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Endocrine and Metabolic Diseases Among Colorectal Cancer Survivors in a Population-Based Cohort

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Abstract

Background: There are an estimated 1.4 million colorectal cancer (CRC) survivors in the United States. Research on endocrine and metabolic diseases over the long term in CRC survivors is limited. Obesity is a risk factor for CRC; thus it is of interest to investigate diseases that may share this risk factor, such as diabetes, for long-term health outcomes among CRC survivors.
Methods: A total of 7114 CRC patients were identified from the Utah Population Database and matched to a general population cohort of 25 979 individuals on birth year, sex, and birth state. Disease diagnoses (assessed over three time periods of 1–5 years, 5–10 years, and >10 years) were identified using electronic medical records and statewide ambulatory and inpatient discharge data. Cox proportional hazard models were used to estimate the risk of endocrine and metabolic disease.
Results: Across all three time periods, risks for endocrine and metabolic diseases were statistically significantly greater for CRC survivors compared with the general population cohort. At 1–5 years postdiagnosis, CRC survivors' risk for diabetes mellitus with complications was statistically significantly elevated (hazard ratio [HR] = 1.36, 99% confidence interval [CI] = 1.09 to 1.70). CRC survivors also experienced a 40% increased risk of obesity at 1–5 years postcancer diagnosis (HR= 1.40, 99% CI= 1.66 to 2.18) and a 50% increased risk at 5–10 years postdiagnosis (HR = 1.50, 99% CI= 1.16 to 1.95).
Conclusions: Endocrine and metabolic diseases were statistically significantly higher in CRC survivors throughout the follow-up periods of 1–5 years, 5–10 years, and more than 10 years postdiagnosis. As the number of CRC survivors increases, understanding the long-term trajectory is critical for improved survivorship care.

Colorectal cancer (CRC) is the third-most common cancer among men and women in the United States (1). There are an estimated 1.4 million CRC survivors and 140 000 new CRC diagnoses each year (2) . For individuals with CRC, the 5-year and 10-year relative survival rates are 65% and 58%, respectively, and those diagnosed with localized disease have a 90% 5-year relative survival rate (3). As the number of CRC survivors increases and survival rates improve, understanding the long-term health trajectory is critical for improved survivorship care.

CRC survivors experience a high prevalence of comorbid conditions (4,5). The prevalence of obesity has continued to rise both in male and female adult cancer survivors, with an especially higher obesity burden in CRC survivors (6). Many of these comorbid conditions, including obesity and diabetes, are not only a risk factor for the incidence of CRC but have also been associated with poor outcomes after a cancer diagnosis (7–12). The presence of these conditions affects cancer-related health outcomes as well as noncancer-related outcomes. For instance, diabetes has been shown to greatly increase the risk for recurrence and mortality in CRC survivors (13–15); it is also a statistically significant predictor of other conditions such as cardiovascular disease and stroke (16).

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CRC survivors have been shown to have poorer health and poorer quality of life compared with healthy individuals (17,18). Some of the common diseases in CRC survivors, often resulting from cancer treatment and therapy, include gastrointestinal issues, anxiety, depression, neuropathy, chronic pain, and bladder issues (19–22). These conditions can be experienced more than 10 years following CRC diagnosis and treatment (20). Because previous research has mostly focused on quality of life measures or comorbidities at diagnosis, there is limited research evaluating the incidence and development of these conditions after the diagnosis of cancer. However, a recent population-based study from Ontario, Canada, reported that CRC patients had a statistically significantly increased risk of developing diabetes after a CRC diagnosis compared with those without cancer (23). This study is one of the first to address endocrine and metabolic disease risks in CRC survivors. Our study builds on this previous research by evaluating additional endocrine and metabolic disease as well as the type of diabetes.

The aim of our study was to evaluate the incidence of endocrine and metabolic diseases and disorders in CRC survivors compared with a general population cohort over three time periods of 1–5 years, 5–10 years, and more than 10 years postdiagnosis. Our results were further stratified by age and sex.

Methods

Study Population

Using the Utah Population Database (UPDB), a cohort of CRC survivors diagnosed between 1997 and 2013 was matched on birth year, sex, and birth state (Utah/not Utah) with up to five cancer-free individuals from the general population. The UPDB links to the Utah Cancer Registry (an original National Cancer Institute Surveillance, Epidemiology, and End Results cancer registry), birth and death certificates, voter registration, residential histories, family history records, statewide health-care data, and electronic medical records in the state of Utah (24). The statewide health-care data included inpatient discharge and ambulatory surgery data spanning the years 1996 to 2013. The electronic medical records data, spanning 1994 to 2016, encompassed the two largest health-care providers in Utah, University of Utah Healthcare and Intermountain Healthcare. Studies using the UPDB have been approved by the University of Utah's Resource for Genetic and Epidemiologic Research and its institutional review board.

We excluded CRC survivors with an "in situ" or "unknown" cancer stage diagnosis (n = 1042) and those with less than 1 year of follow-up time from cancer diagnosis (n = 1832). Follow-up time, both for cancer survivors and the general population, was determined by UPDB through last contact with data sources. Date of death was obtained using the Social Security Death Index, the Utah Cancer Registry, and death certificates. Individuals in the general population were excluded if, at any time, they had an invasive cancer diagnosis (n = 9670).

CRC survivors and the general population were linked to health-care data in the UPDB. From International Classification of Diseases, Ninth Revision (ICD-9) codes, clinically meaningful categories were created using the Clinical Classification for ICD-9, Clinical Modification created by the Healthcare Cost and Utilization Project (25). Four levels were created with the Clinical Classification, with level 1 providing broad disease definitions (eg, diseases of the digestive system) and level 4 providing more specific diagnoses (eg, gastric ulcer).

For this analysis, 23 diagnoses were assessed within endocrine, nutritional, and metabolic diseases and disorders. Level 1 included any diagnosis of an endocrine or metabolic disorder. Level 2 included the following diseases: thyroid disorders; immunity disorders; diabetes without complications; diabetes with complications; nutritional deficiencies; disorders of lipid metabolism; gout and other crystal arthropathies; fluid and electrolyte disorders; other nutritional, endocrine, and metabolic disorders; and other endocrine disorders. Level 3 diseases included the following: thyrotoxicosis with or without goiter; other thyroid disorders; disorders of mineral metabolism; obesity; other and unspecified metabolic, nutritional, and endocrine disorders; unspecified protein-calorie malnutrition; other malnutrition; hypoosmolality; hypovolemia; hyperpotassemia; hypopotassemia; and other fluid and electrolyte disorders. There were no level 4 diseases among the endocrine and metabolic disorders.

Statistical Analysis

The differences in demographic characteristics between CRC survivors and the general population were tested using χ^2 tests and t tests. Cancer-specific information including cancer site, stage, and age at diagnosis of CRC survivors was also reported. Univariate and multivariable Cox proportional hazard models were used to estimate hazard ratios (HRs) and 99% confidence intervals (CIs) after adjusting for matching factors, race, baseline body mass index (BMI), and the baseline Charlson Comorbidity Index. We used 99% confidence intervals to account for the multiple comparisons in our analyses. Follow-up time was calculated from cancer diagnosis date to the date of disease diagnosis. The date of cancer diagnosis from a CRC survivor was used for individuals matched to that patient from the general population cohort. Prevalent cases were identified separately for each follow-up time and were excluded from analysis for Clinical Classification levels 2 and 3.

The analyses were performed across three time periods: 1–5 years, 5–10 years, and more than 10 years from cancer diagnosis. All hazard ratios were tested for proportional hazard violations by testing all time-varying covariates for statistical significance. For all statistically significant violations, a flexible parametric survival model was used to estimate a hazards ratio and 99% confidence interval (26). These hazard ratios and 99% confidence intervals are indicated with an asterisk in the tables. Results were stratified by sex and age at diagnosis. Survival curves were generated using the Kaplan-Meier method, and 95% confidence limits were generated using the Hall-Wellner method (27). A log-rank test with a 0.05 alpha was used to determine statistical significance between the different Kaplan-Meier plots.

Baseline BMI, defined as at least 1 year before cancer diagnosis of the CRC case diagnosis, was missing for approximately 15% of the population. Therefore, baseline BMI was imputed using regression models for the missing values using the modified Charlson Comorbidity Index score, race, cancer status, and age as predictors. To ensure that the imputed BMI did not change our inferences, we compared Cox regression models with the imputed BMI and original BMI variable (complete case analysis).

All statistical tests were two sided and a P value of less than .01 was considered statistically significant.

Results

Demographic and Clinical Characteristics

The final study population included 7114 CRC survivors and 25 979 matched individuals from the general population. CRC survivors had a statistically significantly higher Charlson Comorbidity Index compared with the general population at baseline ($P < .001$; Table 1). Baseline BMI was similar between groups, but a slightly higher percentage of CRC survivors were obese compared with the general population. As shown in Table 2, the majority of CRC survivors were diagnosed in the rectum or rectosigmoid area. Additionally, the majority of CRC survivors were diagnosed with localized disease. The mean [SD] age of CRC diagnosis was 63.7 [14.0] years. Although we matched on birth year, individuals in the general population cohort with a diagnosis of cancer were excluded from this analysis and as such resulted in differences among birth years.

Endocrine and Metabolic Disorder Risks

CRC survivors were almost two times as likely to experience endocrine and metabolic disorders compared with the general population at 1–5 years, 5–10 years, and more than 10 years postdiagnosis (Table 3 and Supplementary Table 1, available online). Figure 1 shows that the cumulative incidence of endocrine and metabolic diseases was higher among CRC survivors and the general population cohorts over the follow-up time. At 1–5 years and 5–10 years from cancer diagnosis, CRC survivors had a roughly 50% increase in risk of obesity ($HR_{1-5} = 1.40$, 99% $CI_{1-5} = 1.66$ to 2.18; $HR_{5-10} = 11.50$, 99% $CI_{5-10} = 1.16$ to 1.95; Table 3). Along with this, the risks for disorders of mineral metabolism as well as other metabolic and nutritional disorders in CRC survivors were statistically significantly elevated. Among CRC survivors who did not have diabetes before cancer diagnosis or in the first year after cancer diagnosis, 7.6% were diagnosed with incident diabetes without complications 1–5 years after cancer diagnosis (Supplementary Table 1, available online). In the next two follow-up periods, the percentage diagnosed with incident diabetes without complications was 9.1% for 5–10 years and 11.5% for more than 10 years after cancer diagnosis.

We conducted a sensitivity analysis of removing the baseline BMI variable from the Cox proportional hazards models, but the risk estimates did not change enough to change the inferences for almost all the outcomes (data not shown). The only outcome for which the inference changed was nutritional deficiencies 1–5 years after cancer diagnosis. With baseline BMI adjustment, the HR was 1.98 (99% CI = 0.67 to 5.84) and without baseline BMI adjustment the HR was 2.21 (99% CI = 1.89 to 2.20).

The risk for diabetes with complications was statistically significant at 1–5 years after a diagnosis ($HR_{1-5} = 1.36$, 99% $CI_{1-5} = 1.09$ to 1.70) but did not remain statistically significant in subsequent time intervals (Table 3). Comparatively, the risk for diabetes without complications was elevated but not statistically significant until greater than 10 years after diagnosis ($HR_{>10} = 1.39$, 99% $CI_{>10} = 1.00$ to 1.93).The risk for nutritional deficiencies and electrolyte disorders in CRC survivors compared with the general population was statistically significant at 5–10 and more than 10 years postdiagnosis ($HR_{5-10} = 1.69$, 99% $CI_{5-10} = 1.38$ to 2.08; $HR_{>10} = 1.76$, 99% $CI_{>10} = 1.32$ to 2.35, respectively). CRC survivors also had statistically significantly higher risk for thyroid disorders at 1–5 years postdiagnosis ($HR_{1-5} = 1.30$, 99% $CI_{1-5} = 1.10$ to 1.55).

Table 1. Demographic characteristics of colorectal cancer survivors compared with the general population cohort

Characteristics	Colorectal cancer survivors n = 7114 No. (%)	General population n = 25 979 No. (%)	P
Birth year			
Before 1920	527 (7.4)	1958 (7.5)	
1920–1929	1251 (17.6)	4101 (15.8)	
1930–1939	1643 (23.1)	5511 (21.2)	
1940–1949	1598 (22.5)	5834 (22.5)	
1950–1959	1271 (17.9)	5060 (19.5)	
>1960	824 (11.6)	3515 (13.5)	<.001*
Sex			
Male	3715 (52.2)	13 548 (52.2)	
Female	3399 (47.8)	12 431 (47.9)	.92*
Race			
White	6864 (96.5)	24 057 (92.6)	
Black	39 (0.6)	121 (0.5)	
American Indian/ Alaskan Native	63 (0.9)	292 (1.1)	
Asian	103 (1.5)	457 (1.8)	
Pacific Islander	37 (0.5)	114 (0.4)	
Unknown	8 (0.1)	938 (3.6)	.05*
Age attained at end of follow-up, y			
<50	525 (7.4)	1701 (6.6)	
50–59	936 (13.2)	3550 (13.7)	
60–69	1630 (22.9)	5809 (22.4)	
70–79	1770 (24.9)	6275 (24.2)	
80–89	1646 (23.1)	6271 (24.1)	
90+	607 (8.5)	2373 (9.1)	.02*
Follow-up period, y			
1–5	3133 (44.0)	7671 (29.5)	
5–10	2170 (30.5)	9487 (36.5)	
10–15	1306 (18.4)	6033 (23.2)	
15+	505 (7.1)	2788 (10.7)	<.001*
Vital status			
Alive	4027 (56.6)	20 226 (77.9)	
Dead	3087 (43.4)	5753 (22.1)	<.001*
Body mass index at baseline,† kg/m^2			
Underweight (<18)	87 (1.2)	346 (1.3)	
Normal weight (18–24.9)	2503 (35.2)	9643 (37.1)	
Overweight (25–29.9)	2857 (40.2)	10 503 (40.4)	
Obese (>30)	1667 (23.4)	5487 (21.1)	<.001*
Charlson Comorbidity Index			
0	3985 (56.0)	17 232 (66.3)	
≥1	3129 (44.0)	8747 (33.7)	<.001*
Charlson Comorbidity Index, mean (SD)	0.95 (1.55)	0.67 (1.29)	<.001‡

*P from two-sided χ^2 test.
†At least 1 year before cancer diagnosis for them or the cancer survivor they are matched to.
‡P from two-sided t test.

Sex

Stratification by sex showed an elevated risk for endocrine and metabolic disease at 1–5 years and 5–10 years postdiagnosis both in male and female CRC survivors ($HR_{1-5} = 1.98$, 99% $CI_{1-5} = 1.64$ to 2.39; $HR_{5-10} = 1.43$, 99% $CI_{5-10} = 1.00$ to 2.04; $HR_{1-5} = 1.86$, 99% $CI_{1-5} = 1.48$ to 2.33; $HR_{5-10} = 1.58$, 99% $CI_{5-10} = 1.08$ to 2.32,

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Table 2. Colorectal cancer demographics

Demographic	No. (%)
Cancer site	
Proximal (n = 2574)	
Cecum	1212 (17.0)
Ascending colon	787 (11.1)
Hepatitic flexure of colon	201 (2.8)
Transverse colon	374 (5.3)
Distal (n = 431)	
Splenic flexure of colon	149 (2.1)
Descending colon	282 (4.0)
Rectum/rectosigmoid (n = 4025)	
Sigmoid colon	1655 (23.2)
Rectosigmoid junction	486 (6.8)
Rectum	1884 (26.5)
Unspecified (n = 84)	
Large intestine, not otherwise specified	84 (1.2)
Cancer stage at diagnosis	
Localized	3643 (51.2)
Regional, direct extension only	736 (10.4)
Regional, regional lymph nodes only	1933 (27.2)
Distant	802 (11.3)
Year of diagnosis	
1997–2000	1550 (21.8)
2001–2005	2099 (29.5)
2006–2010	2204 (31.0)
2011–2013	1261 (17.7)
Age at diagnosis, mean (SD), y	63.7 (14.0)

respectively; Table 4). Male CRC survivors experienced an increase in risk for obesity at 5–10 years postdiagnosis ($HR_{5–10}$ = 1.43, 99% $CI_{5–10}$ = 1.01 to 2.01) compared with the general population of males. This increased risk was also seen in female CRC survivors ($HR_{1–5}$ = 1.50, 99% $CI_{1–5}$ = 1.12 to 2.01; $HR_{5–10}$ = 1.59, 99% $CI_{5–10}$ = 1.08 to 2.35). In men and women alike, this risk did not persist at longer than 10 years postdiagnosis.

The elevated risk of diabetes mellitus with complications was statistically significant for male CRC survivors at 1–5 years postdiagnosis ($HR_{1–5}$ = 1.34, 99% $CI_{1–5}$ = 1.00 to 1.80; Table 4); this risk did not remain statistically significant in the subsequent time periods. Female CRC survivors experienced no greater risk for diabetes mellitus with or without complications compared to the general population.

Age

Endocrine and metabolic disease risk in younger (<50 years) CRC survivors was statistically significantly higher compared with the general population across all time periods ($HR_{1–5}$ = 3.07, 99% $CI_{1–5}$ = 2.55 to 3.69; $HR_{5–10}$ = 2.20, 99% $CI_{5–10}$ = 1.35 to 3.56; $HR_{>10}$ = 1.75, 99% $CI_{>10}$ = 1.33 to 2.30; Table 5). The risks stratified by age for more than 10 years from cancer diagnosis are in Supplementary Table 4 (available online). Younger CRC survivors also experienced a substantially elevated risk for nutritional deficiencies at 1–5 years and 5–10 years compared with the general population ($HR_{1–5}$ = 5.68, 99% $CI_{1–5}$ = 3.33 to 9.70; $HR_{5–10}$ = 2.97, 99% $CI_{5–10}$ = 1.60 to 5.53). There was also a clear increase in risk of obesity at 1–5 years and 5–10 years after

Table 3. Adjusted HR* (99% CI) for endocrine and metabolic disease in colorectal cancer survivors

Diagnosis	1–5 years after cancer diagnosis Adjusted HR (99% CI)	5–10 years after cancer diagnosis Adjusted HR (99% CI)	>10 years after cancer diagnosis Adjusted HR (99% CI)
Endocrine, nutritional, and metabolic diseases and immunity disorders	1.92 (1.66 to 2.22)	1.50 (1.16 to 1.95)	1.30 (0.76 to 2.22)
Thyroid disorders	1.30 (1.10 to 1.55)	1.05 (0.81 to 1.35)	1.28 (0.88 to 1.87)
Thyrotoxicosis with or without goiter	1.50 (1.01 to 2.25)	1.48 (0.84 to 2.62)	1.25 (0.47 to 3.32)
Other thyroid disorders	1.31 (1.10 to 1.56)	1.05 (0.82 to 1.35)	1.35 (0.92 to 1.97)
Immunity disorders	2.83 (1.14 to 6.99)	4.56 (1.36 to 15.31)	8.35 (0.96 to 72.87)
Other nutritional, endocrine, and metabolic disorders	1.90 (1.66 to 2.18)	1.56 (1.30 to 1.88)	1.42 (1.05 to 1.92)
Disorders of mineral metabolism	2.53 (2.18 to 2.95)†	1.77 (1.32 to 2.38)	1.46 (0.94 to 2.27)
Obesity	1.40 (1.13 to 1.74)	1.50 (1.16 to 1.95)	1.08 (0.74 to 1.57)
Other metabolic, nutritional, and endocrine disorders	2.15 (1.83 to 2.51)	1.54 (1.24 to 1.92)	1.96 (1.39 to 2.77)
Diabetes mellitus without complication	1.10 (0.94 to 1.29)	1.10 (0.88 to 1.36)	1.39 (1.00 to 1.93)
Diabetes mellitus with complications	1.36 (1.09 to 1.70)	1.14 (0.84 to 1.56)	0.84 (0.49 to 1.47)
Other endocrine disorders	2.24 (1.86 to 2.70)	1.46 (1.12 to 1.91)	1.28 (0.84 to 1.94)
Nutritional deficiencies	1.98 (0.67 to 5.84)†	1.69 (1.38 to 2.08)	1.76 (1.32 to 2.35)
Unspecified protein-calorie malnutrition	2.40 (2.01 to 2.86)†	1.99 (1.34 to 2.93)	3.30 (1.68 to 6.48)
Other malnutrition	1.96 (1.74 to 2.22)†	1.66 (1.34 to 2.07)	1.59 (1.18 to 2.13)
Disorders of lipid metabolism	1.12 (0.97 to 1.29)	1.15 (0.94 to 1.41)	1.27 (0.85 to 1.89)
Gout and other crystal arthropathies	1.10 (0.81 to 1.48)	1.37 (0.94 to 2.00)	1.27 (0.70 to 2.30)
Fluid and electrolyte disorders	2.11 (1.95 to 2.29)†	1.32 (1.18 to 1.48)†	1.47 (1.07 to 2.02)
Hypoosmolality	2.18 (1.78 to 2.66)	1.49 (1.14 to 1.95)	1.55 (1.04 to 2.32)
Hypovolemia	2.55 (2.32 to 2.80)†	1.80 (1.44 to 2.23)	1.61 (1.13 to 2.30)
Hyperpotassemia	1.87 (1.47 to 2.37)	2.04 (1.50 to 2.78)	1.13 (0.67 to 1.91)
Hypopotassemia	2.23 (1.98 to 2.51)†	1.59 (1.39 to 1.82)†	1.77 (1.17 to 2.66)
Other fluid and electrolyte disorders	2.08 (1.71 to 2.53)	1.77 (1.40 to 2.26)	1.82 (1.28 to 2.60)

*Adjusted for matching factors, race, baseline body mass index, and the baseline Charlson Comorbidity Index. CI = confidence interval; HR = hazard ratio.
†Estimated using flexible parametric model.

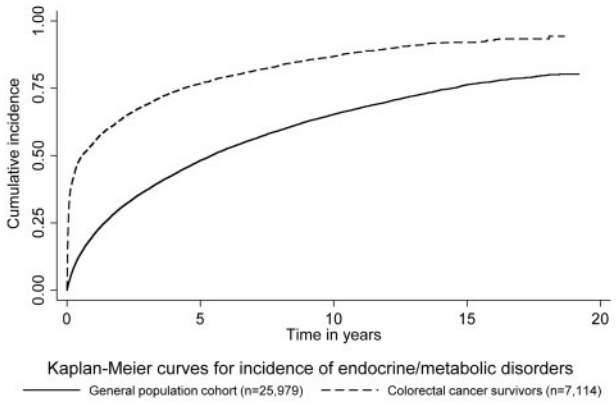

Figure 1. Cumulative incidence of endocrine and metabolic diseases among colorectal cancer survivors and the general population cohorts over the follow-up time. Kaplan-Meier curves: **solid line** shows the cumulative incidence for the general population cohort; **dotted line** shows the cumulative incidence for the colorectal cancer survivors.

cancer diagnosis for young CRC survivors ($HR_{1–5}$ = 3.10, 99% $CI_{1–5}$ = 1.82 to 5.28; $HR_{5–10}$ = 2.33, 99% $CI_{5–10}$ = 1.29 to 4.22).

Survival

Figure 2 shows the all-cause survival in CRC survivors with and without endocrine and metabolic disease. Over time, the all-cause survival in CRC survivors with endocrine or metabolic disease becomes statistically significantly worse than CRC survivors without endocrine or metabolic disease. More specifically, survival rates begin to statistically significantly divert after 5 years since diagnosis. Figure 3 shows the CRC-related survival in CRC patients, which did not appear to differ between patients with and without endocrine or metabolic disease.

Discussion

There is a clear need for improved survivorship care and evaluation of endocrine and metabolic disease in CRC patients in the long term. The findings in this study show CRC survivors experience an elevated risk for endocrine and metabolic disorders after a cancer diagnosis. This risk remains elevated well past the initial diagnosis, and the presence of such conditions statistically significantly reduces survival outcomes over time. It also appears that the relative risk for endocrine and metabolic disease is even greater in individuals diagnosed with CRC before age 50 years. This is particularly important because studies are showing increasing incidence of CRC in younger age groups (28). As the survival of CRC improves, it is essential to address the increasing health-care needs of these survivors.

There is a clear difference in survival probability for CRC survivors with endocrine and metabolic disease compared with those without. However, when considering CRC-related survival alone, those with endocrine and metabolic disease tend to fare better. This would suggest that rather than a CRC-related death, CRC survivors with endocrine and metabolic disease are succumbing to other types of diseases after their CRC diagnosis. Furthermore, although the statistically significant risk of just one of these endocrine and metabolic conditions in CRC patients is concerning, it is quite probable that many CRC survivors are diagnosed with multimorbidities. CRC survivors may have more than one endocrine and metabolic disorder but may also be experiencing other diseases such as hypertension or hyperlipidemia.

Because many endocrine and metabolic diseases can become chronic, the implementation of survivorship care plans is a critical step in improving communication regarding health needs of survivors and recommending interventions to reduce future comorbidities in CRC survivors. Based on these findings, there is a missed opportunity to improve on future health for colorectal survivors; the findings also support research that found primary care providers and oncologists may not be regularly providing and discussing survivorship care plans with their patients (29). It is possible that CRC survivors may not be adopting a healthy lifestyle (diet, exercise) after cancer (30), which would help prevent the risk for increased weight gain and diabetes, and that clinicians may not have addressed this issue with them after a cancer diagnosis.

The large sample of 7114 CRC survivors and more than 10 years of follow-up data for 25% of these survivors in a population-based analysis are major strengths of this study. Similarly, the access to medical records from the two largest health-care providers in Utah (Intermountain Healthcare and University of Utah Healthcare) improved our ability to assess disease for the majority of the population. Finally, the study does not rely on self-report, minimizing survival bias and recall errors.

The homogeneity in demographics and health behaviors (ie, majority white and low rates of tobacco and alcohol use) of the study population in Utah may be a limitation in this analysis because the results may not be generalizable to more diverse populations. There is also the possibility of information bias in our results because CRC survivors may visit the doctor more often compared with the general population. However, we observed increased risks in the later follow-up periods, during which follow-up care guidelines returned to that of the general population. Because our study used only ICD-9 codes to assess disease outcomes, there is also the risk of coding errors from the medical record data. Nevertheless, the likelihood of these errors should be similar among the cancer survivors and the general population. We did not adjust for cancer stage in our analysis because the majority of the population had localized disease, but stratification by stage showed similar risk among groups. Finally, we did not assess cancer treatment in this analysis, which may have influenced health outcomes, but this is a future direction for our project. It is also possible that adjustment for baseline BMI led to an underestimate in true risk differences between CRC survivors and the general population cohort, although we still observed increased risks of disease. We conducted a sensitivity analysis of leaving BMI out of the Cox proportional hazards models, but the risk estimates did not change enough to change the inferences for all but one estimate. Another future direction for our study includes risk prediction modeling to estimate absolute risks of adverse outcomes for different risk factor profiles for each patient.

In conclusion, CRC survivors experience statistically significant and persisting metabolic late effects after a cancer diagnosis. Of concern is the increased risk of these conditions in young-onset CRC patients. The development of survivorship care plans should encompass the evaluation of comorbid metabolic diseases but also incorporate measures to better identify a CRC patient's increased risk of developing these conditions. Future research efforts should be aimed at assessing the impact of treatment on the development of endocrine and metabolic diseases and the development of risk prediction models.

Table 4. Adjusted HR* (99% CI) for endocrine and metabolic disease in colorectal cancer survivors by sex

Diagnosis	1–5 years after cancer diagnosis		5–10 years after cancer diagnosis		>10 years after cancer diagnosis	
	Men Adjusted HR (99% CI)	Women Adjusted HR (99% CI)	Men Adjusted HR (99% CI)	Women Adjusted HR (99% CI)	Men Adjusted HR (99% CI)	Women Adjusted HR (99% CI)
Endocrine, nutritional, and metabolic diseases and immunity disorders	1.98 (1.64 to 2.39)	1.86 (1.48 to 2.33)	1.43 (1.00 to 2.04)	1.58 (1.08 to 2.32)	1.99 (0.97 to 4.09)	0.76 (0.33 to 1.75)
Thyroid disorders	1.58 (1.21 to 2.05)	1.14 (0.91 to 1.43)	1.31 (0.89 to 1.94)	0.90 (0.65 to 1.26)	1.31 (0.77 to 2.22)	1.34 (0.76 to 2.34)
Thyrotoxicosis with or without goiter	1.30 (0.62 to 2.71)	1.60 (0.99 to 2.60)	2.12 (0.78 to 5.74)	1.27 (0.63 to 2.57)	1.89 (0.37 to 9.65)	0.96 (0.26 to 3.54)
Other thyroid disorders	1.57 (1.20 to 2.05)	1.16 (0.93 to 1.45)	1.28 (0.86 to 1.90)	0.93 (0.67 to 1.29)	1.45 (0.86 to 2.44)	1.33 (0.75 to 2.33)
Immunity disorders	6.01 (1.42 to 25.35)	1.62 (0.44 to 5.97)	4.01 (0.74 to 21.75)	5.17 (0.78 to 34.18)	—	12.33 (0.58 to 262.31)
Other nutritional, endocrine, and metabolic disorders	2.04 (1.69 to 2.47)	1.77 (1.46 to 2.15)	1.77 (1.37 to 2.30)	1.36 (1.04 to 1.78)	1.48 (0.95 to 2.28)	1.38 (0.91 to 2.09)
Disorders of mineral metabolism	3.68 (2.65 to 5.11)	2.00 (1.63 to 2.46)†	2.53 (1.60 to 4.00)	1.38 (0.93 to 2.05)	2.14 (1.11 to 4.13)	1.06 (0.58 to 1.94)
Obesity	1.29 (0.94 to 1.76)	1.50 (1.12 to 2.01)	1.43 (1.01 to 2.01)	1.59 (1.08 to 2.35)	1.07 (0.62 to 1.85)	1.10 (0.66 to 1.86)
Other metabolic, nutritional, and endocrine disorders	2.20 (1.75 to 2.75)	2.10 (1.68 to 2.63)	1.85 (1.35 to 2.53)	1.31 (0.96 to 1.79)	1.98 (1.20 to 3.26)	2.01 (1.24 to 3.25)
Diabetes mellitus without complications	1.09 (0.87 to 1.35)	1.12 (0.89 to 1.42)	1.13 (0.84 to 1.52)	1.05 (0.78 to 1.43)	1.49 (0.95 to 2.35)	1.34 (0.82 to 2.18)
Diabetes mellitus with complications	1.98 (1.64 to 2.39)	1.39 (0.98 to 1.97)	1.21 (0.79 to 1.85)	1.07 (0.68 to 1.69)	0.83 (0.39 to 1.78)	0.80 (0.36 to 1.80)
Other endocrine disorders	2.71 (2.08 to 3.52)	1.86 (1.42 to 2.43)	1.62 (1.12 to 2.35)	1.30 (0.88 to 1.92)	1.05 (0.58 to 1.89)	1.59 (0.87 to 2.92)
Nutritional deficiencies	2.11 (1.79 to 2.48)†	1.85 (1.59 to 2.15)†	1.94 (1.43 to 2.64)	1.50 (1.14 to 1.99)	1.79 (1.15 to 2.81)	1.78 (1.22 to 2.61)
Unspecified protein-calorie malnutrition	3.03 (2.10 to 4.36)	2.20 (1.71 to 2.83)†	2.90 (1.68 to 5.00)	1.30 (0.72 to 2.36)	3.57 (1.37 to 9.32)	3.25 (1.21 to 8.68)
Other malnutrition	2.12 (1.77 to 2.54)†	2.03 (1.59 to 2.59)	1.83 (1.31 to 2.56)	1.52 (1.14 to 2.04)	1.70 (1.08 to 2.67)	1.54 (1.04 to 2.28)
Disorders of lipid metabolism	1.14 (0.94 to 1.39)	1.08 (0.88 to 1.33)	1.21 (0.91 to 1.61)	1.04 (0.87 to 1.24)†	1.06 (0.61 to 1.84)	1.60 (0.89 to 2.85)
Gout and other crystal arthropathies	1.01 (0.69 to 1.49)	1.23 (0.76 to 1.98)	1.45 (0.89 to 2.37)	1.25 (0.69 to 2.29)	1.06 (0.46 to 2.40)	1.63 (0.67 to 4.00)
Fluid and electrolyte disorders	2.86 (2.40 to 3.40)	1.79 (1.60 to 2.01)†	1.71 (1.32 to 2.22)	1.18 (1.01 to 1.39)†	1.32 (0.83 to 2.10)	1.62 (1.05 to 2.50)
Hypoosmolality	3.03 (2.24 to 4.11)	1.69 (1.29 to 2.22)	1.94 (1.30 to 2.88)	1.21 (0.84 to 1.76)	1.83 (0.96 to 3.51)	1.40 (0.84 to 2.35)
Hypovolemia	2.90 (2.54 to 3.31)†	2.25 (1.97 to 2.56)†	2.03 (1.48 to 2.79)	1.45 (1.20 to 1.75)†	1.47 (0.87 to 2.49)	1.72 (1.06 to 2.81)
Hyperpotassemia	1.99 (1.43 to 2.77)	1.76 (1.25 to 2.48)	2.44 (1.59 to 3.74)	1.65 (1.04 to 2.61)	1.24 (0.56 to 2.74)	1.04 (0.51 to 2.11)
Hypopotassemia	2.74 (2.11 to 3.56)	2.12 (1.68 to 2.69)	1.74 (1.19 to 2.55)	1.46 (1.05 to 2.02)	1.97 (1.04 to 3.72)	1.63 (0.94 to 2.80)
Other fluid and electrolyte disorders	2.32 (1.77 to 3.03)	1.61 (1.33 to 1.95)†	1.84 (1.50 to 2.25)†	1.61 (1.13 to 2.29)	2.44 (1.45 to 4.11)	1.46 (0.89 to 2.41)

*Adjusted for matching factors, race, baseline body mass index, and the baseline Charlson Comorbidity Index. CI = confidence interval; HR = hazard ratio.
†Estimated using flexible parametric model.

Table 5. Adjusted HR* (99% CI) for endocrine and metabolic disease in colorectal cancer survivors by age of cancer diagnosis and time from diagnosis

	1–5 years after cancer diagnosis			5–10 years after cancer diagnosis		
Diagnosis	<50 years at diagnosis Adjusted HR (99% CI)	50–64 years at diagnosis Adjusted HR (99% CI)	>65 years at diagnosis Adjusted HR (99% CI)	<50 years at diagnosis Adjusted HR (99% CI)	50–64 years at diagnosis Adjusted HR (99% CI)	>65 years at diagnosis Adjusted HR (99% CI)
Endocrine, nutritional, and metabolic diseases and immunity disorders	3.07 (2.55 to 3.69)†	1.98 (1.57 to 2.50)	1.40 (1.11 to 1.76)	2.20 (1.35 to 3.56)	1.47 (0.99 to 2.20)	1.11 (0.68 to 1.83)
Thyroid disorders	1.81 (1.29 to 2.54)†	1.50 (1.23 to 1.84)†	1.05 (0.83 to 1.32)	1.29 (0.66 to 2.50)	0.88 (0.58 to 1.35)	1.13 (0.79 to 1.62)
Thyrotoxicosis with or without goiter	1.09 (0.28 to 4.23)	1.89 (0.92 to 3.88)	1.44 (0.85 to 2.45)	0.52 (0.07 to 4.05)	1.82 (0.76 to 4.37)	1.43 (0.61 to 3.35)
Other thyroid disorders	1.84 (1.31 to 2.60)†	1.61 (1.20 to 2.16)	1.04 (0.82 to 1.31)	1.39 (0.71 to 2.72)	0.82 (0.61 to 1.11)†	1.16 (0.80 to 1.66)
Other nutritional, endocrine, and metabolic disorders	3.45 (2.76 to 4.32)†	1.92 (1.51 to 2.45)	1.54 (1.28 to 1.86)	3.29 (2.06 to 5.25)	1.47 (1.09 to 1.98)	1.24 (0.93 to 1.65)
Disorders of mineral metabolism	8.00 (4.79 to 13.34)†	3.94 (2.59 to 5.98)	1.91 (1.43 to 2.54)	3.23 (1.45 to 7.18)	2.16 (1.26 to 3.71)	1.45 (0.97 to 2.16)
Obesity	3.10 (1.82 to 5.28)	1.37 (0.99 to 1.90)	1.06 (0.75 to 1.49)	2.33 (1.29 to 4.22)	1.55 (1.08 to 2.22)	1.07 (0.66 to 1.72)
Other metabolic, nutritional, and endocrine disorders	4.07 (3.01 to 5.52)†	2.36 (1.76 to 3.18)	1.72 (1.40 to 2.12)	4.19 (2.27 to 7.71)	1.45 (1.01 to 2.08)	1.24 (0.90 to 1.71)
Diabetes mellitus without complications	1.99 (1.22 to 3.26)	1.29 (0.99 to 1.67)	0.89 (0.71 to 1.11)	1.07 (0.56 to 2.02)	1.34 (0.98 to 1.83)	0.91 (0.66 to 1.27)
Diabetes mellitus with complications	1.77 (0.77 to 4.05)	1.37 (0.91 to 2.05)	1.26 (0.94 to 1.68)	2.07 (0.87 to 4.92)	1.00 (0.61 to 1.63)	1.11 (0.69 to 1.77)
Other endocrine disorders	3.03 (1.83 to 5.01)	2.75 (2.02 to 3.73)	1.76 (1.34 to 2.30)	1.97 (1.07 to 3.62)	1.36 (0.87 to 2.13)	1.33 (0.88 to 2.02)
Nutritional deficiencies	5.68 (3.33 to 9.70)	3.07 (2.48 to 3.80)†	1.45 (1.26 to 1.66)†	2.97 (1.60 to 5.53)	1.62 (1.14 to 2.31)	1.59 (1.20 to 2.10)
Unspecified protein-calorie malnutrition	25.94 (6.58 to 102.19)	5.92 (3.28 to 10.69)	1.58 (1.27 to 1.96)†	14.64 (2.72 to 78.94)	2.51 (1.14 to 5.53)	1.43 (0.88 to 2.33)
Other malnutrition	4.25 (2.37 to 7.64)	3.05 (2.43 to 3.82)†	1.49 (1.18 to 1.87)	2.61 (1.38 to 4.91)	1.50 (1.04 to 2.19)	1.64 (1.21 to 2.22)
Disorders of lipid metabolism	1.43 (0.97 to 2.12)	1.16 (0.93 to 1.44)	1.00 (0.82 to 1.23)	1.37 (0.85 to 2.23)	1.19 (0.87 to 1.62)	1.06 (0.88 to 1.28)†
Gout and other crystal arthropathies	1.08 (0.30 to 3.90)	1.57 (0.88 to 2.80)	0.96 (0.67 to 1.39)	1.65 (0.39 to 6.92)	1.10 (0.57 to 2.11)	1.57 (0.95 to 2.60)
Fluid and electrolyte disorders	7.36 (5.74 to 9.43)†	3.71 (2.91 to 4.75)	1.59 (1.36 to 1.87)	3.00 (1.72 to 5.25)	1.81 (1.33 to 2.48)	1.18 (0.92 to 1.51)
Hypoosmolality	17.23 (6.90 to 43.04)	4.29 (2.74 to 6.70)	1.41 (1.10 to 1.81)	3.72 (2.07 to 6.69)†	1.77 (1.08 to 2.90)	1.22 (0.87 to 1.72)
Hypovolemia	8.90 (6.59 to 12.02)†	4.99 (4.08 to 6.10)†	1.72 (1.53 to 1.94)†	3.50 (1.89 to 6.46)	2.46 (1.63 to 3.72)	1.26 (1.05 to 1.50)†
Hyperpotassemia	19.96 (4.53 to 87.98)	4.20 (2.37 to 7.44)	1.31 (0.99 to 1.74)	7.82 (2.64 to 23.18)	1.66 (1.13 to 2.46)†	1.63 (1.10 to 2.43)
Hypopotassemia	6.99 (4.76 to 10.26)†	3.73 (2.65 to 5.26)	1.61 (1.28 to 2.02)	2.59 (1.22 to 5.50)	1.83 (1.21 to 2.78)	1.29 (0.92 to 1.80)
Other fluid and electrolyte disorders	13.45 (6.28 to 28.82)	2.84 (1.93 to 4.17)	1.40 (1.09 to 1.80)	3.78 (1.77 to 8.10)	1.95 (1.26 to 3.01)	1.50 (1.10 to 2.05)

*Adjusted for matching factors, race, baseline body mass index, and the baseline Charlson Comorbidity Index. CI = confidence interval; HR = hazard ratio.
†Estimated using flexible parametric model.

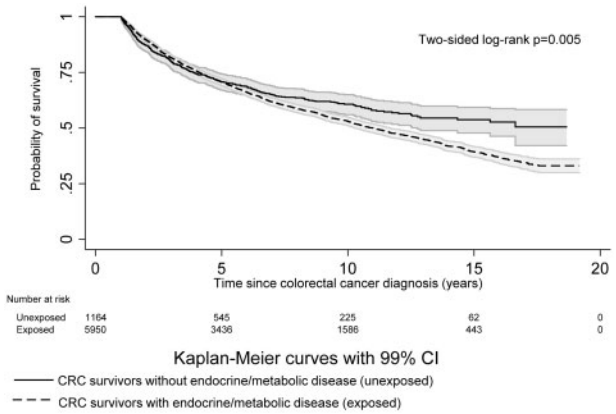

Figure 2. All-cause survival in colorectal cancer (CRC) survivors with and without endocrine and metabolic disease. Kaplan-Meier curves with 99% confidence intervals (CIs), two-sided log-rank test; **solid line** shows the survival curve for CRC patients without endocrine or metabolic diseases; **dotted line** shows the survival curve for CRC patients with endocrine or metabolic diseases.

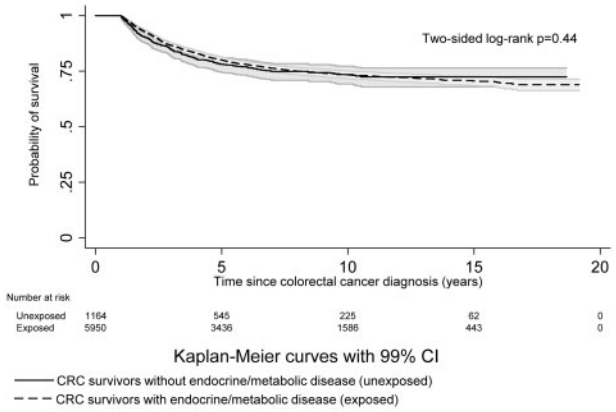

Figure 3. Colorectal cancer (CRC)-related survival in CRC survivors with and without endocrine and metabolic disease. Kaplan-Meier curves with 99% confidence intervals (CIs), two-sided log-rank test; **solid line** shows the survival curve for CRC patients without endocrine/metabolic diseases; **dotted line** shows the survival curve for CRC patients with endocrine/metabolic diseases.

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Notes

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