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ORIGINAL ARTICLE

Retrospective Study

Elevated cardiovascular risk and acute events in hospitalized colon cancer survivors: A decade-apart study of two nationwide cohorts

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Abstract

BACKGROUND

Over the years, strides in colon cancer detection and treatment have boosted survival rates; yet, post-colon cancer survival entails cardiovascular disease (CVD) risks. Research on CVD risks and acute cardiovascular events in colorectal cancer survivors has been limited.

AIM

To compare the CVD risk and adverse cardiovascular outcomes in current colon cancer survivors compared to a decade ago.

METHODS

We analyzed 2007 and 2017 hospitalization data from the National Inpatient Sample, studying two colon cancer survivor groups for CVD risk factors, mortality rates, and major adverse events like pulmonary embolism, arrhythmia, cardiac arrest, and stroke, adjusting for confounders *via* multivariable regression analysis.

RESULTS

Of total colon cancer survivors hospitalized in 2007 (n = 177542) and 2017 (n = 178325), the 2017 cohort often consisted of younger (76 *vs* 77 years), male, African-

American, and Hispanic patients admitted non-electively *vs* the 2007 cohort. Furthermore, the 2017 cohort had higher rates of smoking, alcohol abuse, drug abuse, coagulopathy, liver disease, weight loss, and renal failure. Patients in the 2017 cohort also had higher rates of cardiovascular comorbidities, including hypertension, hyperlipidemia, diabetes, obesity, peripheral vascular disease, congestive heart failure, and at least one traditional CVD ($P < 0.001$) *vs* the 2007 cohort. On adjusted multivariable analysis, the 2017 cohort had a significantly higher risk of pulmonary embolism (PE) (OR: 1.47, 95%CI: 1.37-1.48), arrhythmia (OR: 1.41, 95%CI: 1.38-1.43), atrial fibrillation/flutter (OR: 1.61, 95%CI: 1.58-1.64), cardiac arrest including ventricular tachyarrhythmia (OR: 1.63, 95%CI: 1.46-1.82), and stroke (OR: 1.28, 95%CI: 1.22-1.34) with comparable all-cause mortality and fewer routine discharges (48.4% *vs* 55.0%) ($P < 0.001$) *vs* the 2007 cohort.

CONCLUSION

Colon cancer survivors hospitalized 10 years apart in the United States showed an increased CVD risk with an increased risk of acute cardiovascular events (stroke 28%, PE 47%, arrhythmia 41%, and cardiac arrest 63%). It is vital to regularly screen colon cancer survivors with concomitant CVD risk factors to curtail long-term cardiovascular complications.

Key Words: Colon cancer; Colorectal cancer; Cardiovascular diseases; Cardiovascular disease risk; Cardiac events; Stroke

Core Tip: Colon cancer survivors hospitalized 10 years apart in the United States showed an increased cardiovascular disease risk with an increased risk of acute cardiovascular events (stroke 28%, pulmonary embolism 47%, arrhythmia 41%, and cardiac arrest 63%). Increased screening in this cohort is important.

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INTRODUCTION

Cardiovascular disease (CVD) and cancer remain the leading causes of death in the United States, with colon cancer being the third leading cause of all cancer-related deaths in both men and women. According to 2017 Global Burden of Disease data, there were 1.8 million incident colon cancer cases with an age-standardized incidence rate of 23.2 per 100000 person-years[1]. However, with improvements in screening strategies, early detection and treatment, and better lifestyle modifications, the survival rates have improved significantly[2].

Studies have shown increased CVD risk in cancer survivors which includes heart failure, stroke and coronary artery disease[3]. This is explained by the fact that CVD and colon cancer survivors both share risk factors such as age, obesity, a sedentary lifestyle, and smoking. Patients after cancer chemo and radiotherapy enter a chronic inflammatory state secondary to the cancer burden and the treatment effects. These lead to the development of new chronic conditions such as diabetes, hypertension, and hyperlipidemia, which in themselves increase adverse cardiovascular event risk[4-6]. There is also increased cardiotoxicity from these treatments, which is understudied in colon cancer survivors. The risk of CVD has been well described for breast[7], lung[8,9], lymphoma/leukemias[10] and prostate cancers[11] amongst various population groups however for colon cancer, it is understudied. There has been a paucity of data regarding the CVD burden and trend in colon cancer in the last decade. Hence, it is imperative to understand the CVD risk and how it has varied over time. We therefore performed a retrospective analysis of colon cancer survivors and compared the CVD risk and adverse cardiovascular outcomes in current colon cancer survivors compared to a decade ago.

MATERIALS AND METHODS

We conducted a retrospective analysis of hospitalizations among colon cancer survivors in the years 2007 and 2017 using the National Inpatient Sample (NIS) from the Agency for Healthcare Research & Quality-supported Healthcare Cost Utilization Project[12]. The records of NIS comprise demographics of patients, hospital characteristics, several diagnoses, procedures, and comorbidities with pertinent International Classification of Diseases Clinical Modification, Ninth Revision (ICD-9-CM), or Tenth Revision (ICD-10-CM) codes. As the datasets are publicly available and de-identified, they were exempt from institutional review board approval.

The study included patients from January 1st to December 31st in 2007 and 2017. Using the ICD-9-CM and ICD-10-CM code V10.05 and Z85.038 respectively, we identified patients aged 18 or older who were admitted to the hospital with a prior history of colon cancer. Hospitalization with information missing on age, race, gender, length of stay, cost of a stay, or in-hospital death were excluded. The primary outcomes were major adverse cardiovascular and cerebrovascular events and healthcare resource utilization. Secondary outcomes included the prevalence of CVD risk factors. The ICD-9 and ICD-10 codes for complications are listed in Supplementary Table 1, and the comorbidities were determined using the Elixhauser software.

We performed multivariable regression analysis, adjusting for sociodemographic confounders such as age, sex, median household income, type of admission, teaching facility, and comorbid conditions, to assess the risk of cardiovascular events across these two cohorts a decade apart. We also compared the CVD risk factors and in-hospital outcomes, including all-cause mortality, PE, arrhythmia, atrial fibrillation/flutter, cardiac arrest, including ventricular tachyarrhythmias, stroke, and patient disposition (routine, short-term rehabilitation, including skilled nursing facilities, intermediate care facility, home health, and leaving against medical advice). Categorical and continuous data were assessed using Pearson's chi-square test and the Mann-Whitney U test for non-normally distributed continuous data. Statistical significance was measured at a two-sided *P* value of 0.05. All analyses were conducted using weighted data and complex survey modules in IBM SPSS Statistics version 25.0 (IBM Corp., Armonk, NY, United States).

RESULTS

Of the total hospital admissions among colon cancer survivors in 2007 (n = 177542) and 2017 (n = 178325), the 2017 cohort often consisted of younger [median age: 76 (65-84) *vs* 77 (67-84) years], black (12.2% *vs* 9.6%), Asian or Pacific Islander (2.9% *vs* 2.2%), and Hispanic (7.3% *vs* 5.4%), males (50.2% *vs* 48.9%) ($P < 0.001$) and a lower median household income quartile (26.4% *vs* 25.6%). There were also more non-elective admissions (82.9% *vs* 76.9%) from urban teaching facilities (53.2%) *vs* 50.9% ($P < 0.001$) (Table 1).

Furthermore, the 2017 cohort had higher rates of smoking (40.9% *vs* 17.6%), alcohol abuse (2.2% *vs* 1.7%), drug abuse (1.5% *vs* 0.7%), coagulopathy (6.5% *vs* 3.2%), liver disease (3.8% *vs* 1.9%), weight loss (8.6% *vs* 3.4%), and renal failure (19.7% *vs* 10.9%). The 2017 cohort of colon cancer survivors also had higher rates of cardiovascular comorbidities, including hypertension (73.9% *vs* 61.8%), hyperlipidemia (43.5% *vs* 26.4%), diabetes (29.7% *vs* 25.0%), obesity (11.1% *vs* 4.5%), peripheral vascular disease (6.7% *vs* 6.4%), congestive heart failure (14.3% *vs* 10.3%), and at least one traditional CVD (89.5% *vs* 77.9%) ($P < 0.001$).

Comparing colon cancer survivors from 2007 and 2017, the 2017 cohort had a significantly higher risk of PE (1.4% *vs* 1.3%, OR: 1.47, 95%CI: 1.37-1.48), arrhythmia (30.6% *vs* 23.6%, OR: 1.41, 95%CI: 1.38-1.43), atrial fibrillation/flutter (25.2% *vs* 17.6%, OR: 1.61, 95%CI: 1.58-1.64), cardiac arrest, However, there was no significant difference in all-cause mortality (2.9% *vs* 3.0%, OR: 0.99, 95%CI: 0.95-1.04, $P = 0.77$) (Table 2).

DISCUSSION

In this nationwide study, we compare cardiovascular risk factors and outcomes among colon cancer survivors in 2017 with those in 2007. Cardiovascular risk has been shown to be elevated in patients diagnosed with colon cancer in several studies[13-15]. However, CVD risk in survivors hasn't been extensively studied[16]. In an era with an increasing prevalence of both colon cancer survivors and cardiovascular disease, it is paramount to explore cardiovascular morbidity and mortality. The key findings from our study were: (1) The number of colon cancer survivors has almost remained the same, but they are younger; (2) CVD risk factors were significantly higher in the 2017 cohort; (3) The 2017 cohort also had higher rates of in-hospital complications such as PE, atrial and ventricular tachyarrhythmias, cardiac arrest, and stroke; and (4) Despite increased complication rates and overall CVD morbidity, all-cause mortality was not significant in the 2017 cohort.

With improvements in screening criteria and advancements in treatment modalities, colon cancer is being diagnosed earlier. In one of the studies from the National Cancer Database (2004-2015), it was found that cancer is being diagnosed at a much younger age compared to 2005[17]. This is also concerning, as there has been an increase in colon cancer incidence in the younger population (50 years old)[18]. This warrants further exploration to see if this is due to early diagnosis and effective therapeutics that has developed in the past decade[19], or if it is due to rising sedentary lifestyles, obesity, and alcohol use, which are co-existent with cardiovascular diseases[20]. It is already established that cardiovascular risk is high[13,14], and with the increased pool of colon cancer survivors cardiovascular disease risk factors would be expected to be high. Our study supported this by demonstrating that the 2017 cohort of colon cancer survivors had a higher prevalence of the current increase in CVD risk factors, such as obesity, hypertension, diabetes, and hyperlipidemia.

The rise in the prevalence of cardiovascular risk factors over time may help to explain why we are seeing an increase in complication rates for cardiovascular end-points like PE, cardiac arrhythmia, stroke, and cardiac arrests in our study. Colon cancer itself is a risk factor for the development of these complications, and it has been studied for other cancers as well. Hence, it is particularly important to identify at-risk population groups and control these risks to prevent worse outcomes.

Table 1 Demographics and comorbidities of hospitalizations among colon cancer survivors a decade apart: Propensity matched analysis

Variable	2007 (*n* = 177542)	2017 (*n* = 178325)	*P* value
Age (yr) at admission, median (IQR)	77 (67-84)	76 (65-84)	< 0.001
Sex, *n* (%)			
Male	86792 (48.9)	89485 (50.2)	< 0.001
Female	90750 (51.1)	88840 (49.8)	
Race			
White	142763 (80.4)	132770 (74.5)	< 0.001
Black	16975 (9.6)	21750 (12.2)	
Hispanic	9506 (5.4)	13045 (7.3)	
Asian or Pacific Islander	3962 (2.2)	5140 (2.9)	
Native American	836 (0.5)	830 (0.5)	
Others	3499 (2.0)	4790 (2.7)	
Median household income quartile, *n* (%)			< 0.001
0^{th}-25^{th}	45378 (25.6)	47100 (26.4)	
76^{th}-100^{th}	44838 (25.3)	41700 (23.4)	
Urban teaching facility, *n* (%)	90450 (50.9)	94790 (53.2)	< 0.001
Non-elective admission, *n* (%)	136359 (76.9)	147545 (82.9)	< 0.001
Comorbidities, *n* (%)			
Alcohol abuse	3069 (1.7)	3835 (2.2)	< 0.001
Congestive heart failure	18256 (10.3)	25510 (14.3)	< 0.001
Coagulopathy	5738 (3.2)	11535 (6.5)	< 0.001
Hypertension	109779 (61.8)	131870 (73.9)	< 0.001
Hyperlipidemia	46873 (26.4)	77505 (43.5)	< 0.001
Diabetes	44331 (25.0)	52910 (29.7)	< 0.001
Smoking	31260 (17.6)	72955 (40.9)	< 0.001
Obesity	8031 (4.5)	19750 (11.1)	< 0.001
At least 1 Traditional CVD risk factor	138285 (77.9)	159640 (89.5)	< 0.001
Peripheral vascular diseases	11370 (6.4)	11890 (6.7)	0.001
Renal failure	19316 (10.9)	35075 (19.7)	< 0.001
Liver disease	3369 (1.9)	6760 (3.8)	< 0.001
Weight loss	5993 (3.4)	15405 (8.6)	< 0.001
Drug abuse	1165 (0.7)	2650 (1.5)	< 0.001

IQR: Interquartile range; CVD: Cardiovascular disease.

Despite increasing cardiovascular morbidity and complication rates, overall mortality was not found to be significantly higher in the 2017 cohort compared to 2007. This provides an opportunity to shed more light on the fact that in the past decade, the intensive management of cardiovascular issues has changed[23,24]. With improved cardiac critical care management, including the implementation of evidence-based protocols[25], rapid recognition of life-threatening conditions, and attention to patient safety, we have been able to reduce cardiovascular mortality in the past decade[24].

We used the data from a publicly accessible database, which has limited applicability since cancer-related information like the stage of colon cancer, any second incident malignancies, the exact type of chemotherapy, and the history of past treatment are not specified. Additionally, there was conflicting information regarding the number of years that patients survive after receiving a cancer diagnosis and whether they are still battling the disease or have it in remission. The cohorts were sampled from patients all over the United States, and our analysis requires external validation from other regions. Also, there is unclear data on whether these patients had any previous cardiovascular diseases before a diagnosis

Table 2 Hospitalization outcomes among colon cancer survivors a decade apart: Propensity matched analysis

Variable	2007 (*n* = 177542)	2017 (*n* = 178325)	OR	CI (UL-LL)	Adjusted P value
All-cause mortality	5245 (3.0)	5165 (2.9)	0.32	0.99 (0.95-1.04)	0.77
Pulmonary embolism	2290 (1.3)	2470 (1.4)	0.013	1.47 (1.37-1.58)	< 0.001
Arrhythmia	41948 (23.6)	54595 (30.6)	< 0.001	1.41 (1.38-1.43)	< 0.001
Atrial fibrillation/flutter	31280 (17.6)	44875 (25.2)	< 0.001	1.61 (1.58-1.64)	< 0.001
Cardiac arrest including ventricular tachyarrhythmias	609 (0.3)	1065 (0.6)	< 0.001	1.63 (1.46-1.82)	< 0.001
Stroke	4409 (2.5)	5675 (3.2)	< 0.001	1.28 (1.22-1.34)	< 0.001
Routine discharge	97712 (55.0)	86785 (48.7)	< 0.001		

Multivariable analysis was adjusted for demographics, hospital characteristics and all relevant comorbidities. IQR: Interquartile range; CVD: Cardiovascular disease.

of colon cancer. Apart from that, there might be inherent errors in coding. And lastly, no associations can be made between cardio-cerebrovascular outcomes and a previous history of colon cancer.

CONCLUSION

With increasing cardiovascular risk factors in the general population and increasing cancer survivorship, we have found that the prevalence of CVD and its complications is higher than ever. With improvements in acute cardiovascular treatment, we haven't seen an improvement in mortality, which we would expect. Hence, we need better control of the cardiovascular risk factor from a primary care standpoint as well to prevent worse outcomes in colon cancer survivors. We need further studies comparing cardiovascular morbidity and outcomes in colon cancer survivors with other cancer survivors, which are more extensively studied, and how they have evolved in the past years.

FOOTNOTES

Author contributions: Desai R, Singh S and Chauhan S conceptualized the methodology of manuscript; Desai R and Mondal A collected resources to write the manuscript; Desai R, Patel V, Singh S, Chauhan S and Jain A reviewed and edited the manuscript; Desai R analyzed the manuscript with software; Desai R, Mondal A, Singh S, Chauhan S and Jain A visualized the results; Singh S, Chauhan S and Jain A supervised the manuscripts. All authors have read and approved the final manuscript.

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