

# Association of Comorbid Diabetes With Clinical Outcomes and Healthcare Utilization in Colorectal Cancer Survivors

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**OBJECTIVES:** To compare clinical outcomes and healthcare utilization in colorectal cancer (CRC) survivors with and without diabetes.

**SAMPLE & SETTING:** CRC survivors (N = 3,287) were identified from a statewide electronic health record database using International Classification of Diseases (ICD) codes. Data were extracted on adults aged 21 years or older with an initial diagnosis of stage II or III CRC with diabetes present before CRC diagnosis or no diagnosis of diabetes (control).

**METHODS & VARIABLES:** ICD codes were used to extract diabetes diagnosis and clinical outcome variables. Healthcare utilization was determined by encounter type. Data were analyzed using descriptive statistics, multivariable logistic, and Cox regression.

**RESULTS:** CRC survivors with diabetes were more likely to develop anemia and infection than CRC survivors without diabetes. In addition, CRC survivors with diabetes were more likely to utilize emergency resources sooner than CRC survivors without diabetes.

**IMPLICATIONS FOR NURSING:** Oncology nurses can facilitate the early identification of high-risk survivor groups, reducing negative clinical outcomes and unnecessarily high healthcare resource utilization in CRC survivors with diabetes.

**KEYWORDS** clinical outcomes; healthcare utilization; colorectal cancer survivors; diabetes

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Colorectal cancer is the third most common cancer diagnosed in men and women in the United States (Giovannucci et al., 2010), and there are about 1.5 million individuals living with colorectal cancer in the United States as of 2021 (American Cancer Society, 2021). Because individuals with colorectal cancer are living longer as a result of advances in screening and treatment, the potential for living with comorbid medical conditions has increased. Type 2 diabetes is a common comorbid condition among individuals with colorectal cancer (Peeters et al., 2015; Tsilidis & Ioannidis, 2015), with a reported 20% of individuals with colorectal cancer having a type 2 diabetes diagnosis (De Bruijn et al., 2013) compared to about 10% of the general population (Centers for Disease Control and Prevention, 2020). The higher prevalence of diabetes among individuals with colorectal cancer may, in turn, contribute to poorer clinical outcomes and increased utilization of healthcare resources.

Individuals with colorectal cancer and diabetes have poorer survival rates (American Cancer Society, 2021; Prieto et al., 2017; Storey et al., 2017; Storey & Von Ah, 2012), increased mortality (Prieto et al., 2017; Tao et al., 2020), and poorer quality of life (Vissers et al., 2013, 2014) than colorectal cancer survivors without diabetes. In general, individuals with colorectal cancer receiving chemotherapy are primarily managed in the outpatient setting. However, some survivors experience poorer clinical outcomes, such as bone marrow suppression (neutropenia, anemia) (Busti et al., 2018; Weycker et al., 2015), infection (Hong et al., 2014), diarrhea (Bultman, 2017; Dávila et al., 2018; González et al., 2017; Meyerhardt et al., 2003; Piper & Saad, 2017), and dehydration (El-Sharkawy et al., 2015), all of which may require the utilization of additional

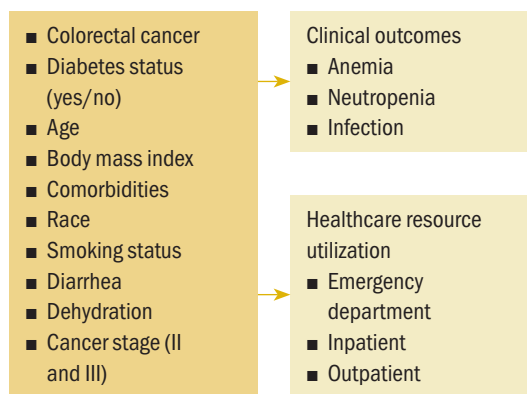
healthcare resources, such as emergency departments and/or inpatient hospitalizations (Brooks et al., 2015; Foltran et al., 2014). Comorbid diabetes in individuals with colorectal cancer may accelerate the onset of these clinical outcomes, increasing the utilization of healthcare resources.

Despite the high prevalence of diabetes among individuals with colorectal cancer, there is a paucity of research on differences in clinical outcomes and utilization of healthcare resources between individuals with colorectal cancer with and without diabetes. However, research suggests that demographic and clinical characteristics may play a role in clinical outcomes and healthcare resource utilization. For example, older age is a risk factor for diabetes (Bigelow & Freeland, 2017; Katz et al., 2013), colorectal cancer (Brown et al., 2020; de Kort et al., 2017), and poor clinical outcomes (Chang et al., 2019). With age, there is a gradual deterioration of the immune system (immunosenescence), which increases vulnerability to myelosuppression and infection (Aiello et al., 2019). Body mass index (BMI) also is a risk factor for diabetes and colorectal cancer (American Cancer Society, 2021; González et al., 2017; Peeters et al., 2015). Research has noted that individuals with a higher BMI have poorer clinical outcomes (Kalb et al., 2019) and utilize more healthcare resources (Nørtoft et al., 2018). Comorbidities also are associated with poorer clinical outcomes and increased demand for healthcare resources (McPhail, 2016; Safarti et al., 2016; Vegda et al., 2009). Gender may also play a role in complications associated with diabetes, with women having an increased likelihood of complications (Huebschmann et al., 2019; Peters & Woodward, 2018). Research also indicates that

women utilize more healthcare resources than men (Wang et al., 2019). There is compelling evidence that race and ethnicity (Black and Hispanic) is a risk factor for poorer clinical outcomes and higher utilization of healthcare resources because of delays in seeking treatment (Fiscella & Sanders, 2016; Tawk et al., 2016; Walker et al., 2016). Smoking may also affect clinical outcomes; it has been shown to exacerbate diabetes-related complications (Campagna et al., 2019). A common troublesome symptom among people with diabetes and colorectal cancer is diarrhea (McQuade et al., 2014), which contributes to dehydration, poor clinical outcomes, and increased healthcare utilization. Lastly, cancer stage is important because individuals with diabetes often have more advanced-stage cancers at diagnosis than those without diabetes (Lipscombe et al., 2015). Advanced-stage cancer at diagnosis can lead to poorer clinical outcomes and greater healthcare resource utilization (Yabroff et al., 2013). Although there is ample research showing that these characteristics contribute to poorer outcomes among individuals with diabetes or colorectal cancer, research on the combined effect of having diabetes and colorectal cancer is limited. Therefore, the purpose of this study was to use data from electronic health records to compare individuals with colorectal cancer with and without diabetes in terms of (a) clinical outcomes (anemia, neutropenia, and infection) and (b) utilization of healthcare resources (emergency department services, outpatient services, and inpatient services) while controlling for age, BMI, comorbidities, gender, race, smoking status, diarrhea, dehydration, and cancer stage. The findings from the current study can be used to identify high-risk survivor groups, mitigate negative clinical outcomes by developing targeted interventions, and reduce unnecessarily high healthcare resource utilization.

The conceptual framework for this study was derived from Hammer et al's. (2019) conceptual model of hyperglycemia in patients with cancer, which describes the physiological linkages between cancer, hyperglycemia (a common characteristic of diabetes), and clinical outcomes. Specifically, this model depicts the intracellular processes initiated by hyperglycemia, which contributes to myelosuppression and, subsequently, an increased risk for infection, organ dysfunction, and death. The deleterious impact of diabetes has been demonstrated in other populations of patients with cancer (Ma et al., 2019; Seymour et al., 2015; Storey et al., 2017, 2019; Storey & Von Ah, 2012). However, this has not been fully examined

**FIGURE 1. Conceptual Framework**



among individuals with colorectal cancer. For this study, the current authors modified Hammer et al.'s (2019) model to not only include clinical outcomes of myelosuppression and infection but also health-care resource utilization (emergency department services, inpatient services, and outpatient services) because it is often associated with poor clinical outcomes (Epstein et al., 2020; Erichsen et al., 2013). To better evaluate the contributions of diabetes to clinical outcomes and healthcare resource utilization, the current study focused on individuals with colorectal

cancer with and without diabetes, while controlling for known covariates identified in the literature (see Figure 1).

## Methods

### Design

This is a retrospective cohort study of individuals with colorectal cancer with and without diabetes treated in a large hospital system in the midwestern United States between 2007 and 2017. Clinical data were extracted from a statewide healthcare network,

**TABLE 1. Colorectal Cancer Survivor Characteristics by Group**

Characteristic	Patients Without Diabetes (N = 2,632)		Patients With Diabetes (N = 655)		All Patients (N = 3,287)		p
	$\bar{X}$	SD	$\bar{X}$	SD	$\bar{X}$	SD	
Age (years)	59.01	12.69	63.3	10.83	59.86	12.46	< 0.0001
Body mass index	28.64	6.58	31.64	7.31	29.43	6.91	< 0.0001
Charlson Comorbidity Index	0.32	0.77	1.24	1.29	0.52	0.98	< 0.0001
Characteristic	n	%	n	%	n	%	p
<b>Cancer stage</b>							0.3832
II	830	32	195	30	1,025	31	
III	1,802	68	460	70	2,262	69	
<b>Dehydration</b>							< 0.0001
No	2,438	93	574	88	3,012	92	
Yes	194	7	81	12	275	8	
<b>Diarrhea</b>							0.0122
No	2,399	91	576	88	2,975	91	
Yes	233	9	79	12	312	9	
<b>Gender</b>							0.0152
Male	1,359	52	373	57	1,732	53	
Female	1,272	48	282	43	1,554	47	
Missing data	1	< 1	–	–	1	< 1	
<b>Race</b>							0.0065
White	2,442	93	586	89	3,028	92	
Black	165	6	64	10	229	7	
Missing data	25	1	5	1	30	1	
<b>Smoking status</b>							< 0.0001
Current	129	5	63	10	192	6	
Former	75	3	50	8	125	4	
No history of smoking	884	34	224	34	1,108	34	
Missing data	1,544	59	318	49	1,862	57	

**Note.** Because of rounding, percentages may not total 100.

**Note.** Charlson Comorbidity Index scores range from 0 to 6, with higher scores indicating increased severity of condition.

and the state cancer registry was used to determine cancer diagnosis.

### Eligibility

Eligible patients were selected from the cohort if they met the following inclusion criteria for the study: (a) having a nonmetastatic diagnosis of colorectal cancer (stage II or III) per International Classification of Diseases (ICD) code; (b) receiving chemotherapy either alone or in combination with other adjuvant therapy (surgery and/or radiation therapy); (c) having a diagnosis of type 2 diabetes prior to the diagnosis of cancer (i.e., colorectal cancer with diabetes) or no diagnosis of diabetes; and (d) being an adult aged 21 years or older (colorectal cancer is rare in children). Exclusion criteria were (a) having another diagnosis

of cancer, except basal or squamous skin cancer; (b) having metastatic colorectal cancer; and (c) receiving subsequent chemotherapy after the initial chemotherapy for their cancer diagnosis.

### Procedures

A total of 19,032 patients with colorectal cancer were identified based on ICD codes (Centers for Medicare and Medicaid Services, 2020a, 2020b). ICD codes for type 2 diabetes were used to determine those individuals with colorectal cancer and diabetes, along with reviews of medication lists for antidiabetes medications. After applying the inclusion and exclusion criteria, 3,287 individuals with colorectal cancer were included in the study cohort. Demographic and clinical information was extracted from electronic health

TABLE 2. Multivariate Logistic Regression: Association Between Clinical Outcome and Survivor Factors						
Variable	Anemia (N = 170)		Neutropenia (N = 191)		Infection (N = 507)	
	OR	95% CI	OR	95% CI	OR	95% CI
Age						
Overall	1	[0.99, 1.02]	0.98	[0.97, 0.99]	0.99	[0.98, 1]
Dehydration						
Yes	3.91	[2.62, 5.85]	2.75	[1.85, 4.09]	2.17	[1.6, 2.93]
No (ref)	-	-	-	-	-	-
Diabetes						
Yes	1.45	[1.04, 2.01]	1.07	[0.77, 1.47]	2.09	[1.71, 2.56]
No (ref)	-	-	-	-	-	-
Diarrhea						
Yes	2.39	[1.59, 3.59]	2.51	[1.7, 3.72]	1.79	[1.33, 2.42]
No (ref)	-	-	-	-	-	-
Gender						
Female	1.37	[0.99, 1.88]	1.44	[1.07, 1.95]	1.32	[1.08, 1.61]
Male (ref)	-	-	-	-	-	-
Race						
Black	1.21	[0.67, 2.17]	1.17	[0.68, 2.03]	0.96	[0.66, 1.4]
Unknown	0.77	[0.14, 4.34]	0.86	[0.16, 4.62]	0.7	[0.24, 2.04]
White (ref)	-	-	-	-	-	-
Smoking status						
Former	1.78	[1.1, 2.88]	0.56	[0.31, 1.02]	1.14	[0.84, 1.55]
Unknown	1.01	[0.69, 1.47]	0.9	[0.65, 1.26]	0.45	[0.36, 0.57]
Current	0.79	[0.43, 1.46]	0.72	[0.42, 1.24]	0.88	[0.64, 1.2]
No history (ref)	-	-	-	-	-	-
CI—confidence interval; OR—odds ratio; ref—reference						

records to describe the sample. Clinical outcomes, including anemia and neutropenia, were identified based on the ICD codes. Healthcare utilization was extracted from the electronic health record based on documented encounters (visits) to emergency department services, inpatient services, and outpatient services. Accuracy of the data set was verified in two ways. First, the data extraction was repeated, and the number of records and variables was reviewed and compared with the original data set. In addition, a second data analyst verified the data code used to conduct the extraction and create the data set. This study was approved by the Indiana University Institutional Review Board.

### Statistical Analysis

Descriptive statistics were used to analyze the demographic and clinical characteristics of the sample. The primary independent variable was diabetes status, categorized as a dichotomous variable (yes or no). All analyses regarding the effect of diabetes on clinical outcomes and healthcare utilization were adjusted for potential confounding covariates, including age, BMI, comorbidity, gender, race, smoking status, diarrhea, dehydration, and cancer stage (II or III). Multivariable logistic regression was performed to evaluate the relationship between diabetes and clinical outcomes (e.g., anemia, neutropenia, infection). Cox regression analysis was used to predict factors associated with time to utilization of emergency department services, inpatient services, or outpatient services. All analyses were performed using SAS, version 9.4.

## Results

### Patient Characteristics

Table 1 shows the characteristics of the colorectal cancer cohort ( $N = 3,287$ ). The mean age was 59.86 years. Most were male (53%) and White (92%). Only 4% reported being a former smoker, whereas 6% reported being a current smoker. A little less than one-third had stage II cancer, and more than two-thirds had stage III cancer. Approximately 20% of patients also had type 2 diabetes. In this sample, individuals with colorectal cancer and diabetes were older, had a higher BMI, and had more comorbidities than individuals with colorectal cancer without diabetes.

### Clinical Outcomes

**Anemia:** Table 2 shows the results of multivariable logistic regression analyses. A diagnosis of diabetes

increased the odds of anemia in individuals with colorectal cancer by 1.45 (95% confidence interval [CI] [1.04, 2.01]), when controlling for age, gender, race, smoking, diarrhea, and dehydration. Smoking status also was a predictor of anemia. Being a former smoker (versus a nonsmoker) was associated with higher odds (odds ratio [OR] = 1.78; 95% CI [1.10, 2.88]) of anemia. In addition, the presence of diarrhea (OR = 2.39; 95% CI [1.59, 3.59]) and dehydration (OR = 3.91; 95% CI [2.62, 5.85]) predicted anemia.

**Neutropenia:** In this sample of individuals with colorectal cancer, diabetes was not associated with an increased risk of neutropenia. However, being a woman with colorectal cancer increased the odds for neutropenia (OR = 1.44; 95% CI [1.07, 1.95]). Having diarrhea (OR = 2.51; 95% CI [1.7, 3.72]) and dehydration (OR = 2.75; 95% CI [1.85, 4.09]) also were associated with higher odds of having neutropenia.

**Infection:** Individuals with colorectal cancer and diabetes were more likely to develop an infection than individuals with colorectal cancer without diabetes (OR = 2.09; 95% CI [1.71, 2.56]). Women with colorectal cancer were more likely to develop an infection (OR = 1.32; 95% CI [1.08, 1.61]) than their male counterparts. Having diarrhea (OR = 1.79; 95% CI [1.33, 2.42]) and dehydration (OR = 2.17; 95% CI [1.6, 2.93]) also increased the odds of an infection.

### Healthcare Utilization

Table 3 shows the results of the Cox regression model. Individuals with colorectal cancer and diabetes were more likely to utilize emergency department resources (hazard ratio [HR] = 1.11; 95% CI [1.01, 1.21]) compared to individuals with colorectal cancer without diabetes. Diarrhea also was associated with shorter time to emergency department utilization (HR = 1.62, 95% CI [1.4, 1.88]) and higher inpatient visit utilization (HR = 1.27; 95% CI [1.14, 1.41]). Lastly, dehydration (HR = 1.47; 95% CI [1.26, 1.71]) was associated with shorter time to emergency department utilization.

## Discussion

This study comprehensively examines clinical outcomes and healthcare utilization of individuals with colorectal cancer with and without diabetes. Using a large data set, a cohort of individuals with colorectal cancer was identified; about 20% of individuals within the cohort had diabetes, which is comparable to other studies showing the prevalence of diabetes among individuals with colorectal cancer to be as high as 24% (Prieto et al., 2017; Vissers et al., 2013, 2014).

Importantly, the current study found that individuals with colorectal cancer and diabetes were more likely to have anemia and infection and utilize emergency department resources.

### Clinical Outcomes

Results indicate that individuals with colorectal cancer and diabetes were more likely to have anemia than those without diabetes. Anemia is common in individuals with colorectal cancer (Khanbhai et al., 2014; Ludwig et al., 2004), with about 40% experiencing anemia as a result of cancer or its treatment (Busti et al., 2018). Colorectal cancer and diabetes are both inflammatory disease processes (Andrews & Arredondo, 2012), which may lead to epigenetic changes that alter the structure and function of bone

marrow (Gallagher et al., 2015; Keating & El-Osta, 2013; Maiuri & O'Hagan, 2016; Parcesepo et al., 2016; Shurin, 2012; Tsilidis & Ioannidis, 2015). Therefore, it is plausible that the combination of these co-occurring inflammatory conditions (colorectal cancer and diabetes) may cause more profound bone marrow suppression, resulting in an increased risk of anemia among individuals with colorectal cancer and diabetes. More research is needed to understand how comorbid diabetes affects the bone marrow of individuals with colorectal cancer.

The current authors also found that a history of smoking was associated with anemia. Smoking stimulates inflammation (Levitzky et al., 2008) and has adverse effects on the hematologic system (Malenica et al., 2017). The current study found anemia to be

TABLE 3. Cox Regression: Association Between Healthcare Resource Utilization and Survivor Factors				
Variable	Emergency Department Services (N = 2,166)		Inpatient Services (N = 2,820)	
	HR	95% CI	HR	95% CI
<b>Age</b>				
Overall	0.98	[0.98, 0.98]	0.99	[0.98, 0.99]
<b>Dehydration</b>				
Yes	1.47	[1.26, 1.71]	0.88	[0.78, 0.98]
No (ref)	–	–	–	–
<b>Diabetes</b>				
Yes	1.11	[1.01, 1.21]	1.08	[1, 1.17]
No (ref)	–	–	–	–
<b>Diarrhea</b>				
Yes	1.62	[1.4, 1.88]	1.27	[1.14, 1.41]
No (ref)	–	–	–	–
<b>Gender</b>				
Female	1.06	[0.98, 1.16]	1	[0.93, 1.08]
Male (ref)	–	–	–	–
<b>Race</b>				
Black	1.15	[0.96, 1.39]	1.11	[0.97, 1.28]
Unknown	1.37	[0.86, 2.16]	1.41	[1.05, 1.89]
White (ref)	–	–	–	–
<b>Smoking status</b>				
Former	0.92	[0.79, 1.07]	0.78	[0.68, 0.88]
Unknown	1.04	[0.94, 1.14]	0.87	[0.8, 0.95]
Current	0.95	[0.81, 1.13]	0.8	[0.71, 0.9]
No history (ref)	–	–	–	–
CI—confidence interval; HR—hazard ratio; ref—reference				
<b>Note.</b> Outpatient services are ref among types of healthcare resource utilization.				



greater among former smokers compared to current smokers. In this sample, it was not possible to determine the length of time since smoking cessation had occurred. However, the long-term effects of smoking on red blood cells may persist well beyond cessation (Pedersen et al., 2019), remaining a contributing factor for anemia.

Diarrhea and dehydration also were associated with anemia in this sample. Cancer therapies can cause epigenetic changes in the gastrointestinal tract and to the structure and functions of the colon, resulting in diarrhea (Bultman, 2017; Dávila et al., 2018; González et al., 2017; Meyerhardt et al., 2003; Piper & Saad, 2017). Changes in the lining of the gastrointestinal tract can cause a disturbance in iron metabolism (Qijeg et al., 2011), which may be a contributing factor to the risk of anemia. In addition, it is possible that severe diarrhea can lead to intermittent blood loss and exacerbation of anemia. Erythrocytes (red blood cells) require cellular hydration to function and survive (Gallagher, 2017). Dehydration can cause perturbations in the intracellular water of erythrocytes, further exacerbating anemia (Gallagher, 2017). The relationship of diarrhea and dehydration with anemia bears further investigation.

In the current study, an association was not found between diabetes and neutropenia. Neutropenia is associated with cancer and cancer therapies, and it is estimated to occur in about 11% of individuals with colorectal cancer (Weycker et al., 2015). In patients with diabetes, a hyperglycemic state decreases the mobilization, chemotaxis, and phagocytic activity of neutrophils (Peleg et al., 2007; Vardakas et al., 2007). The role of diabetes in neutropenia in individuals with colorectal cancer has not been fully explored. Only one systematic review (Alenzi & Kelley, 2017) has examined the impact of diabetes and hyperglycemia on neutropenia in other solid tumor (breast, lung, and ovarian) populations. Alenzi and Kelley (2017) noted that cancer survivors with hyperglycemia and diabetes had increased odds of chemotherapy-induced neutropenia. It is possible that the current authors did not find an association between diabetes and neutropenia in individuals with colorectal cancer because those with diabetes were well controlled or, more likely, there were individuals with colorectal cancer with prediabetes in the control, which may have influenced findings. In addition, neutropenia was identified using ICD codes rather than laboratory values, which may have precluded some individuals with colorectal cancer and neutropenia. More research is needed to examine the impact of hyperglycemia and diabetes on neutropenia among individuals with colorectal cancer.

The current authors found that being female and having diarrhea and dehydration increased the odds of experiencing neutropenia. The increased risk of neutropenia among women with colorectal cancer may be related to the fact that right-sided colon cancer, which is more common among women, has been associated with increased leukopenia, including neutropenia (Chansky et al., 2005; Katz et al., 2013; Kim et al., 2015, 2018). In addition, right-sided colorectal cancer is associated with increased diarrhea (Kim et al., 2018), which can result in dehydration. Studies assessing the impact of gender differences in clinical outcomes among individuals with colorectal cancer are important for understanding the biological and sociocultural risks and responses to colorectal cancer treatment.

The current authors found that individuals with colorectal cancer and diabetes were more likely to develop an infection. Other researchers also have found that individuals with colorectal cancer and diabetes had a higher risk for infection-related adverse events, per the Common Terminology Criteria for Adverse Events (Hong et al., 2014). The hyperglycemic environment caused by diabetes contributes to increased virulence of some pathogenic organisms, increasing susceptibility to infection (Casqueiro et al., 2012).

In the current study, women with colorectal cancer were more likely than their male counterparts to have infections. Because women are at a higher risk for leukopenia and neutropenia (Chansky et al., 2005; Katz et al., 2013; Kim et al., 2015, 2018), the resultant compromised immune status may place them at increased risk for developing infections. Prospective studies examining the role of gender in individuals with colorectal cancer are warranted.

The current authors found that diarrhea and dehydration were associated with infection. Colorectal cancer and its treatment can cause diarrhea. Changes in the intestinal milieu co-occurring with immunosuppression can increase the vulnerability of colorectal cancer survivors to life-threatening infections (Bossi et al., 2018). Dehydration is often associated with diarrhea in individuals with colorectal cancer, particularly during cancer treatment. Dehydration also is associated with infection, including urinary tract infection (El-Sharkawy et al., 2015).

#### Healthcare Utilization

The current study demonstrated that individuals with colorectal cancer and diabetes utilized healthcare resources more than individuals with colorectal cancer without diabetes. Specifically, the authors found that individuals with colorectal cancer and diabetes utilized

emergency resources more than individuals with colorectal cancer without diabetes. In a study of breast and colorectal cancer survivors by Yao et al. (2015), those with diabetes received poorer diabetes management after their cancer diagnosis than before their cancer diagnosis. Healthcare providers are focused on curative intent and may not focus on the management of diabetes (Yao et al., 2015). In addition, individuals with cancer and diabetes often prioritize self-management of treatment side effects over self-management of diabetes (Hershey et al., 2012). It is plausible that poor diabetes management among individuals with colorectal cancer could increase toxicity, side effects, or acute symptoms, leading to greater utilization of emergency department services. Additional studies on the challenges of self-management among individuals with colorectal cancer and diabetes are needed to develop interventions specific to this high-risk subgroup of cancer survivors.

Although the current authors could not directly determine if emergency visits of individuals with colorectal cancer with diabetes were related to either colorectal cancer or diabetes, findings from this study showed that individuals with co-occurring conditions were more likely to utilize these resources. Independently, both cancer and diabetes place a substantial financial burden on society (Agency for Healthcare Research and Quality, n.d.; American Diabetes Association, n.d.). However, research describing the impact of diabetes in addition to colorectal cancer on the utilization and subsequent costs of healthcare services is lacking. More research is needed to determine the cost of healthcare utilization and the personal financial burden for individuals with colorectal cancer and diabetes.

Lastly, data from the electronic health records of individuals with colorectal cancer were used to expand on the original conceptual model of hyperglycemia in a patient with cancer (Hammer et al., 2019). Information was added related to the impact of diabetes on myelosuppression (anemia), and the model was expanded to include other clinical outcomes. Findings of the current study support this revised model depicting the deleterious role of diabetes on infection, myelosuppression (anemia), and healthcare utilization, all of which are important to identify, given that cancer survivors are living longer with comorbid conditions that can greatly affect resources.

### Strengths and Limitations

This study filled a gap in knowledge about clinical outcomes and healthcare utilization among individuals

### KNOWLEDGE TRANSLATION

- Colorectal cancer survivors with comorbid diabetes may be more likely to experience poor clinical outcomes, including anemia and infection.
- Colorectal cancer survivors with comorbid diabetes may be more likely to utilize emergency department resources.
- Oncology nurses can facilitate the early identification of high-risk survivor groups, reducing negative clinical outcomes and unnecessarily high resource utilization in colorectal cancer survivors with diabetes.

with colorectal cancer and diabetes. It included a large sample size with a focus on a specific common cancer (colorectal cancer) and comorbid diabetes. In addition, it used data from electronic health records to examine the influence of comorbid diabetes on clinical outcomes and healthcare resource utilization. Big data from electronic health records provide a rich source of information for biomedical research (Duan et al., 2014), allowing researchers to capture real-world data that otherwise would be costly and difficult to acquire in a longitudinal trial. This study provides a foundation for the development of prospective studies on clinical outcomes and healthcare utilization of individuals with colorectal cancer with type 2 diabetes.

These findings should be considered in light of several limitations. Although the current study provides preliminary data that are useful for guiding the development of future prospective studies, the descriptive, retrospective study design precludes the ability to establish causality. The goal of this study was to compare clinical outcomes and healthcare utilization among individuals with colorectal cancer with and without diabetes. Therefore, the authors did not examine the role of other comorbidities on these outcomes, which may have affected the findings. More research is needed to understand the influence of comorbidities on these and other outcomes of cancer survivors. Lastly, it is possible that clinicians may have incorrectly assigned or omitted some health data and ICD codes in the electronic health record. However, to mitigate this risk, the diagnosis of type 2 diabetes was verified by a review of medication lists. Given that the prevalence of diabetes is increasing (Rowley et al., 2017), prospective studies exploring the differences in clinical outcomes and healthcare resource utilization among other cancer survivor groups with diabetes are important.



## Implications for Nursing

The current study supports prior studies that showed poorer clinical outcomes for individuals with colorectal cancer and diabetes while also adding important information about healthcare utilization. Oncology nurses' understanding of the contribution of comorbid diabetes to poor outcomes in individuals with colorectal cancer can inform the development of proactive assessment, intervention, monitoring, and treatment strategies, improving clinical outcomes and reducing the utilization of healthcare resources. The current study identified important outcomes for future interventional research. Such research should apply these findings to develop evidence-based interventions that target clinical outcomes and healthcare resource utilization among high-risk survivor groups. Lastly, future research should look specifically at hyperglycemia and outcomes, as suggested in the model.

## Conclusion

Individuals with colorectal cancer and diabetes experienced more anemia, infection, and emergency department visits than survivors without diabetes. The best approach for the clinical management of comorbid diabetes in individuals with colorectal cancer remains unclear. Most clinical practice guidelines focus on a single disease, limiting guidance for clinicians in the treatment of cancer survivors with diabetes (Deshields et al., 2013; Lee et al., 2017; Storey et al., 2017), while also possibly placing this subset of individuals with colorectal cancer at risk for poorer clinical outcomes and higher utilization of healthcare resources. Because cancer survivors are living longer, it is imperative to understand the ramifications that comorbid conditions have on the survivorship experience. More studies are needed to explore the impact of comorbid conditions on clinical outcomes and healthcare utilization in individuals with colorectal cancer.

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## REFERENCES

- Agency for Healthcare Research and Quality. (n.d.). Medical Expenditure Panel Survey. <https://meps.ahrq.gov/mepsweb>
- Aiello, A., Farzaneh, F., Candore, G., Caruso, C., Davinelli, S., Gambino, C.M., . . . Accardi, G. (2019). Immunosenescence and its hallmarks: How to oppose aging strategically? A review of potential options for therapeutic intervention. *Frontiers in Immunology*, 10, 2247. <https://doi.org/10.3389/fimmu.2019.02247>
- Alenzi, E.O., & Kelley, G.A. (2017). The association of hyperglycemia and diabetes mellitus and the risk of chemotherapy-induced neutropenia among cancer patients: A systematic review with meta-analysis. *Journal of Diabetes and its Complications*, 31(1), 267–272. <https://doi.org/10.1016/j.jdiacomp.2016.09.006>
- American Cancer Society. (2021, January 12). Key statistics for colorectal cancer. <https://www.cancer.org/cancer/colon-rectal-cancer/about/key-statistics.html>
- American Diabetes Association. (n.d.). The cost of diabetes. <https://www.diabetes.org/resources/statistics/cost-diabetes>
- Andrews, M., & Arredondo, M. (2012). Ferritin levels and hepcidin mRNA expression in peripheral mononuclear cells from anemic type 2 diabetic patients. *Biological Trace Element Research*, 149, 1–4. <https://doi.org/10.1007/s12011-012-9389-6>
- Bigelow, A., & Freeland, B. (2017). Type 2 diabetes care in the elderly. *Journal for Nurse Practitioners*, 13(3), 181–186. <https://doi.org/10.1016/j.nurpra.2016.08.010>
- Bossi, P., Antonuzzo, A., Cherny, N.I., Rosengarten, O., Pernot, S., Trippa, F., . . . Ripamonti, C.I. (2018). Diarrhoea in adult cancer patients: ESMO clinical practice guidelines. *Annals of Oncology*,

- 29(Suppl. 4), IV126–IV142. <https://doi.org/10.1093/annonc/mdy145>
- Brooks, G.A., Kansagra, A.J., Rao, S.R., Weitzman, J.I., Linden, E.A., & Jacobsen, J.O. (2015). A clinical prediction model to assess risk for chemotherapy-related hospitalization in patients initiating palliative chemotherapy. *JAMA Oncology*, 1(4), 441–447. <https://doi.org/10.1001/jamaoncol.2015.0828>
- Brown, J.C., Zhang, S., Ou, F.-S., Venook, A.P., Niedzwiecki, D., Lenz, H.-J., . . . Meyerhardt, J.A. (2020). Diabetes and clinical outcome in patients with metastatic colorectal cancer: CALGB 80405 (Alliance). *JNCI Cancer Spectrum*, 4(1), pkz078. <https://doi.org/10.1093/jncics/pkz078>
- Bultman, S.J. (2017). Interplay between diet, gut microbiota, epigenetic events, and colorectal cancer. *Molecular Nutrition and Food Research*, 61(1), 1500902. <https://doi.org/10.1002/mnfr.201500902>
- Busti, F., Marchi, G., Ugolini, S., Castagna, A., & Girelli, D. (2018). Anemia and iron deficiency in cancer patients: Role of iron replacement therapy. *Pharmaceuticals*, 11(4), 94. <https://doi.org/10.3390/ph11040094>
- Campagna, D., Alamo, A., Di Pino, A., Russo, C., Calogero, A.E., Purrello, F., & Polosa, R. (2019). Smoking and diabetes: Dangerous liaisons and confusing relationships. *Diabetology and Metabolic Syndrome*, 11, 85. <https://doi.org/10.1186/s13098-019-0482-2>
- Casqueiro, J., Casqueiro, J., & Alves, C. (2012). Infections in patients with diabetes mellitus: A review of pathogenesis. *Indian Journal of Endocrinology and Metabolism*, 16(7), 27–36. <https://doi.org/10.4103/2230-8210.94253>
- Centers for Disease Control and Prevention. (2020). *National diabetes statistics report, 2020: Estimates of diabetes and its burden in the United States*. <https://www.cdc.gov/diabetes/pdfs/data/statistics/national-diabetes-statistics-report.pdf>
- Centers for Medicare and Medicaid Services. (2020a). ICD-9-CM diagnosis and procedure codes: Abbreviated and full code titles. <https://www.cms.gov/Medicare/Coding/ICD9ProviderDiagnosticCodes/codes>
- Centers for Medicare and Medicaid Services. (2020b). ICD-10. <https://www.cms.gov/Medicare/Coding/ICD10/index.html>
- Chang, A.Y., Skirbekk, V.F., Tyrovolas, S., Kassebaum, N.J., & Dieleman, J.L. (2019). Measuring population ageing: An analysis of the Global Burden of Disease Study 2017. *Lancet Public Health*, 4(3), e159–e167. [https://doi.org/10.1016/s2468-2667\(19\)30019-2](https://doi.org/10.1016/s2468-2667(19)30019-2)
- Chansky, K., Benedetti, J., & Macdonald, J.S. (2005). Differences in toxicity between men and women treated with 5-fluorouracil therapy for colorectal carcinoma. *Cancer*, 103(6), 1165–1171. <https://doi.org/10.1002/cncr.20878>
- Dávila, L.A., Pirela, V.B., Díaz-Vasquez, W., Villasmil, N.R., León, S.C., Contreras, M.C.E., . . . Valdebenito, F. (2018). The microbiome and the epigenetics of diabetes mellitus. In V.Y. Waisundara (Ed.), *Diabetes food plan* (pp. 11–31). IntechOpen. <https://doi.org/10.5772/intechopen.76201>
- De Bruijn, K.M.J., Arends, L.R., Hansen, B.E., Leeftang, S., Ruiter, R., & van Eijck, C.H.J. (2013). Systematic review and meta-analysis of the association between diabetes mellitus and incidence and mortality in breast and colorectal cancer. *BJS*, 100(11), 1421–1429. <https://doi.org/10.1002/bjs.9229>
- de Kort, S., Masclee, A.A.M., Sanduleanu, S., Weijenberg, M.P., van Herk-Sukel, M.P.P., Oldenhof, N.J.J., . . . Janssen-Heijnen, M.L. (2017). Higher risk of colorectal cancer in patients with newly diagnosed diabetes mellitus before the age of colorectal cancer screening initiation. *Scientific Reports*, 7, 46527. <https://doi.org/10.1038/srep46527>
- Deshields, T.L., Potter, P., Olsen, S., & Liu, J. (2013). The persistence of symptom burden: Symptom experience and quality of life of cancer patients across one year. *Supportive Care in Cancer*, 22(4), 1089–1096. <https://doi.org/10.1007/s00520-013-2049-3>
- Duan, W., Shen, X., Lei, J., Xu, Q., Yu, Y., Li, R., . . . Ma, Q. (2014). Hyperglycemia, a neglected factor during cancer progression. *BioMed Research International*, 2014, 461917. <https://doi.org/10.1155/2014/461917>
- El-Sharkawy, A.M., Sahota, O., & Lobo, D.N. (2015). Acute and chronic effects of hydration status on health. *Nutrition Reviews*, 73(Suppl. 2), 97–109. <https://doi.org/10.1093/nutrit/nuv038>
- Epstein, R.S., Aapro, M.S., Roy, U.K.B., Salimi, T., Krenitsky, J., Leone-Perkins, M.L., . . . Crawford, J. (2020). Patient burden and real-world management of chemotherapy-induced myelosuppression: Results from an online survey of patients with solid tumors. *Advances in Therapy*, 37(8), 3606–3618. <https://doi.org/10.1007/s12325-020-01419-6>
- Erichsen, R., Horváth-Puhó, E., Iversen, L.H., Lash, T.L., & Sørensen, H.T. (2013). Does comorbidity interact with colorectal cancer to increase mortality? A nationwide population-based cohort study. *British Journal of Cancer*, 109(7), 2005–2013. <https://doi.org/10.1038/bjc.2013.541>
- Fiscella, K., & Sanders, M.R. (2016). Racial and ethnic disparities in the quality of health care. *Annual Review of Public Health*, 37, 375–394. <https://doi.org/10.1146/annurev-publhealth-032315-021439>
- Foltran, L., Aprile, G., Pisa, F.E., Ermacora, P., Pella, N., Iaiza, E., . . . Fasola, G. (2014). Risk of unplanned visits for colorectal cancer outpatients receiving chemotherapy: A case-crossover study. *Supportive Care in Cancer*, 22(9), 2527–2533. <https://doi.org/10.1007/s00520-014-2234-z>
- Gallagher, K.A., Joshi, A., Carson, W.F., Schaller, M., Allen, R., Mukerjee, S., . . . Kunkel, S.L. (2015). Epigenetic changes in bone marrow progenitor cells influence the inflammatory phenotype and alter wound healing in type 2 diabetes. *Diabetes*, 64(4), 1420–1430. <https://doi.org/10.2337/db14-0872>
- Gallagher, P.G. (2017). Disorders of erythrocyte hydration. *Blood*, 130(25), 2699–2708. <https://doi.org/10.1182/blood-2017-04-590810>
- Giovannucci, E., Harlan, D.M., Archer, M.C., Bergenstal, R.M., Gapstur, S.M., Habel, L.A., . . . Yee, D. (2010). Diabetes and cancer: A consensus report. *Diabetes Care*, 33(7), 1674–1685. <https://doi.org/10.2337/dc10-0666>

- González, N., Prieto, I., del Puerto-Nevado, L., Portal-Núñez, S., Ardura, J.A., Corton, M., . . . Ortiz, A. (2017). 2017 update on the relationship between diabetes and colorectal cancer: Epidemiology, potential molecular mechanisms and therapeutic implications. *Oncotarget*, 8(11), 18456–18485. <https://doi.org/10.18632/oncotarget.14472>
- Hammer, M., Storey, S., Hershey, D.S., Brady, V.J., Davis, E., Mandolof, N., . . . Olausson, J. (2019). Hyperglycemia and cancer: A state-of-the-science review. *Oncology Nursing Forum*, 46(4), 459–472. <https://doi.org/10.1188/19.ONF.459-472>
- Hershey, D.S., Tipton, J., Given, B., & Davis, E. (2012). Perceived impact of cancer treatment on diabetes self-management. *Diabetes Educator*, 38(6), 779–790. <https://doi.org/10.1177/0145721712458835>
- Hong, Y.J., Han, H.-S., Jeong, Y., Jeong, J., Lim, S.-N., Choi, H.J., . . . Lee, K.H. (2014). Impact of hyperglycemia on survival and infection-related adverse events in patients with metastatic colorectal cancer who were receiving palliative chemotherapy. *Cancer Research and Treatment*, 46(3), 288–296. <https://doi.org/10.4143/crt.2014.46.3.288>
- Huebschmann, A.G., Huxley, R.R., Kohrt, W.M., Zeitler, P., Regensteiner, J.G., & Reusch, J.E.B. (2019). Sex differences in the burden of type 2 diabetes and cardiovascular risk across the life course. *Diabetologia*, 62(10), 1761–1772. <https://doi.org/10.1007/s00125-019-4939-5>
- Kalb, M., Langheinrich, M.C., Merkel, S., Krautz, C., Brunner, M., Bénard, A., . . . Weber, G.F. (2019). Influence of body mass index on long-term outcome in patients with rectal cancer—A single centre experience. *Cancers*, 11(5), 609. <https://doi.org/10.3390/cancers11050609>
- Katz, M., Parrish, M.E., Li, E., Zhang, Y., Zhu, W., Shroyer, K., . . . Williams, J.L. (2013). The effect of race/ethnicity on the age of colon cancer diagnosis. *Journal of Health Disparities Research and Practice*, 6(1), 62–69.
- Keating, S.T., & El-Osta, A. (2013). Epigenetic changes in diabetes. *Clinical Genetics*, 84(1), 1–10. <https://doi.org/10.1111/cge.12121>
- Khanbhai, M., Shah, M., Cantanhede, G., Ilyas, S., & Richards, T. (2014). The problem of anaemia in patients with colorectal cancer. *ISRN Hematology*, 2014, 547914. <https://doi.org/10.1155/2014/547914>
- Kim, H.-I., Lim, H., & Moon, A. (2018). Sex differences in cancer: Epidemiology, genetics and therapy. *Biomolecules and Therapeutics*, 26(4), 335–342. <https://doi.org/10.4062/biomolther.2018.103>
- Kim, S.-E., Paik, H.Y., Yoon, H., Lee, J.E., Kim, N., & Sung, M.-K. (2015). Sex- and gender-specific disparities in colorectal cancer risk. *World Journal of Gastroenterology*, 21(17), 5167–5175. <https://doi.org/10.3748/wjg.v21.i17.5167>
- Lee, S.J., Kim, J.H., Park, S.J., Ock, S.Y., Kwon, S.K., Choi, Y.S., & Kim, B.K. (2017). Optimal glycemic target level for colon cancer patients with diabetes. *Diabetes Research and Clinical Practice*, 124, 66–71. <https://doi.org/10.1016/j.diabres.2016.12.009>
- Levitzy, Y.S., Guo, C.-Y., Rong, J., Larson, M.G., Walter, R.E., Keaney, J.F., Jr., . . . Benjamin, E.J. (2008). Relation of smoking status to a panel of inflammatory markers: The Framingham offspring. *Atherosclerosis*, 201(1), 217–224. <https://doi.org/10.1016/j.atherosclerosis.2007.12.058>
- Lipscombe, L.L., Fischer, H.D., Austin, P.C., Fu, L., Jaakkimainen, R.L., Ginsburg, O., . . . Paszat, L. (2015). The association between diabetes and breast cancer stage at diagnosis: A population-based study. *Breast Cancer Research and Treatment*, 150(3), 613–620. <https://doi.org/10.1007/s10549-015-3323-5>
- Ludwig, H., Van Belle, S., Barrett-Lee, P., Birgegård, G., Bokemeyer, C., Gascón, P., . . . Schrijvers, D. (2004). The European Cancer Anaemia Survey (ECAS): A large, multinational, prospective survey defining the prevalence, incidence, and treatment of anaemia in cancer patients. *European Journal of Cancer*, 40(15), 2293–2306. <https://doi.org/10.1016/j.ejca.2004.06.019>
- Ma, J., Wang, J., Ge, L., Long, B., & Zhang, J. (2019). The impact of diabetes mellitus on clinical outcomes following chemotherapy for the patients with pancreatic cancer: A meta-analysis. *Acta Diabetologica*, 56(10), 1103–1111. <https://doi.org/10.1007/s00592-019-01337-2>
- Maiuri, A.R., & O'Hagan, H.M. (2016). Interplay between inflammation and epigenetic changes in cancer. *Progress in Molecular Biology and Translational Science*, 144, 69–117. <https://doi.org/10.1016/bs.pmbts.2016.09.002>
- Malenica, M., Prnjavorac, B., Bego, T., Dujic, T., Semiz, S., Skrbo, S., . . . Causevic, A. (2017). Effect of cigarette smoking on haematological parameters in healthy population. *Medical Archives*, 71(2), 132–136. <https://doi.org/10.5455/medarh.2017.71.132-136>
- McPhail, S.M. (2016). Multimorbidity in chronic disease: Impact on health care resources and costs. *Risk Management and Health-care Policy*, 9, 143–156. <https://doi.org/10.2147/RMHP.S97248>
- McQuade, R.M., Bornstein, J.C., & Nurgali, K. (2014). Anti-colorectal cancer chemotherapy-induced diarrhoea: Current treatments and side-effects. *International Journal of Clinical Medicine*, 5(7), 393–406. <https://doi.org/10.4236/ijcm.2014.57054>
- Meyerhardt, J.A., Catalano, P.J., Haller, D.G., Mayer, R.J., MacDonald, J.S., Benson, A.B., III, & Fuchs, C.S. (2003). Impact of diabetes mellitus on outcomes in patients with colon cancer. *Journal of Clinical Oncology*, 21(3), 433–440. <https://doi.org/10.1200/JCO.2003.07.125>
- Nørtoft, E., Chubb, B., & Borglykke, A. (2018). Obesity and health-care resource utilization: Comparative results from the UK and the USA. *Obesity Science and Practice*, 4(1), 41–45. <https://doi.org/10.1002/osp4.148>
- Parcesepe, P., Giordano, G., Laudanna, C., Febbraro, A., & Pacione, M. (2016). Cancer-associated immune resistance and evasion of immune surveillance in colorectal cancer. *Gastroenterology Research and Practice*, 2016, 6261721. <https://doi.org/10.1155/2016/6261721>
- Pedersen, K.M., Çolak, Y., Ellervik, C., Hasselbalch, H.C., Bojesen, S.E., & Nordestgaard, B.G. (2019). Smoking and increased

- white and red blood cells: A Mendelian randomization approach in the Copenhagen General Population Study. *Arteriosclerosis, Thrombosis, and Vascular Biology*, 39(5), 965–977. <https://doi.org/10.1161/ATVBAHA.118.312338>
- Peeters, P.J.H.L., Bazelier, M.T., Leufkens, H.G.M., de Vries, F., & De Bruin, M.L. (2015). The risk of colorectal cancer in patients with type 2 diabetes: Associations with treatment stage and obesity. *Diabetes Care*, 38(3), 495–502.
- Peleg, A.Y., Weerathna, T., McCarthy, J.S., & Davis, T.M.E. (2007). Common infections in diabetes: Pathogenesis, management and relationship to glycaemic control. *Diabetes/Metabolism Research and Reviews*, 23(1), 3–13. <https://doi.org/10.1002/dmrr.682>
- Peters, S.A.E., & Woodward, M. (2018). Sex differences in the burden and complications of diabetes. *Current Diabetes Reports*, 18(6), 33. <https://doi.org/10.1007/s11892-018-1005-5>
- Piper, M.S., & Saad, R.J. (2017). Diabetes mellitus and the colon. *Current Treatment Options in Gastroenterology*, 15(4), 460–474. <https://doi.org/10.1007/s11938-017-0151-1>
- Prieto, I., del Puerto-Nevado, L., Gonzalez, N., Portal-Nuñez, S., Zazo, S., Corton, M., . . . Garcia-Foncillas, J. (2017). Colon cancer modulation by a diabetic environment: A single institutional experience. *PLOS ONE*, 12(3), e0172300.
- Qujeq, D., Sadogh, M., & Savadkahi, S. (2011). Association between helicobacter pylori infection and serum iron profile. *Caspian Journal of Internal Medicine*, 2(3), 266–269.
- Rowley, W.R., Bezold, C., Arian, Y., Byrne, E., & Krohe, S. (2017). Diabetes 2030: Insights from yesterday, today, and future trends. *Population Health Management*, 20(1), 6–12. <https://doi.org/10.1089/pop.2015.0181>
- Safarti, D., Koczwara, B., & Jackson, C. (2016). The impact of comorbidity on cancer and its treatment. *CA: A Cancer Journal for Clinicians*, 66(4), 337–350. <https://doi.org/10.3322/caac.21342>
- Seymour, E.K., Saiya-Cork, K., Parkin, B., Shedden, K., Griggs, J., & Malek, S.N. (2015). The impact of diabetes on clinical outcomes in chronic lymphocytic leukemia. *Blood*, 126(23), 2095. <https://doi.org/10.1182/blood.V126.23.2095.2095>
- Shurin, M. (2012). Cancer as an immune-mediated disease. *ImmunoTargets and Therapy*, 2012(1), 1–6.
- Storey, S., Cohee, A., Gathirua-Mwangi, W.G., Vachon, E., Monahan, P., Otte, J., . . . Champion, V. (2019). Impact of diabetes on the symptoms of breast cancer survivors. *Oncology Nursing Forum*, 46(4), 473–484. <https://doi.org/10.1188/19.ONF.473-484>
- Storey, S., & Von Ah, D. (2012). Impact of malglycemia on clinical outcomes in hospitalized patients with cancer: A review of the literature. *Oncology Nursing Forum*, 39(5), 458–465. <https://doi.org/10.1188/12.ONF.458-465>
- Storey, S., Von Ah, D., & Hammer, M. (2017). Measurement of hyperglycemia and impact on health outcomes in people with cancer: Challenges and opportunities. *Oncology Nursing Forum*, 44(4), E141–E151. <https://doi.org/10.1188/17.ONF.E141-E151>
- Tao, H., O'Neil, A., Choi, Y., Wang, W., Wang, J., Wang, Y., . . . Chen, X. (2020). Pre- and post-diagnosis diabetes as a risk factor for all-cause and cancer-specific mortality in breast, prostate, and colorectal cancer survivors: A prospective cohort study. *Frontiers in Endocrinology*, 11, 60. <https://doi.org/10.3389/fendo.2020.00060>
- Tawk, R., Abner, A., Ashford, A., & Brown, C.P. (2016). Differences in colorectal cancer outcomes by race and insurance. *International Journal of Environmental Research and Public Health*, 13(1), 48. <https://doi.org/10.3390/ijerph13010048>
- Tsilidis, K.K., & Ioannidis, J.P.A. (2015). Authors' reply to editorial linked to their umbrella review of meta-analyses of observational studies on type 2 diabetes and cancer. *BMJ*, 350, h711. <https://doi.org/10.1136/bmj.h711>
- Vardakas, K.Z., Siempos, I.I., & Falagas, M.E. (2007). Diabetes mellitus as a risk factor for nosocomial pneumonia and associated mortality. *Diabetic Medicine*, 24(10), 1168–1171. <https://doi.org/10.1111/j.1464-5491.2007.02234.x>
- Vegda, K., Nie, J.X., Wang, L., Tracy, C.S., Moineddin, R., & Upshur, R.E.G. (2009). Trends in health services utilization, medication use, and health conditions among older adults: A 2-year retrospective chart review in a primary care practice. *BMC Health Services Research*, 9, 217.
- Visser, P.A.J., Thong, M.S.Y., Pouwer, F., den Ouden, B.L., Nieuwenhuijzen, G.A.P., & van de Poll-Franse, L.V. (2014). The individual and combined effect of colorectal cancer and diabetes on health-related quality of life and sexual functioning: Results from the PROFILES registry. *Supportive Care in Cancer*, 22(11), 3071–3079.
- Visser, P.A.J., Thong, M.S.Y., Pouwer, F., Zanders, M.M.J., Coebergh, J.W.W., & van de Poll-Franse, L.V. (2013). The impact of comorbidity on health-related quality of life from cancer survivors: Analyses of data from the PROFILES registry. *Journal of Cancer Survivorship*, 7(4), 602–613. <https://doi.org/10.1007/s11764-013-0299-1>
- Walker, R.J., Williams, J.S., & Egede, L.E. (2016). Impact of race, ethnicity, and social determinants of health on diabetes outcomes. *American Journal of Medical Sciences*, 351(4), 366–373. <https://doi.org/10.1016/j.amjms.2016.01.008>
- Wang, M.-J., Hung, L.-C., & Lo, Y.-T. (2019). Gender and age differences in health care utilization and spending among the older adult outpatient with multimorbidity. *Journal of Men's Health*, 15(4), 1–11.
- Weycker, D., Li, X., Edelsberg, J., Barron, R., Kartashov, A., Xu, H., & Lyman, G.H. (2015). Risk and consequences of chemotherapy-induced febrile neutropenia in patients with metastatic solid tumors. *Journal of Oncology Practice*, 11(1), 47–54.
- Yabroff, K.R., Borowski, L., & Lipscomb, J. (2013). Economic studies in colorectal cancer: Challenges in measuring and comparing costs. *JNCI Monographs*, 2013(46), 62–78. <https://doi.org/10.1093/jncimonographs/igt001>
- Yao, N., Camacho, F.T., Chukmaitov, A.S., Fleming, S.T., & Anderson, R.T. (2015). Diabetes management before and after cancer diagnosis: Missed opportunity. *Annals of Translational Medicine*, 3(5), 72.