comorbidity Index

Comorbidities before colorectal cancer were measured using the Royal College of Surgeons (RCS) adaptation of the Charlson comorbidity index.[1] Cardiovascular risk factors were removed from the overall RCS score to avoid multicollinearity in regression analysis. The remaining comorbidities in the index, including peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, rheumatic disease, liver disease, hemiplegia/paraplegia, renal disease, and AIDS/HIV infection, were combined into the score.

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eAppendix 3. Statistical Analysis Using Flexible Parametric Competing Risk Modeling Framework

The follow-up times for cardiovascular diseases (CVDs) continued until the first diagnosis of a CVD event, cancer recurrence, noncardiac death, or censor date, whichever was earlier. We censored patients who remained alive and had not developed CVD or cancer recurrence by the end of follow-up on October 31, 2021. Follow-up started after the date of the last adjuvant chemotherapy dose. We only counted the events if the diagnosis of CVD occurred beyond a landmark period of 2 months after the date of operation because most patients would have recovered from the operation and started adjuvant treatment by that time.

We evaluated the cause-specific cumulative incidence (csCI) of CVD with adjuvant chemotherapy using a flexible parametric competing risk modeling framework. We derived the csCI after adjusting for age, sex, need for medical fee waiver (surrogate of socioeconomic status), preexisting cardiovascular risk factors (chronic obstructive pulmonary disease or smoking, alcohol-related diseases, atrial fibrillation, hypertension, hyperlipidemia, dyslipidemia, diabetes mellitus, and depression) (see supplemental eTable 2), and Royal College of Surgeons (RCS) comorbidity score, which were established or theoretical risk factors for CVD.

We presented the csCIs plots of CVD for the patients who received adjuvant chemotherapy and the comparison group. As secondary analyses, we included the csCI plots of each CVD endpoints (ie, ischemic heart disease, heart failure and cardiomyopathy, and stroke) for both groups. We also presented the csCI of CVD for patients exposed to different adjuvant chemotherapy regimens. Furthermore, we computed the ratios of predicted cumulative incidence of CVD, colorectal cancer relapse, and cancer-specific death among patients at 5 and 10 years and computed their respective 95% confidence intervals by bootstrapping with 1,000 resamplings. Finally, we performed sensitivity analyses to test whether the results were robust with respect to the absence of a landmark period, and to adjust for additional cardiovascular risk factors (chronic kidney disease, peripheral vascular disease, and anemia) in addition to the RCS comorbidity score.

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