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The Role of Pre-Existing Type 2 Diabetes Mellitus in Colorectal Cancer Stage and Survival in Elderly Americans: A Seer-Medicare Population-Based Study 2002-~2011

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THE ROLE OF PRE-EXISTING TYPE 2 DIABETES MELLITUS IN COLORECTAL CANCER STAGE AND SURVIVAL IN ELDERLY AMERICANS: A SEER-MEDICARE POPULATION-BASED STUDY 2002-2011

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ABSTRACT

Diabetes is a common comorbid condition among colorectal cancer (CRC) patients, yet its effects in CRC outcomes, particularly stage at diagnosis, risk of death and variations by diabetes severity (complications vs no complications) and Hispanic ethnicity have not been adequately studied. The purpose of this study was to investigate the association between pre-existing T2DM and advanced stage at diagnosis in elderly patients with CRC; to examine whether diabetes is an independent predictor of poor survival from all-cause and CRC-specific mortality; to assess whether variations exist by diabetes severity and to analyze the outcomes for the Hispanic group.

The Surveillance Epidemiology and End Results (SEER)-Medicare linked datasets were used to extract data on Medicare beneficiaries 67 years and older residing in the SEER areas who were diagnosed with CRC between 2002 and 2011. These datasets provided clinical, demographic, administrative claims and enrollment information for the Medicare population under study. Pre-existing T2DM was ascertained from the Medicare inpatient and outpatient claims using validated algorithms.

The association of advanced stage at diagnosis with CRC was compared between pre-diabetic and non-diabetic patients using logistic regression. All-cause and CRC cause-specific death risk differences were compared using Cox proportional hazards model and hazard ratios were compared in relation to prior T2DM diagnosis and diabetes severity status. All models were adjusted for relevant factors including demographic characteristics such as age, sex, marital status, race/ethnicity and census poverty level. Clinical factors adjusted for included comorbidity score, grade, histology, stage at diagnosis, year of diagnosis and cancer registry.

The analyses included 93,710 CRC patients. Among the study population, 22,155 (24%) had diabetes prior to CRC diagnosis and, of these, 17% had diabetes-related complications (neuropathy, nephropathy, retinopathy or peripheral circulatory disorders). Diabetic patients were more likely to be older, male, non-White, lived in medium to high poverty level areas, had at least one or more comorbidities, and had tumors in the proximal colon. From the regression models, diabetes was not significantly associated with CRC advanced stage at diagnosis (odds ratio (OR) = 0.986; 95% confidence interval (CI) = 0.953-1.02 for diabetes without complications and OR = 0.963; 95% CI = 0.897-1.034 for diabetes with complications). Similar results were observed for Hispanic patients. Overall mortality was significantly higher among diabetic patients compared to non-diabetic patients (hazard ratio (HR) = 1.198; 95% CI = 1.169-1.228). The results were more pronounced for diabetes with complications (HR = 1.467; 95% CI = 1.339-1.538). Patients who had diabetes with complications were 16% more likely to die of colorectal cancer compared to patients without diabetes in the fully adjust model (HR = 1.162; 95% CI = 1.083-1.247). Among Hispanics, diabetes was an independent predictor of poor survival from all-cause mortality but not CRC specific of death.

This study used population-based data and the findings indicate that pre-existing diabetes contributes to poorer overall survival in patients with colorectal cancer and increased mortality from CRC in diabetes with complications. Because these diseases are more prevalent among the elderly, this group is more likely to have both diseases at the same time and more clinicians will need to develop care plans that are interdisciplinary and take into consideration the added burden of diabetes among CRC patients.

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As the saying goes "it takes a village to raise a child", indeed, it took an entire community to get me to this point in my academic career.

This is for you Adam, I love you

Mom

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CHAPTER 1: INTRODUCTION

Colorectal cancer (CRC) and type 2 diabetes mellitus (T2DM) are major causes of morbidity and death in the Unites States. Both diseases are preventable through screening and lifestyle changes. CRC and T2DM share many common risk factors that characterize the Western lifestyle including physical inactivity; obesity, especially, abdominal adiposity; and unhealthy diet (Chan, Rimm, Colditz, Stampfer, & Willett, 1994; Fung, Schulze, Manson, Willett, & Hu, 2004; Giovannucci et al., 1995; van Dam, Rimm, Willett, Stampfer, & Hu, 2002).

A major characteristic of T2DM is hyperinsulinemia which is related with many chronic diseases such as cardiovascular diseases and carcinogenesis (Alberti et al., 2009; Shanik et al., 2008). Researchers have found that diabetes is an independent factor in carcinogenesis for many common cancers including breast, bladder, liver, pancreatic, and CRC among others (Coughlin, Calle, Teras, Petrelli, & Thun, 2004).

The association of diabetes and increase of CRC risk has been explored by many researchers, however, studies assessing the relationship of pre-existing T2DM and CRC stage at diagnosis are lacking. Stage at diagnosis is an important determinant of treatment course and prognosis. Understanding how diabetes status affects earlier CRC diagnosis would help clinicians improve recommendations of diabetes control and CRC screening. Moreover, the association of diabetes and risk of unfavorable survival by diabetes severity (presence of complications), are inadequately studied.

Colorectal cancer and diabetes are experienced differently among racial and ethnic groups. Among Hispanics, colorectal cancer is the second most common diagnosed cancer

(compared to third among non-Hispanic Whites) (Siegel et al., 2015). Although incidence and mortality rates of colorectal cancer are slightly lower in Hispanics compared to non-Hispanic Whites, Hispanics are more likely to be diagnosed at an advanced stage of disease and they suffer from slightly lower cancer-specific 5-year survival (Siegel et al., 2015). Moreover, there is a trend of increased CRC incidence among young Hispanics (Wang et al., 2017). On the other hand, Hispanics experience higher prevalence of diabetes in relation to their White counterparts and the incidence trend is upwards over time (Schiller, Lucas, Ward, & Peregoy, 2012). Understanding how diabetes affects prognosis of Hispanic CRC patients is crucial to reduce morbidity and mortality among this growing population.

The purpose of this study is to investigate the association between pre-existing T2DM and risk of advanced CRC stage at diagnosis and poorer survival in a population of patients 67 years and older who were diagnosed with CRC in one of the areas covered by the Surveillance, Epidemiology and Ends Results (SEER) program. Among CRC patients, stage at diagnosis was compared between those who have T2DM prior to CRC diagnosis and those without a T2DM diagnosis. CRC survival differences for overall mortality and CRC cause-specific mortality by diabetes status and diabetes severity status were examined. Variations in outcomes for the Hispanic group were analyzed.

Data was obtained retrospectively from the SEER-Medicare linked data files. These files contain clinical and demographic information as well as claims data for the Medicare beneficiaries who have a cancer diagnosis. The Medicare program managed by the Centers for Medicare and Medicaid Services records claims of services received by Medicare beneficiaries and provide a continuum of care from enrollment until patients' death regardless of patients' place of residence.

To our knowledge, this is the first study to assess the association of pre-existing T2DM and colorectal cancer stage at diagnosis and survival differences by diabetes severity with a focus on elder Hispanics using a population-based dataset. Findings from this study will bring more evidence to the increasing need to prevent and control diabetes especially in a population that is disproportionately affected by this disease such as the Hispanic population.

CHAPTER 2: BACKGROUND AND SIGNIFICANCE

Section 1: The burden of colorectal cancer (CRC) and type 2 diabetes mellitus (T2DM)

CRC in the United States

CRC characteristics

Colorectal cancer is cancer that forms in the colon or rectum area of the digestive system. CRC starts as abnormal growths called polyps that form in the inner wall of the colon or rectum. These polyps can be removed early before they develop into cancer preventing CRC. The majority of CRC cancers are adenocarcinomas (Centers of Disease Control and Prevention, (CDC), 2015).

CRC risk factors

Definitive etiological factors causing CRC have not been identified, however, there are several risk factors that are related to developing the disease. Incidence of CRC is higher among the elderly; over 90% of CRC patients are over 50 years of age. Additional risk factors include: inflammatory bowel disease; Crohn's disease, or ulcerative colitis; personal or family history of CRC or colorectal polyps; and genetic syndromes (familial adenomatous polyposis (FAP) or Lynch syndrome) (Jaruvongvanich, Sanguankeo, Wijarnpreecha, & Upala, 2017; Jasperson, Tuohy, Neklason, & Burt, 2010).

Many lifestyle factors have been linked to CRC. Heavy alcohol consumption is associated with a 60% increase in getting CRC compared to no or light consumption (relative risk (RR) = 1.56, 95% confidence interval (CI) = 1.42–1.70) (Huxley et al., 2009). The risk associated with alcohol consumption increases particularly in individuals with mismatch repair

gene mutation (Ghazaleh Dashti et al., 2017). Other lifestyle risk factors include smoking, obesity and high meat intakes (Huxley et al., 2009; Wu, Paganini-Hill, Ross, & Henderson, 1987). Obesity and weight gain association with CRC differs by gender; in women, weight gain in early life is a determinant of CRC risk more so than later life obesity. However, in men, it is the later in life obesity that increases the risk for CRC (Kim & Giovannucci, 2017).

Contrary to factors that increase risk of CRC, physical activity is protective against colorectal cancer. In a review study, it was found that highly active individuals benefited from a 20% lower risk of CRC compared with individuals with lower physical activity levels (RR = 0.81, 95% CI = 0.77–0.86) (Huxley et al., 2009).

CRC screening

CRC can be prevented with screening tests that remove polyps or diagnosed early when treatment is most effective (US Preventive Services Task Force, 2015). CRC screening tests include high-sensitivity fecal occult blood test (FOBT), flexible sigmoidoscopy, and colonoscopy. Recommendations and guidelines on screening use, frequency and appropriate age are set by the U.S. Preventive Services Task Force. On a population level, rates of new cases of CRC have been steadily declining which is likely associated with higher uptake of CRC screening. For instance, recent national surveys show that colonoscopy uptake increased from 19% in 2000 to 55% in 2013 among adults aged 50 to 75 years of age (Siegel, Miller, & Jemal, 2016a). Screening uptake is generally higher among women than men particularly for colonoscopy, conversely, screening is lower among Hispanics compared to non-Hispanics (Steele et al., 2013).

CRC statistics

CRC is the third most common cancer in both men (after prostate and lung cancer) and women (after breast and lung cancer) in the United States (Siegel, Miller, & Jemal, 2016b). In 2016, there were 134,490 projected new cases (70,820 cases in men and 63,670 in women) and an estimated 49,190 total deaths due to CRC. Colorectal cancer is the second leading cause of cancer death among men aged 60 to 79 and third leading cause of cancer death among women in the same age group (Siegel et al., 2016a).

Men experience higher CRC incidence compared to women particularly at older age (rate ratio = 1.39, $P < 0.05$). Incidence rates differ by race and ethnicity; Blacks have highest incidence compared to Whites and other races. On the other hand, Hispanics have historically had lower incidence in relation to their White counterparts (Rim, Seeff, Ahmed, King, & Coughlin, 2009). These racial disparities are more pronounced among individuals 65 years or younger.

Overall, CRC incidence has been declining for both men and women at about 3% per year from 2003 through 2012 which is largely attributed to increased uptake of screening and removal of precancerous lesions (Cress, Morris, Ellison, & Goodman, 2006). Distal colon cancer is more prevalent among elder men, while distal tumors are more prevalent in younger women (Devesa & Chow, 1993; Murphy et al., 2011).

Stage at diagnosis and survival

Stage at diagnosis is highly associated with prognosis in malignancies (Siegel et al., 2016a). Among CRC patients, 39% are diagnosed at an early stage and 20% are diagnosed at an advanced stage. Overall, the five-year relative survival rate for CRC is 65%; however, survival

drops considerably form 90% in patients diagnosed at a localized stage to only 13% for distant stage (Siegel et al., 2016b).

Type 2 Diabetes (T2DM) in the United States

T2DM characteristics

T2DM, or non-insulin dependent diabetes, is a form of diabetes that starts primarily in adults, although, children and adolescents are increasingly affected with this disease. T2DM is characterized by imbalance between the body's sensitivity to insulin and insulin secretion by the pancreatic beta cells. T2DM is usually preceded with insulin resistance (Martin et al., 1992). This occurs when body cells, particularly, muscle, liver, and fat cells do not use insulin properly resulting in blood glucose build up. As a result, the beta cells produce more insulin; however, this increase in insulin secretion causes the beta cells to gradually lose the ability to secrete the hormone to compensate for insulin resistance (Centers for Disease Control and Prevention, 2011; DeFronzo, 1992).

T2DM risk factors

Weight gain and obesity, particularly high waist circumference, increase the risk of T2DM. Other risk factors include older age; family history of diabetes; Western diet high in processed foods; low physical activity; a previous diagnosis of gestational diabetes; glucose intolerance; and particular racial/ethnic groups (Chan et al., 1994; Fung et al., 2004; Haffner, 1998; Shai et al., 2006).

T2DM statistics

Diabetes diagnosis indicates blood glucose levels above normal (fasting plasma glucose of 126 mg/dL or above). According to the 2012 National Health and Nutrition Examination Survey estimates, diabetes mellitus affects nearly 10% of Americans representing a total of 29.1 million people of all ages (Centers for Disease Control and Prevention, 2014). Every year, about 1.4 million people are newly diagnosed with diabetes. In the US, diabetes is the seventh leading cause of death (National Center for Health Statistics, (US, 2016). From these most recent estimates, almost 30% of diabetics do not know they have diabetes. Moreover, 86 million Americans aged 20 years or older have prediabetes and, therefore, are at higher risk of developing the disease (American Diabetes Association, 2014).

Diabetes demographics

Diabetes affects more men than women and is higher among elderly people with a prevalence of 25.9% seniors diagnosed. Minorities have higher prevalence of diabetes compared to Non-Hispanic whites; however, the prevalence varies by minority group. For instance, 24.1% of Southern Arizona American Indians have been diagnosed with diabetes compared to only 6% of Alaska Natives. (American Diabetes Association, 2014; Schneiderman et al., 2014)

T2DM complications

Uncontrolled diabetes may result in serious complications. Diabetic patients are at 2 to 4 fold increased likelihood of developing macrovascular complications (cardiovascular and coronary heart disease) (Brownlee, 2001; Feldman, 2003). Moreover, nearly all individuals with diabetes will eventually be affected by some or all diabetes-specific microvascular complications

including diabetes retinopathy, diabetic nephropathy and diabetic neuropathy (Brownlee, 2001). In the US, 32% of diabetic patients have diabetic retinopathy (Wong et al., 2006) and 40% develop diabetic nephropathy. Almost 50% of all incident cases of end-stage renal disease (ESRD) are attributed to kidney-related complications among diabetic patients (National Institutes of Health, 2010). Other complications associated with diabetes include diabetic neuropathy with peripheral nerve dysfunction which is present in more than half of diabetic patients and is the leading cause of non-traumatic amputations and autonomic failure (Feldman, 2003).

Section 2: Pathophysiology of T2DM and CRC link

Insulin resistance & hyperinsulinemia

The early stages of T2DM are characterized with insulin resistance. Insulin resistance indicates impaired hepatic and muscle tissue sensitivity to insulin. The inability of insulin to stimulate use and storage of glucose causes diminished glucose uptake by the liver and muscle tissues. This insulin dysfunction promotes pancreatic beta cells to increase their insulin secretion to compensate for the increased blood circulating glucose inducing a state of hyperinsulinemia (DeFronzo, 1992).

Insulin, IGF-1, and colorectal malignancy

Insulin has growth factor properties on normal and carcinogenic colonic cells in vitro (Godsland, 2010; Kabat et al., 2012; Koenuma, Yamori, & Tsuruo, 1989; Watkins, Lewis, & Levine, 1990). Insulin stimulating action is mediated through hepatic growth hormone receptors. In turn, growth hormone regulates the production of insulin-like growth factor 1 (IGF-1) in the liver (Jones & Clemmons, 1995). Another mechanism by which insulin increases levels of free IGF-1 is inhibition of insulin growth factor binding proteins (IGFBP-1 and IGFBP-2) (Nam et al., 1997; Ooi, Tseng, Tran, & Rechler, 1992).

Insulin-like growth factor 1 is a polypeptide produced by the liver and acts similarly as insulin (Rinderknecht & Humbel, 1978). IGF-1 is involved in cellular growth and inhibition of apoptosis and therefore is associated with increased carcinogenesis risk in many types of cancers (Aaronson, 1991; Grimberg & Cohen, 2000). IGF-1 is particularly involved in the pathogenesis of CRC. IGF-1 receptors (IGF-1R) are present in colon epithelial cells with high level binding

and potential influence on CRC pre-malignancy (Laburthe, Rouyer-Fessard, & Gammeltoft, 1988). Moreover, the majority of CRC tumor cells express IGF-1R which resembles insulin receptors (Hakam et al., 1999; Pollak, Perdue, Margolese, Baer, & Richard, 1987; Weber et al., 2002).

In vivo and in vitro studies on animal models have shown that human insulin and IGF-1 stimulate malignant cells proliferation in mice with colon adenocarcinoma in a dose-dependent manner. These growth factors stimulate the DNA synthesis of malignant cells particularly the high-metastatic tumor cells. Consequently, growth factors have the ability to augment the formation of tumor metastasis (Koenuma, Yamori, & Tsuruo, 1989).

High fasting glucose and CRC risk

In addition to hyperinsulinemia and IGF-1 etiological pathways, hyperglycemia is also related with increased CRC risk. Investigators found that patients who had the highest level of fasting glucose had a remarkable two fold increased risk of CRC (Schoen et al., 1999). Likewise, uncontrolled hyperglycemia, signaled by a high hemoglobin A1c levels, significantly increases risk of CRC (Stocks et al., 2008).

Epidemiologic studies of T2DM as a risk factor for CRC

The plausibility of the association between diabetes and CRC has been explored through epidemiological studies. Researchers have used observational studies to investigate diabetes mellitus as a risk factor for CRC risk and mortality in different settings and populations.

In a large prospective cohort, the National Health and Nutrition Survey I, Steenland, Nowlin, and Palu (1995) analyzed diabetes as a risk factor for multiple cancers. Although they

found an overall increased risk for all cancers in diabetics (Odds ratio (OR) = 1.38; 95% confidence interval (CI): 1.00-1.91), the increased risk for CRC did not reach significance in both men and women (OR = 1.43; 95% CI: 0.61-3.31 and OR = 1.4; 95% CI: 0.61-3.10 respectively). Flood, Strayer, Schairer, and Schatzkin, (2010) compared CRC risk in a cohort of women with and without diabetes. They found diabetic women to have increased risk of CRC (multivariate relative risk (RR) = 1.60, 95% CI 1.18–2.18) with a time-dependent association.

Diabetes exposure has been studied as part of the metabolic syndrome. In the Physicians' Health Study, men with diabetes had a 50% increased risk of CRC compared to men without diabetes (RR = 1.50; 95% CI: 1.1-2.0) (Sturmer et al., 2006). Similarly, Ahmed, Schmitz, Anderson, Rosamond, and Folsom (2006) observed a 39% increase in CRC risk in diabetic participants (RR = 1.39; 95% CI: 1.0-1.8). In addition to CRC risk, diabetes is implicated in increased CRC mortality. In a large prospective cohort study, Coughlin and colleagues (2004) found diabetes to be associated with fatal colon cancer in both men and women (RR = 1.20; 95% CI: 1.06-1.37) and RR = 1.24, 95% CI: 1.07, 1.43 respectively). Whaheed, Azad, S. Waheed, and Yeh (2014) explored survival disparities among adults with CRC stratified by race. They found that diabetes is an effect modifier in the relationship between race and CRC survival.

Women from the Iowa Women's Health Study had a significant increased relative risk of CRC in women with T2DM in relation to women without T2DM (RR = 1.4; 95% CI: 1.1-1.8), particularly for the proximal colon subsite (Limburg et al., 2005). Likewise, type 2 diabetic women in the Nurses' Health Study had a 43% increased risk of CRC compared to non-diabetics (RR = 1.43; 95% CI: 1.10-1.87) (Hu et al., 1999).

Section 3: CRC and T2DM among Hispanics

Hispanics are the second largest racial/ethnic minority group in the US. It is estimated that this group will continue growing and double by 2050 (Ennis, Rios-Vargas, & Albert, 2015). Cancer disparities are documented for Hispanics based on low levels of health insurance, higher poverty and different exposures in terms of behavioral and environmental factors that contribute to disproportionate cancer outcomes. The experience of cancer varies markedly between Hispanics and Non-Hispanic Whites and also among Hispanic subgroups (Mexican, Puerto Rican, Salvadoran, Cuban, and Dominican). These variations are driven by lifestyle patterns and cancer-causing exposures particularly obesity and diabetes (National Center for Health Statistics, 2016; Ward et al., 2004).

CRC in Hispanics

Among Hispanics, colorectal cancer is the second most common cancer among men and the third most common diagnosed cancer in women (Siegel et al., 2015). In 2015, the estimated new cases of CRC were 6,400 in men and 5,300 in women. In same year, it was estimated that CRC was the cause of 12% of cancer deaths in Latino males and 9% in Latina females (Siegel et al., 2015). About 5-10% of CRC in Hispanics is hereditary and is associated with familial adenomatous polyposis (FAP) and Lynch Syndrome (LS) (Cruz-Correa et al., 2017). Although CRC is higher among older Hispanics, new trends show that CRC incidence is increasing among younger patients (Wang et al., 2017).

CRC incidence and death in Hispanics is slightly lower than among Non-Hispanic Whites (NHW), however, variations exist among Hispanic subgroups (Pinheiro et al., 2009). Although incidence and mortality rates of CRC are slightly lower in Hispanics compared to NHW,

Hispanics are slightly more likely to present with distant stage disease (Siegel et al., 2015). Hispanics with CRC have unfavorable five-year cancer-specific survival in relation to NHW particularly among men. Compared to other Hispanic subgroups, Cubans have the highest CRC mortality rates (Pinheiro et al., 2017).

CRC screening uptake is overall modest among all racial ethnic groups, nonetheless, Hispanics have some of the lowest rates. The use of CRC screening is noticeably lower in Hispanics (44.9%) compared to NHW (60.5%). The proportion of screening is even lower among uninsured Hispanics at only 11%. By Hispanic subgroup, Dominicans and Cubans have the lowest screening rates (below 40%), while Puerto-Ricans have the highest screening prevalence at 56% (Siegel et al., 2015).

Hispanics suffer disproportionately from CRC risk factors, particularly obesity (Eheman et al., 2012). The prevalence of obesity in adult Hispanic females is 45.2% compared to 33.3% in NHW females and 40.9% in Hispanic males compared to 32.8% in NHW males (Siegel et al., 2015). Although the prevalence of obesity has stabilized in more recent years for NHW, it is rapidly increasing for Mexican men (Fryar, Carroll, & Ogden, 2012).

Diabetes in Hispanics

Diabetes affects 16.9% of Hispanics living in the U.S. (compared to 7.6% in NHW) (Schneiderman et al., 2014). This prevalence increases to 22.4% among obese patients. Other authors found that within Hispanic sub-groups, diabetes prevalence varies considerably; it is highest among Mexicans, Dominicans and Puerto Ricans (at 18%) and lowest among South Americans at 10.2%. Diabetes prevalence in Hispanics is positively related to length of US

residence and it continues to increase even though it has remained stable nationally (Geiss et al., 2014).

In addition to high prevalence rates of diabetes, Hispanics suffer from inadequate education about the disease. Additionally, Hispanic patients have low health insurance coverage (52.4%) (Schneiderman et al., 2014). Moreover, Hispanics are more likely to have poorer diabetes control (29.8%) compared to NHW (16.6%) (National Center for Health Statistics, 2016).

Diabetes is the number four killer for both males and females in Hispanics vs number seven in Whites. Similarly, death from this disease is higher among Hispanics (25.1%) compared to NHW (18.6%) (National Center for Health Statistics, 2016).

Section 4: Study rationale and significance

Study rationale

A review of the current literature shows that diabetes increases the risk of developing colorectal cancer; however, studies assessing whether pre-existing T2DM is associated with advanced stage at diagnosis of CRC using population-based datasets are lacking. CRC prognosis depends largely on stage at diagnosis with advanced stage leading to the poorest survival rates. Understanding how diabetes status affects earlier CRC diagnosis would help clinicians improve recommendations of diabetes control and CRC screening.

Development of diabetes-related complications among diabetic patients is very likely, yet, the effect of diabetes complications on survival outcomes in CRC patients has not been fully examined. An analysis of how diabetes with and without complications is likely to affect survival is paramount to inform clinical decisions in terms of CRC management and treatment.

A rising trend of diabetes combined with suboptimal rates of CRC screening in Hispanics poses considerable risks of unfavorable health outcomes. The increasing burden of diabetes in Hispanics may halt or even reverse the recent gains in terms of reduction in CRC incidence among Hispanics. Further, the importance of this shift may be even stronger in the instance that diabetes is related to increased risk of late stage at diagnosis of CRC. In this case, evidence-based action is needed.

Significance to Public Health

This study can help make an effective change in the health of CRC patients. Results from this investigation will orient public health interventions to a more aggressive focus on colorectal

screening in higher risk populations with diabetes. Tailored messages and programs to special demographic groups will be necessary to lower the risk of CRC.

CHAPTER 3: METHODS

Section 1: Study purpose and hypotheses

Study purpose

The purpose of this study is to investigate the association between pre-existing T2DM and advanced CRC stage at diagnosis; the association of pre-existing diabetes (with and without complications) and higher risk of poorer overall and CRC-specific mortality compared to patients without diabetes; and whether variations exist for the Hispanic subgroup. This study used data from Surveillance Epidemiology and End Results (SEER)-Medicare program. The cohort consisted of Medicare beneficiaries 67 years and older diagnosed with CRC between 2002 and 2011. These datasets provide clinical, demographic, administrative claims and enrollment information for the Medicare population under study. Pre-existing T2DM is ascertained from the Medicare inpatient and outpatient claims using validated algorithms.

Hypotheses

The main hypotheses examined under this study are:

Hypothesis 1:

- H0: There is no difference in the odds of advanced stage at diagnosis among CRC patients who have pre-existing diabetes compared to those who do not have diabetes
- H1: The odds of advanced stage at diagnosis among CRC patients are higher in subjects with diabetes compared to those without diabetes
    - Outcome variable: CRC stage at diagnosis

- Independent variable: pre-existing diabetes
- Study group: overall study population

Hypothesis 2:

- H0: There is no difference in risk of overall mortality in CRC patients with pre-existing diabetes, with and without complications, compared to those without diabetes
- H1: Risk of all-cause mortality in CRC patients is higher among those with diabetes with and without complications, compared to those without diabetes
  - Outcome variable: overall mortality
  - Independent variable: pre-existing diabetes, with and without complications
  - Study group: overall study population

Hypothesis 3:

- H0: There is no difference in risk of colorectal cancer-specific mortality in patients with pre-existing diabetes, with and without complications, compared to those without diabetes
- H1: Risk of colorectal cancer-specific mortality is higher in CRC patients with diabetes, with and without complications, compared to those without diabetes
  - Outcome variable: colorectal cancer-specific mortality
  - Independent variable: pre-existing diabetes, with and without complications
  - Study group: overall study population

Hypothesis 4:

- H0: There is no difference in risk of overall and cause-specific mortality in Hispanic CRC patients with pre-existing diabetes, with diabetes with and without complications, compared to those without diabetes
- H1: Risk of all-cause and cancer-specific mortality is higher in Hispanic CRC patients with diabetes, with and without complications, compared to those without diabetes
    - Outcome variable: overall mortality
    - Independent variable: pre-existing diabetes, with and without complications
    - Study group: Hispanic subgroup

Section 2: Data source

Medicare Program

The Medicare program under the Centers of Medicaid and Medicare Services (CMS) is a Federal health insurance plan that offers health insurance for qualifying elders 65 years and older and select disabled adults. Eligible beneficiaries are entitled for the Part A plan which covers hospitalizations, hospice, home health, and skilled nursing facilities. Beneficiaries may purchase a supplemental medical insurance under Part B to cover physician and outpatient care. Since 2006, beneficiaries may purchase medication coverage policy under Part D. Medicare enrollees must have both Part A and Part B to be eligible for full Fee For Service (FFS) benefits. Approximately 94% of enrollees have both Part A and Part B (Centers for Medicare & Medicaid Services, 2013).

The SEER Program

Since its inception in the 70s, the National Cancer institute's Surveillance, Epidemiology and End Results (SEER) program has been collecting data on every case in the covered areas with a case ascertainment level as high as 95%. The SEER cancer registries collect data under rigorous standards to maintain accuracy and timeliness. The program includes 20 U.S. geographic areas covering about 28% of the domestic population (Surveillance, Epidemiology, and End Results (SEER) Program, 2013). Data from this program is used extensively across the spectrum of the research community as well as health officials and community members. Data from the SEER program allow to generate periodic cancer statistics at a population level and helps steer policies and recommendations in terms of cancer prevention and control (Siegel et al., 2016a).

SEER-Medicare linked data files

The files contain clinical and demographic information about Medicare beneficiaries with cancer. Researchers have used these data to conduct studies about a variety of outcomes including cancer risk factors, cancer treatment costs, and cancer survival determinants. The SEER files provide clinical, demographic and cause of death information for persons with cancer while the Medicare files provide detailed claims of services received by Medicare beneficiaries and a continuum of care until patients' death. The SEER and Medicare data are linked every two years and each linkage successfully matches 93 percent of persons age 65 and older SEER cases to their Medicare enrollment and claims files (Warren, Klabunde, Schrag, Bach, & Riley, 2002).

The SEER-Medicare datasets have been used extensively by researchers in all fields. There have been over 1400 manuscripts published that used these data in nearly 250 national and international journals some of those journals include JAMA, Lancet oncology, the Journal of American Heart Association, European Journal of Cancer, American Journal of Public Health. The top 3 journals with highest number of publications using the SEER-Medicare are Cancer, Journal of Clinical Oncology and Medical Care.

Section 3: Data files

The SEER-Medicare data refer to a series of files. The SEER data are included in one of the files while the Medicare claims data are found in the remaining files for each specific type of service (e.g. hospital, physician, outpatient, medication, home health, etc.). This study utilized the following files:

The Patient Entitlement and Diagnosis Summary file (PEDSF)

The PEDSF includes both demographic and clinical information on each person such as date of birth, date of death, sex, race, and state of residence, date of diagnosis, first course of treatment, survival in months, stage at diagnosis, source of diagnosis, etc. It also contains variables from the Medicare enrollment file such as Medicare eligibility and reason for eligibility, enrollment status in health maintenance organization (HMO), the level of match of the birth date and the death date between SEER and Medicare, etc.

The Medicare Provider Analysis and Review (MEDPAR)

The MEDPAR file includes long, short stay and skilled nursing facility claims for part A beneficiaries. Each time a patient is admitted to an inpatient facility, a claim is recorded.

The Outpatient Claims file

Claims from institutional outpatient providers are found in the Outpatient Claims file.

Section 4: Study population and design

Study Population

The cohort under study includes elderly patients aged 67 years and older diagnosed with CRC between 2002 and 2011 in one of the SEER area. CRC cases are identified in the PEDSF which has one row per patient. Only patients who have CRC cancer listed as primary cancer are considered for the analysis. Patients are de-identified and each one is given a random patient ID that can be used to link with the Medicare claims datasets.

Study design

The SEER-Medicare datasets allow the use of different observational study designs. The SEER program collects data on all incident cancers in the SEER areas with a 95% case ascertainment. The cancer registries actively follow cancer patients and record death/alive status at the end of each submission. Similarly, CMS reports information on all beneficiaries from entitlement to death regardless of place of residence.

The association of pre-existing T2DM and CRC stage at diagnosis is analyzed using a cross-sectional design. All cancer cases that fit the inclusion and exclusion criteria are assessed at a single point in time with stage at diagnosis as the outcome and pre-existing T2DM as the exposure. On the other hand, cancer cases are followed retrospectively using a retrospective cohort design to examine the effect of T2DM diagnosis on CRC survival.

Section 5: Analytic variables and inclusion criteria

This study requires the use of variables for the analytical models and other variables to build the study population file. Moreover, many variables will need to be recoded (age, histology, stage, race, marital status, etc.). The Medicare enrollment file is used to restrict the study population to those who have Part A and Part B and were not enrolled in Health Management Organizations (HMO) 24 month prior to CRC diagnosis. On the other hand, Medicare claims files are used to ascertain pre-existing diabetes and comorbidities.

Medicare entitlement and enrollment

Patients can become eligible for Medicare coverage through age (65 years and older), disability (any age) or End Stage Renal Disease (ESRD) (any age). Patients remained in the analysis file only if they were Medicare entitled by age. Patients entitled through disability or ESRD were excluded.

CMS records Medicare entitlement for each beneficiary each month of a calendar year. Patients are included if they have continuous Medicare part A and part B entitlement and no HMO entitlement 24 months prior to CRC diagnosis date and three months after.

Demographic variables

Age

Age was restricted to 67 years or older at the time of CRC diagnosis. The exclusion of patients younger than 67 years old allows to have at least two years of Medicare claims history for each patient. Three age groups were created (67-75, 76-85, and 85 years old and older).

Marital status

Marital status was recoded to: single, married, separated/divorced, widowed, and unknown.

Race Ethnicity

The SEER program tracks race and ethnicity separately. The race variable was combined with the Hispanic ethnicity variable which tracks whether a patient is of Hispanic origin. Patients of any race that were flagged as having Hispanic origin were grouped as Hispanics irrespective of race. The combined variable included these race/ethnic groups: White non-Hispanic, Black non-Hispanic, Hispanic, non-Hispanic Asian Pacific Islander, and non-Hispanic American Indians/ Alaska Natives.

Census tract median income

The SEER program does not record socio-economic status (SES) at the individual level, therefore, an ecological measure is used to indicate SES based on census tract. Each patient in the SEER file was assigned a census tract ID based on the year of CRC diagnosis which then was used to link to the Census Tract File. This file used Census 1990, Census 2000 and the American Community Survey (ACS) 2008-2012. The variable median household income for census tract was grouped into quartiles (low, medium, medium high and high poverty level).

Clinical variables

The PEDSF file contains the clinical information on CRC patients such as stage, morphology, histology and tumor behavior. Patients were restricted to those who have CRC

listed as first primary diagnosis sequence 0 and 1 and those with malignant tumors (excluded benign, borderline and in situ). Patients were also excluded if the month of diagnosis was missing and if they were diagnosed at autopsy or death certificate (src1=6 or src1=7); these patients usually do not have information on stage at diagnosis and other clinical variables and; therefore, do not have the information needed for the analysis. The analysis was also restricted to patients diagnosed in 2002 and onward.

Tumor site

Colon tumor sites included: ascending, transverse, descending and sigmoid; hepatic and splenic flexure and other colon sites not otherwise specified (NOS). Patients diagnosed in sites other than colon or rectum were excluded. Table 1 shows the International Classification of Diseases for Oncology 3rd edition (ICD-O-3) site codes used to select the patients with colorectal cancer. The CRC site variable was then recoded to four categories: proximal colon (cecum to splenic flexure), distal colon (descending and sigmoid colon), colon NOS, and rectum.

Table 1. Colorectal Cancer Sites

ICD-O-2/3	Term
Colon	
C18.0	Cecum
C18.1	Appendix
C18.2	Ascending colon; Right colon
C18.3	Hepatic flexure of colon
C18.4	Transverse colon
C18.5	Splenic flexure of colon
C18.6	Descending colon; Left colon
C18.7	Sigmoid colon
C18.8	Overlapping lesion of colon
C18.9	Colon, NOS
Rectosigmoid junction	
C19.9	Rectosigmoid junction
Rectum	
C20.9	Rectum, NOS

Source: National Cancer Institute, SEER Training Modules, retrieved from https://training.seer.cancer.gov/colorectal/abstract-code-stage/codes.html

Histology

Tumors have different histological types based on their microscopic composition. Staging of tumors relies predominantly on histology type which in turn determines the course of treatment for each cancer patient. Coding histology types follows The International Classification of Diseases for Oncology, Third Edition (ICD-O-3) standards of reference. In this study, histology categories were grouped into: adenocarcinomas, carcinomas, and carcinomas NOS.

Grade

Tumor grade is used extensively in patient treatment course and prognosis. Grade was grouped into: Grade I (well differentiated), grade II (moderately differentiated), grade III (poorly differentiated) and grade IV (undifferentiated).

Comorbidity score

In order to adjust for comorbidities, a comorbidity index is calculated using validated algorithms and helps to control for disease burden in patients. The initial Charlson comorbidity score is a weighted score based on identified comorbid conditions (Charlson, Pompei, Ales, & MacKenzie, 1987). It has been adapted by Richard Deyo and Patrick Romano for use with administrative data (Deyo, Cherkin, & Ciol, 1992; Romano, Roos, & Jollis, 1993). The comorbidity index has been updated by the National Cancer Institutes which is a cancer-specific index including 14 conditions which excludes solid tumors, leukemias, and lymphomas (Klabunde, Legler, Warren, Baldwin, & Schrag, 2007).

For this study, inpatient and outpatient claims files were used to extract claims with comorbid diagnoses. Claims were searched for 24 month prior to CRC diagnosis using International Classification of Disease 9th revision (ICD-9) diagnosis codes and ICD-9 procedure codes. Because diabetes is the exposure of interest in this study, diabetes diagnosis codes were excluded. A comprehensive list of conditions and corresponding definition and codes can be found in Table 12, Appendix A. When using the outpatient claims, a rule-out macro is submitted to avoid overestimation of diagnoses listed to "rule-out" conditions. Thus, in order to consider a diagnosis from the outpatient claims, this diagnosis must appear at least two times in two different claims separated by more than 30 days. In contrast, a diagnosis can appear only once in

the hospital claims to be considered. All the claims files were prepared based on the data source (MEDPAR or OUTPAT) and called on by a SAS macro to calculate the comorbidity score. The final comorbidity scores were grouped to: no comorbidity, 1 comorbidity, and 2 or more comorbidities.

Section 6: Outcome and exposure variables

Outcome variables

Stage at diagnosis

SEER registries record stage at diagnosis in a simplified version: localized, regional, distant, & unknown. For the purposes of this study, these values are combined further into a dichotomous variable: localized and advanced (includes regional and distant).

Death risk

Information about date of death is tracked in both SEER and Medicare enrollment files. Records were included if the patient's month of death agreed in both files or were off by 1-3 months. Survival in months is recoded by the SEER program after active follow up and are computed using complete dates including days. At the study cutoff (December 31, 2011), vital status is recorded "alive" or "dead". Patients are censored if they were "alive" at the cutoff date or if they died after the cutoff date. Death risk is assessed as overall mortality and CRC-specific mortality.

Exposure variable

Pre-existing T2DM

The main exposure variable under study is pre-existing diabetes status. Pre-existing T2DM was ascertained from the Medicare inpatient and outpatient claims using a validated algorithm developed by Hebert and colleagues (Hebert et al., 1999a). This algorithm provides high sensitivity (90.4%), specificity (95.1%) and positive predictive value. To identify diabetes and diabetes severity status ICD-9 codes, the algorithm looks at the interval of two years prior and three months after CRC diagnosis if it appears in a single hospital claim or two or more outpatient claims separated by more than 30 days to avoid "rule out" diagnoses. Table 2 lists the diagnosis codes used to identify diabetes with and without complications. Patients were identified as having pre-existing diabetes if they had any of the diabetes ICD-9 codes irrespective of complication status. Medication was not included in the algorithm for identifying patients with diabetes because CMS started covering medication in Part D only since 2006.

Table 2. Diabetes ICD-9 Codes by Diabetes Severity Status

Condition	Reference Period	ICD-9 codes	Number / Type of Claims to Qualify
Diabetes without complications	2 years prior CRC diagnosis + 3 months after	250.00, 250.01, 250.02, 250.03, 250.10, 250.11, 250.12, 250.13, 250.20, 250.21, 250.22, 250.23, 250.30, 250.31, 250.32, 250.33	At least 1 inpatient or 2 outpatient claims
Diabetes with complications	2 years prior CRC diagnosis + 3 months after	250.40, 250.41, 250.42, 250.43, 250.50, 250.51, 250.52, 250.53, 250.60, 250.61, 250.62, 250.63, 250.70, 250.71, 250.72, 250.73, 250.80, 250.81, 250.82, 250.83, 250.90, 250.91, 250.92, 250.93, 357.2, 362.01, 362.02, 362.03, 362.04, 362.05, 362.06, 366.41	At least 1 inpatient or 2 outpatient claims

Source: Centers for Medicare & Medicaid Services

Section 7: Statistical analyses

Descriptive analyses

Descriptive analyses include frequency tables of colorectal cancer cases characteristics by diabetes status and diabetes complications status. Chi-square tests assessed differences between groups for categorical variables.

Statistical models

Logistic regression

The association between diabetes and advanced stage of diagnosis compared to localized CRC stage is examined by the logistic regression models. The Multivariate logistic regression models are controlled for socio-demographic and clinical characteristics. SAS PROC LOGIT procedure is used to estimate the odds ratios and generate the 95% confidence intervals (CI).

Kaplan Meier survival curve

Survival curves by diabetes status are plotted using the Kaplan Meier function. Significant difference in survival curves is tested with the Log-Rank test with the SAS LIFETEST Procedure.

Cox proportional hazards model

The Cox proportional hazards regression generated hazard ratios (HR) of death for CRC cases by diabetes and diabetes with complications status while controlling for relevant confounders. Risk of death is calculated for all-cause mortality and cancer-specific cause of death. Models are generated in an iterative fashion starting with the univariate model and adding

other covariates while monitoring the model goodness of fit. The full multivariate model includes the relevant covariates. Tied data were adjusted using the Efron approximation. The 95% confidence intervals (CI) for the HRs were generated.

Version 9.4 of the SAS statistical software was used for the analyses (SAS Institute, Cary, NC)

CHAPTER 4: RESULTS

Section 1: Descriptive Analyses

After applying the inclusion and exclusion criteria, a total of 93,710 colorectal cancer (CRC) patients diagnosed between 2002 and 2011 remained for the analyses.

Cohort overall characteristics

The mean age of the study population was 78 years and the median was 77 (Standard deviation (SD) = 7; range 67 to 108). The majority of patients were aged between the 67 and 85 age group. There were slightly more females than males (55% vs. 45% respectively). The predominant race/ethnicity was White (78%) followed by Black (9%) and Hispanic (6%). Subjects were mostly either married (49%) or widowed (32%). Only 8% of the cohort lived in high poverty level census tracts (Table 3).

A quarter of the cohort had one or more comorbidities (19% had one comorbidity and 6% had two or more comorbidities). Patients were more likely to be diagnosed at an advanced stage (50% at regional and distant combined). Half the subjects were diagnosed with tumors in the proximal area of the colon (cecum to splenic flexure). More patients had moderately differentiated tumors (61%) (Table 4).

Cohort characteristics by diabetes status

Among the study subjects, 22,155 (24%) had diabetes prior to CRC diagnosis. Patients with diabetes were more likely to be in the 67 to 75 years of age bracket compared to those without pre-existing diabetes (45% vs. 41% respectively). There were slightly more female patients without

diabetes than with diabetes (55% vs. 53% respectively). The distribution of diabetes by race/ethnicity was significantly different. The proportion of diabetes was higher among non-Whites compared to Whites; 12% vs 8% for Blacks; 8% vs 5% for Hispanics and 6% vs 5% for Asian/Pacific Islanders. Marital status was evenly distributed among diabetic and non-diabetic patients. Significantly more diabetic patients lived in medium to high poverty areas compared to non-diabetics (21% vs 18% respectively lived in medium poverty level areas and 10% vs 7% lived in high poverty level areas) (Table 3). In terms of clinical characteristics, diabetic patients were more likely to have at least one comorbidity (26% vs 17%) and two or more comorbidities (12% vs 4%) compared to non-diabetic patients. No substantial differences were found in terms of CRC stage at diagnosis and grade among patients by diabetes status. More diabetic patients were diagnosed with CRC in the proximal colon (52% vs 49%) and less at the rectum area (21% vs 25%) compared to non-diabetic patients (Table 4).

Table 3. Demographic Distribution of the Colorectal Cancer Cohort by Diabetes Status

Patient Demographics	Total (%)	No Diabetes (%)	Diabetes (%)	P value
	93710	71555 (76)	22155 (24)	
Age				<.0001
67-75	39364 (42)	29471 (41)	9893 (45)	
76-85	40137 (43)	30589 (43)	9548 (43)	
86+	14209 (15)	11495 (16)	2714 (12)	
Sex				<.0001
Male	42626 (45)	32104 (45)	10522 (47)	
Female	51084 (55)	39451 (55)	11633 (53)	
Race/Ethnicity				<.0001
White NH	74931 (78)	58645 (82)	16286 (74)	
Black NH	8217 (9)	5488 (8)	2729 (12)	
Hispanic	5180 (6)	3461 (5)	1719 (8)	
American Indian/Alaska Native	266 (0)	174 (0)	92 (0)	
Asian or Pacific Islander	4745 (5)	3479 (5)	1266 (6)	
Unknown	371 (0)	308 (0)	63 (0)	
Marital Status				0.0052
Single	7631 (8)	5824 (8)	1807 (8)	
Married	45572 (49)	34941 (49)	10631 (48)	
Separated / divorced	6563 (7)	4892 (7)	1671 (8)	
Widowed	29792 (32)	22720 (32)	7072 (32)	
Unknown	4152 (4)	3178 (4)	974 (4)	
Poverty Level				<.0001
0%-<5% poverty	43276 (46)	34076 (48)	9200 (42)	
5% to <10% poverty	24800 (26)	18804 (26)	5996 (27)	
10% to <20% poverty	17331 (18)	12728 (18)	4603 (21)	
20% to 100% poverty	7801 (8)	5551 (7)	2250 (10)	
Unknown	502 (1)	396 (1)	106 (0)	

Table 4. Clinical Characteristics of the Colorectal Cancer Cohort by Diabetes Status

	Total (%)	No Diabetes (%)	Diabetes (%)	P value
Total patients	93710	71555 (76)	22155 (24)	
Comorbidities				<.0001
No comorbidity	70023 (75)	56397 (79)	13626 (62)	
One comorbidity	18031 (19)	12213 (17)	5818 (26)	
Two or more comorbidities	5656 (6)	2945 (4)	2711 (12)	
CRC stage				<.0001
Localized	41785 (45)	31766 (44)	10019 (45)	
Regional	34037 (36)	25854 (36)	8183 (37)	
Distant	13513 (14)	10554 (15)	2959 (13)	
Unknown stage	4375 (5)	3381 (5)	994 (5)	
CRC site				<.0001
Proximal	46896 (50)	35413 (49)	11483 (52)	
Distal	21236 (23)	15958 (22)	5278 (24)	
Rectum	22712 (24)	17990 (25)	4722 (21)	
Colon, NOS	2866 (3)	2194 (3)	672 (3)	
Grade				<.0001
Well differentiated	8312 (9)	6360 (9)	1952 (9)	
Moderately differentiated	57464 (61)	43529 (61)	13935 (63)	
Poorly differentiated	15361 (16)	11818 (17)	3543 (16)	
Undifferentiated	1392 (1)	1055 (1)	337 (2)	
Unknown grade	11174 (12)	8788 (12)	2386 (11)	
Histology				0.0003
Adenocarcinomas	80066 (85)	60987 (85)	19079 (86)	
Carcinomas	11194 (12)	8624 (12)	2570 (12)	
Carcinomas, NOS	2443 (3)	1944 (3)	506 (2)	

Distribution by diabetes complication status

Among the diabetic group, 3,827 patients (17%) had diabetes related complications (neuropathy, nephropathy, retinopathy or peripheral circulatory disorders). Patients who had pre-existing diabetes with complications were more likely to be males, of non-White race/ethnicity, unmarried, have one or more comorbidities, and with tumors at the proximal area of the colon. There were no significant differences for poverty level, stage at diagnosis or grade (Table 5, 6).

Table 5. Demographic Characteristics by Diabetes Complication Status

	Diabetes (%)	With complications (%)	Without complications (%)
Total patients	22155 (24)	3827 (17)	18328 (83)
Age			
67-75	9893 (45)	1720 (45)	8173 (45)
76-85	9548 (43)	1672 (44)	7876 (43)
86+	2714 (12)	435 (11)	2279 (12)
Sex			
Male	10522 (47)	1875 (49)	8647 (47)
Female	11633 (53)	1952 (51)	9681 (53)
Race/Ethnicity			
White NH	16286 (74)	2622 (69)	13664 (75)
Black NH	2729 (12)	627 (16)	2102 (11)
Hispanic	1719 (8)	323 (8)	1396 (8)
American Indian/Alaska Native	92 (0)	22 (0)	70 (0)
Asian or Pacific Islander	1266 (6)	222 (6)	1044 (6)
Unknown	63 (0)	<11	52 (0)
Marital status			
Single (never married)	1807 (8)	344 (9)	1463 (8)
Married	10631 (48)	1701 (44)	8930 (49)
Separated / divorced	1671 (8)	335 (9)	1336 (7)
Widowed	7072 (32)	1277 (33)	5795 (32)
Unknown	974 (4)	170 (4)	804 (4)
Poverty level			
0%-<5% poverty	9200 (42)	1568 (41)	7632 (42)
5% to <10% poverty	5996 (27)	1014 (27)	4982 (27)
10% to <20% poverty	4603 (21)	800 (21)	3803 (21)
20% to 100% poverty	2250 (10)	422 (11)	1828 (10)
Unknown	106 (0)	23 (1)	83 (0)

Table 6. Clinical Characteristics by Diabetes Complication Status

	Diabetes (%)	With complication (%)	Without complication (%)
Total patients	22155 (24)	3827 (17)	18328 (83)
Comorbidities			
No comorbidity	13626 (62)	1510 (39)	12116 (66)
One comorbidity	5818 (26)	1225 (32)	4593 (25)
Two or more comorbidities	2711 (12)	1092 (29)	1619 (9)
CRC stage			
Localized	10019 (45)	1768 (46)	8251 (45)
Regional	8183 (37)	1351 (35)	6832 (37)
Distant	2959 (13)	507 (13)	2452 (13)
Unknown stage	994 (5)	201 (5)	793 (4)
CRC site			
Proximal	11483 (52)	2063 (54)	9420 (51)
Distal	5278 (24)	915 (24)	4363 (24)
Rectum	4722 (21)	726 (19)	3996 (22)
Colon, NOS	672 (3)	123 (3)	549 (3)
Grade			
Well differentiated	1952 (9)	353 (9)	1599 (9)
Moderately differentiated	13935 (63)	2376 (62)	11559 (63)
Poorly differentiated	3543 (16)	604 (16)	2939 (16)
Undifferentiated	337 (2)	56 (1)	281 (2)
Unknown grade	2386 (11)	437 (11)	1949 (11)
Histology			
Adenocarcinomas	80066 (85)	76769 (85)	3297 (86)
Carcinomas	11194 (12)	10755 (12)	439 (11)
Carcinomas, NOS	2443 (3)	2359 (3)	91 (2)

Section 2: Statistical Models

Logistic Regression Analyses

Logistic regression models assessed the association of pre-existing diabetes and higher odds of advanced stage at diagnosis. The univariate model and the model with addition of age as a covariate showed lower odds of advanced stage at diagnosis in patients with diabetes complications compared to patients without diabetes (odds ratio (OR) = 0.92; 95% CI = 0.86-0.98 and OR = 0.91; 95% CI = 0.85-0.98 respectively) compared to patients with no history of diabetes (Table 7, Model 1-2). In the multivariate models, there was no significant increased odds of advanced stage of CRC based on pre-existing diabetes (Table 7, Models 3-4). Stratification by race did not affect the results (Table 7, Models 5-7). Similarly, stratification by sex showed no association of diabetes and CRC stage for both men and women (Table 7, Models 8-9). Other factors that increase the odds of being diagnosed at an advanced stage of CRC compared to localized stage include high poverty level, non-White race, and cancers with no specified site (Table 13, Appendix A).

Table 7. Logistic Regression Models

Regression Models	Diabetes without Complications			Diabetes with Complications		
	OR	Lower CI	Upper CI	OR	Lower CI	Upper CI
Model 1	**0.98**	0.95	1.02	**0.92**	0.86	0.98
Model 2	**0.98**	0.95	1.01	**0.91**	0.86	0.98
Model 3	**1.00**	0.97	1.04	**1.00**	0.94	1.07
Model 4	**0.99**	0.95	1.02	**0.97**	0.91	1.04
Stratified by race						
Model 5	**1.01**	0.88	1.15	**0.92**	0.72	1.19
Model 6	**1.02**	0.92	1.14	**1.01**	0.84	1.21
Model 7	**0.98**	0.94	1.02	**0.95**	0.88	1.04
Stratified by sex						
Model 8	**0.97**	0.92	1.02	**0.93**	0.84	1.03
Model 9	**0.98**	0.93	1.03	**0.99**	0.89	1.09

OR: Odds ratio, CI: confidence interval
Model 1: Univariate with diabetes only
Model 2: model 1 + age
Model 3: Model 2 + comorbidity
Model 4: full model (model 3 + race, marital status, poverty level, histology, grade, registry, year of diagnosis and cancer site).
Model 5: full model stratified by race, Hispanics
Model 6: full model stratified by race, Blacks
Model 7: full model stratified by race, Whites
Model 8: full model stratified by sex, males
Model 9: full model stratified by sex, females

Survival analyses

Death distribution

Over the study period (2002-2011), 44,688 (48%) subjects died of all causes and 26,037 (28%) died from CRC. Among patients without diabetes, 47% died of all causes and 28% died from CRC. Patients with pre-existing diabetes with complications died at a higher percentage of all-cause mortality compared to those with diabetes without complications (56% vs. 49%), however, there were no differences in proportion of death for CRC cause-specific mortality (Table 8).

Table 8. Distribution of CRC Deaths by Diabetes Status

Mortality	Total deaths (%)	Diabetes Status		
		No Diabetes (%)	Diabetes without complications (%)	Diabetes with Complications (%)
Overall mortality	44688 (48)	33510 (47)	8905 (49)	2273 (56)
CRC cause-specific death	26037 (28)	20306 (28)	4733 (26)	998 (26)

Survival analysis

The median survival months for overall mortality was 61 months (95% CI = 60-62). The five year survival rate from any cause for the study cohort was 51% (Standard error (SE) = 0.00186).

Kaplan Meier survival curves

Survival curves were generated for overall survival and for survival from CRC by diabetes status: no diabetes (blue line), diabetes without complications (red line), and diabetes with complications (green line). Diabetes with complications had the most unfavorable crude survival rates followed by those with diabetes without complications (log-rank test P-value <0.0001) (Figure 1). Similarly, diabetes with complications contributed to lowest CRC specific survival rate (log-rank test P-value <0.0001), however; there were no differences between non-diabetic patients and diabetic patients without complications (Figure 2).

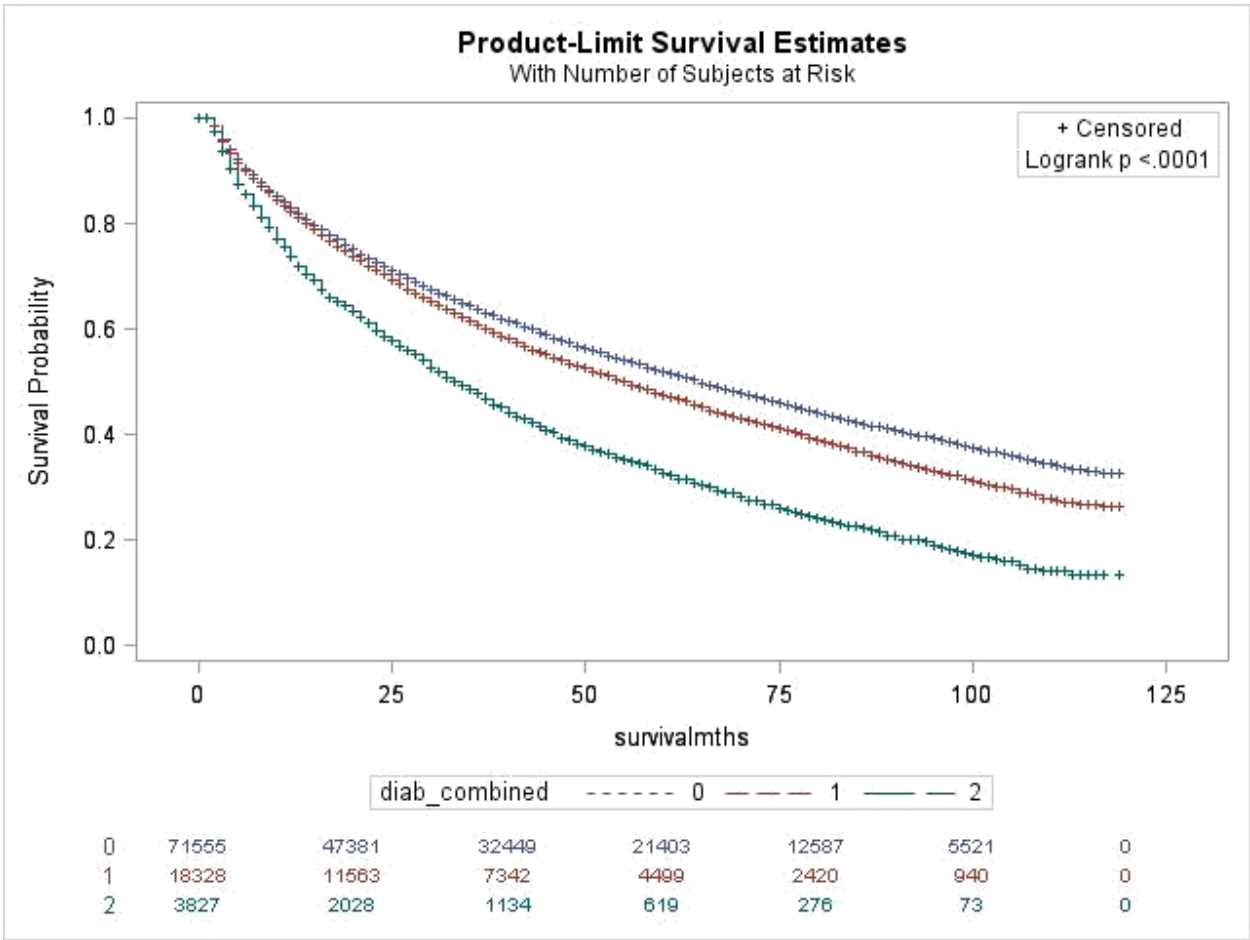

Figure 1. Crude total survival curve by diabetes status. 0: no diabetes; 1: diabetes without complications; 2: diabetes with complications

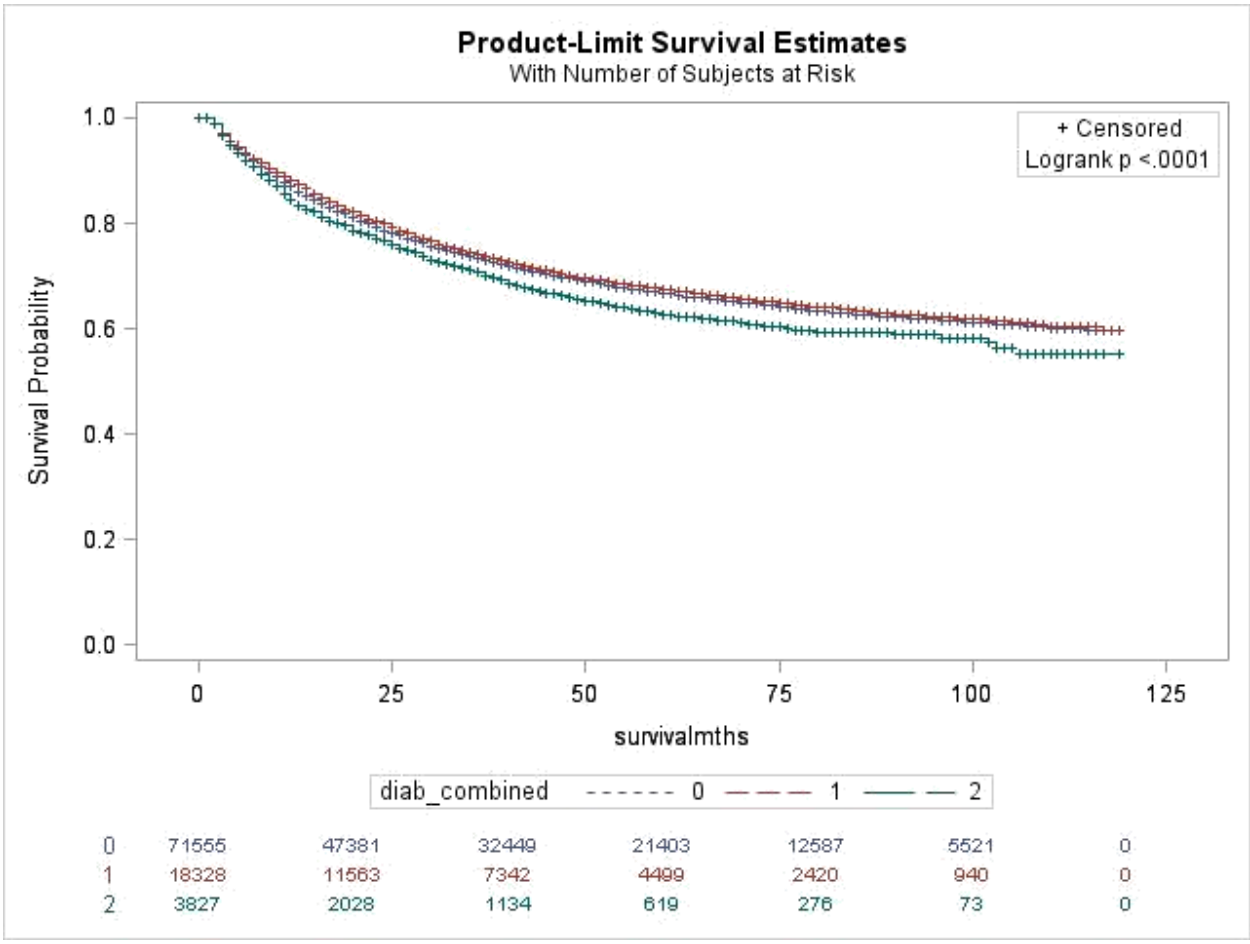

Figure 2. Crude CRC cancer-specific survival curve by diabetes status. 0: no diabetes; 1: diabetes without complications; 2: diabetes with complications

Cox proportional hazards regression analyses

In the univariate Cox regression model, CRC patients with diabetes have 21% increased risk of total mortality (hazard ratio (HR) = 1.21; 95% CI = 1.18-1.23). The mortality risk is particularly higher among diabetic patients with complications (HR = 1.69; 95% CI = 1.62-1.76) (Table 9, Model 1). Significant results were only observed for diabetes with complications in colorectal cancer specific-cause mortality (HR = 1.14; 95% CI = 1.07-1.22). Similar results were observed when adjusted for age and comorbidities, although the effects were reduced after the introduction of comorbidities (Table 9, Model 2-3).

The fully adjusted model was controlled for age, sex, marital status, race/ethnicity, poverty level, comorbidities, stage, histology, grade, year of diagnosis, and registry. Colorectal cancer patients in the fully adjusted model were more likely to die of all cause if they were diagnosed with diabetes prior to their CRC diagnosis particularly those with complications compared to those with no prior diabetes diagnosis (HR = 1.20; 95% CI = 1.17-1.23 for diabetes and HR = 1.47; 95% CI = 1.34-1.54 for diabetes with complications). Patients with diabetes with complications were 16% more likely to die of colorectal cancer compared to patients without diabetes in the fully adjust model (HR = 1.16; 95% CI = 1.08-1.25) (Table 9, Model 4).

Table 9. Effect of Pre-Existing Diabetes on Total Mortality and CRC Cause-Specific Mortality in Patients with Colorectal Cancer

Parameter	Cause specific mortality			All-cause mortality		
	Hazard Ratio	95% Confidence Interval		Hazard Ratio	95% Confidence Interval	
		Lower limit	Upper limit		Lower limit	Upper limit
Model 1: Univariate with diabetes						
No diabetes	Referent			Referent		
Diabetes	**0.99**	0.96	1.02	**1.21**[a]	1.18	1.23
Diabetes without complications	**0.97**	0.94	1.00	**1.13**[a]	1.10	1.16
Diabetes with complications	**1.14**	1.07	1.22	**1.69**[a]	1.62	1.76
Model 2: Model 1 + age						
No diabetes	Referent			Referent		
Diabetes	**1.02**	0.99	1.05	**1.27**[a]	1.24	1.29
Diabetes without complications	**0.99**	0.96	1.02	**1.18**[a]	1.15	1.21
Diabetes with complications	**1.18**[a]	1.11	1.26	**1.78**[a]	1.71	1.86
Model 3: Model 2 + comorbidity						
No diabetes	Referent			Referent		
Diabetes	**0.99**	0.96	1.02	**1.16**[a]	1.13	1.18
Diabetes without complications	**0.97**	0.94	1.00	**1.11**[a]	1.08	1.13
Diabetes with complications	**1.10**[a]	1.03	1.17	**1.43**[a]	1.37	1.50
Model 4: Fully adjusted model						
No diabetes	Referent			Referent		
Diabetes	**1.05**[a]	1.02	1.09	**1.20**[a]	1.17	1.23
Diabetes without complications	**1.04**	0.99	1.08	**1.15**[a]	1.12	1.18
Diabetes with complications	**1.16**[a]	1.08	1.25	**1.47**[a]	1.40	1.54

[a] statistically significant at $p<0.05$.

Stratified models

Stratification by race/ethnicity

Hispanic diabetic patients were more likely to die of all-cause mortality compared to those with no diabetes and the risk was higher for patients who had diabetes with complications with a 27% increased risk (HR = 1.27; 95% CI = 1.06-1.20). However, among Hispanics, colorectal cancer specific mortality was not affected by diabetes status. Similar findings were observed among Black patients. Pre-existing diabetes was a determinant of increased risk of both colorectal cancer and total mortality among White patients (Table 10).

Table 10. Effect of Pre-existing Diabetes on Death Risk in Patients with CRC by Race

Parameter	Cause specific mortality			All-cause mortality		
	Hazard Ratio	95% Confidence Interval		Hazard Ratio	95% Confidence Interval	
		Lower limit	Upper limit		Lower limit	Upper limit
Hispanics						
No diabetes	Referent			Referent		
Diabetes	**1.04**	0.91	1.18	**1.14[a]**	1.03	1.26
Diabetes without complications	**1.03**	0.90	1.19	**1.11[a]**	1.00	1.24
Diabetes with complications	**1.11**	0.87	1.42	**1.27[a]**	1.06	1.52
Blacks						
No diabetes	Referent			Referent		
Diabetes	**0.96**	0.88	1.06	**1.11[a]**	1.04	1.20
Diabetes without complications	**0.96**	0.87	1.07	**1.07**	0.99	1.16
Diabetes with complications	**1.01**	0.85	1.19	**1.29[a]**	1.15	1.45
Whites						
No diabetes	Referent			Referent		
Diabetes	**1.07[a]**	1.03	1.11	**1.22[a]**	1.18	1.25
Diabetes without complications	**1.05[a]**	1.01	1.09	**1.17[a]**	1.13	1.20
Diabetes with complications	**1.21[a]**	1.12	1.32	**1.53[a]**	1.45	1.62

[a] statistically significant at $p<0.05$.

*Stratified models are adjusted for age, sex, marital status, race/ethnicity, poverty level, comorbidities, histology, grade, year of diagnosis, and registry.

Stratification by stage

Total mortality was affected by pre-existing diabetes for all stages. The effect was strongest for diabetes with complications. For instance, CRC patients diagnosed at a localized stage who had diabetes with complications had 77% increased risk of all mortality compared to patients without diabetes (HR = 1.77; 95% CI = 1.65-1.90). Similar results were observed for patients with regional and distant stage at diagnosis (Table 11). Overall, diabetes contributed to higher risk of death at 28% and 10% for localized and advanced stage respectively.

Colorectal cancer specific mortality was significantly affected by pre-existing diabetes with complications at localized and advanced stages. The observed increase in CRC mortality was 22% for localized CRC (HR = 1.22; 95% CI = 1.05-1.41); 16% for regional stage (HR = 1.16; 95% CI = 1.04-1.30) and 14% for distant stage (HR = 1.14; 95% CI = 1.02-1.27) (Table 11).

Table 11. Effect of Pre-Existing Diabetes on Death Risk in Patients with CRC by Stage at Diagnosis

Parameter	Cause specific mortality*			All-cause mortality*		
	Hazard Ratio	95% Confidence Interval		Hazard Ratio	95% Confidence Interval	
		Lower limit	Upper limit		Lower limit	Upper limit
Localized						
No diabetes	Referent			Referent		
Diabetes	**1.03**	0.95	1.12	**1.29**[a]	1.24	1.35
Diabetes without complications	**1.00**	0.92	1.08	**1.22**[a]	1.17	1.27
Diabetes with complications	**1.22**[a]	1.05	1.41	**1.77**[a]	1.65	1.90
Regional						
No diabetes	Referent			Referent		
Diabetes	**1.03**	0.98	1.09	**1.18**[a]	1.13	1.23
Diabetes without complications	**1.00**	0.94	1.05	**1.12**[a]	1.07	1.16
Diabetes with complications	**1.16**[a]	1.04	1.30	**1.47**[a]	1.36	1.58
Distant						
No diabetes	Referent			Referent		
Diabetes	**1.06**[a]	1.01	1.13	**1.10**[a]	1.05	1.16
Diabetes without complications	**1.04**	0.98	1.09	**1.08**[a]	1.03	1.14
Diabetes with complications	**1.14**[a]	1.02	1.27	**1.17**[a]	1.06	1.29
Unknown						
No diabetes	Referent			Referent		
Diabetes	**1.09**	0.97	1.22	**1.19**[a]	1.09	1.31
Diabetes without complications	**1.08**	0.97	1.21	**1.15**[a]	1.05	1.26
Diabetes with complications	**0.86**	0.68	1.10	**1.24**[a]	1.05	1.47

[a]Statistically significant at $p<0.05$.

*Stratified models are adjusted for age, sex, marital status, race/ethnicity, poverty level, comorbidities, histology, grade, year of diagnosis, and registry.

CHAPTER 5: DISCUSSION

Section 1: Study findings summary

The aim of this study was to analyze the influence of pre-existing diabetes mellitus and diabetes with complications on survival and stage of diagnosis for the overall population of Medicare beneficiaries diagnosed with colorectal cancer between 2002 and 2011 and, particularly, for the Hispanic group.

In the analytical cohort, almost one of every four colorectal cancer patients had pre-existing diabetes and of these diabetic patients, almost one of every five patients had diabetes with complications. The logistic model revealed that diabetes, regardless of severity, is not associated with CRC stage at diagnosis on a population basis. Stratifying by race/ethnicity or sex did not change these results. On the other hand, the study reports that pre-existing diabetes is a predictor of significantly higher risk of death from all-cause mortality in elderly patients with CRC compared to non-diabetic cancer patients. Diabetes with complications had the poorest outcomes. Total mortality increased risk was not modified by race/ethnicity. Hispanic patients with diabetes had poorer overall survival compared to Hispanic patients without diabetes irrespective of diabetes severity. Diabetes was associated significantly with higher risk of total mortality in patients at all stages of diagnosis. Risk of colorectal cancer specific mortality among all patients and all stages was only increased by diabetes with complications. Diabetes did not affect risk of death from CRC among Hispanic patients. Overall, diabetes with complications had the poorest outcomes compared to diabetes without complications and no diabetes.

Section 2: Discussion of results

Diabetes and effect on CRC stage of diagnosis

The association of pre-existing diabetes and CRC stage at diagnosis has not been comprehensively studied in the literature. To our knowledge the current study is the first to assess this relationship in a cohort of American elderly patients. In this study, diabetes was not associated with advanced stage at diagnosis in CRC patients. Although diabetes is a known risk factor for colorectal cancer, it appears that having diabetes does not predict being diagnosed at a more advanced stage of the disease, which is known to contribute to poorer prognosis.

Few studies examined the association of diabetes status and colorectal tumor stage (Siddiqui et al., 2008; van de Poll-Franse, Lonneke V et al., 2007). Researchers from China found a positive association of diabetes and advanced tumor stage (Feng, Zhou, & Mao, 2011). These authors used a smaller sample (733 patients) from a single institution in China. In another earlier study from the Netherlands, authors observed a higher likelihood of advanced stage at diagnosis among colon cancer patients with diabetes (van de Poll-Franse, Lonneke V et al., 2007). However, this study used non-American subjects, assessed only colon cancer and combined type I and type II diabetes. In another study, researchers observed that when patients have poorly controlled diabetes, they are more likely to have higher number of colonic adenomatous polyps, more advanced lesions and greater use of exogenous insulin compared to those with controlled diabetes (Siddiqui et al., 2008). In our study, we did not have information about diabetes control which is usually measured by Hemoglobin A1c (HbA1c) levels. Nonetheless, we examined whether diabetes with complications was associated with advanced colorectal tumors; however, we did not observe a significant association.

Screening is a major determinant of stage at diagnosis for colorectal cancer. Patients who follow the screening guidelines of CRC are more likely to detect colon polyps early-on before they become cancerous or detect the disease at an earlier stage when treatment is more effective. Although CRC screening in the US is not optimal, it seems as diabetic patients might have more opportunities to interact with physicians in the course of diabetes management and potentially receive CRC screening recommendations from their care providers. For instance, authors found a dose-response relationship between having multiple morbidities- including diabetes- and a greater likelihood of adherence to CRC screening (Fleming, Steven T. et al). This is especially relevant among primary care physicians as they are increasingly incentivized to increase their CRC screening recommendations by the Centers of Medicare and Medicaid Services in the context of clinical quality measures improvement (Rosenthal, Fernandopulle, Song, & Landon, 2004) .

Although researchers observed higher number of physician visits among diabetic patients compared to non-diabetics (van de Poll-Franse, Lonneke V et al., 2007), nonetheless, it is unclear whether physicians are adequately recommending CRC screening, especially, to diabetic patients. This study did not observe an association of diabetes and CRC stage at diagnosis for both men and women. However, the literature seems to indicate that there are differences by gender in CRC screening among diabetic patients. For instance, it was found that elderly women with diabetes are actually less likely to receive CRC screening compared to women without diabetes (McBean & Yu, 2007). Yet, in another study, authors found that older men were more likely to be up to date with CRC screening, as indicated in the guidelines, if they had diabetes than if they did not (Miller, Tarasenko, Parker, & Schoendorf, 2014). Therefore, the relationship of diabetes and CRC screening needs to be examined further and physicians treating diabetic

patients need to promote recommended screenings to their patient population during routine visits.

Diabetes and risk of overall death

This study found a significant association between pre-existing diabetes and all-cause mortality in a cohort of elderly patients with colorectal cancer. These results are in agreement with some previous studies with an HR ranging from 1.23-1.42 (Bella et al., 2013; Gross et al., 2006a; Y. Huang, Lin, Chen, Lin, Yang, Jiang, Chang, Lan, Wang, & Liu, 2011; Jullumstr, Kollind, Lydersen, & Edna, 2009; Luo, Lin, He, & Hendryx, 2014; Meyerhardt et al., 2003a; Polednak, 2006; van de Poll-Franse, Lonneke V et al., 2007). In our study, we found a significant HR of 1.20 for overall mortality for diabetics compared to non-diabetics. In a population based study, Gauss et al. found a 23% increase in risk from all-cause mortality in patients with comorbid diabetes (Gross et al., 2006a). Patients in a clinical trial had poorer prognosis if they had diabetes at colorectal cancer diagnosis with a 42% increased risk of overall death (Meyerhardt et al., 2003a). Similarly, patients from the Connecticut cancer registry were found to have a 38% elevated risk of death from any cause (Polednak, 2006). Bella et al. found a 41% increased risk of all-cause mortality among adult Italian diabetic patients irrespective of sex or subsite (Bella et al., 2013).

Other evidence that used a systematic review of identified articles reported similar results. In a meta-analysis, Barone et al. observed 41% increase in risk of overall mortality in patients with pre-existing diabetes compared to patients without a history of diabetes from the analysis of 23 studies (Barone et al., 2008). Another meta-analysis from 15 articles found that compared to those without diabetes mellitus, persons with pre-existing diabetes had poorer

prognosis in terms of short and long term mortality with a 32% increase in all-cause mortality (Stein et al., 2010)

In contrast to most findings, some studies did not observe a significant relationship between a history of diabetes and overall mortality (Chen et al., 2010; C. Huang et al., 2012; Jullumstr et al., 2009). However, these studies had non-US subjects, used small samples, used subjects restricted to one institution, examined short term survival, and did not adjust for relevant confounders.

Diabetes and risk of colorectal cancer death

In the present study, although we found a significant association between pre-existing diabetes and colorectal cancer specific cause of death, the effect was minimal (HR = 1.051, 95% CI = 1.016-1.087). In the current literature, the association of pre-existing diabetes with colorectal cancer cause of death is not clear. For instance, a study found a significant impact on colon specific survival among Taiwanese patients who had diabetes. These findings were particularly significant in patients with advanced stage (Y. Huang, Lin, Chen, Lin, Yang, Jiang, Chang, Lan, Wang, & Liu, 2011). Researchers from Italy found also a significant relationship between diabetes and colorectal cancer death (HR 1.36; 95 % CI = 1.11–1.67) in patients 15 years and older (Bella et al., 2013). In a meta-analysis, the authors found a 12% increased risk of colorectal cancer-specific mortality in diabetic patients compared to their non-diabetic counterparts from the analysis of 26 manuscripts (Mills, Bellows, Hoffman, Kelly, & Gagliardi, 2013). Patients in the Cancer Prevention Study-II Nutrition Cohort were more likely to die of CRC if they had comorbid diabetes (RR = 1.29; 95% CI = 0.98-1.70) (Dehal et al., 2011). In

contrast, other researchers did not find elevated risk in cause of death from CRC among diabetic patients (Polednak, 2006; Stein et al., 2010).

The effect of diabetes with complications on CRC prognosis

In our study, we found a more pronounced effect on colorectal cancer mortality, both overall and cause-specific, in those who had diabetes with complications (neuropathy, nephropathy, retinopathy or peripheral circulatory disorders). We observed almost a 50% increase in risk of death from all causes and a 16% increase in CRC specific death. These findings are unique as most studies did not distinguish diabetes status by severity (Bao et al., 2010; Bella et al., 2013; Dehal et al., 2011; Feng et al., 2011; Gross et al., 2006a; Y. Huang et al., 2011; Jullumstr et al., 2009; Meyerhardt et al., 2003a; Meyerhardt et al., 2003b; Polednak, 2006; van de Poll-Franse, Lonneke V et al., 2007).

Section 3: Explanations of the main findings

The exact reasons of how diabetes mellitus affects colorectal cancer prognosis are not clear; however, there are potential explanations on how diabetes might directly or indirectly influence increased risk of colorectal cancer mortality.

Some physiological pathways observed, including hyperinsulinemia and hyperglycemia, are known factors that contribute to increased risk of colorectal carcinogenesis and tumor metastasis and; therefore, might also directly affect the outcomes of the disease (Bao et al., 2010; Giovannucci, 2007; Tsai & Giovannucci, 2012). Moreover, it has been found that diabetes increases risk of colorectal cancer recurrence which might contribute to poorer prognosis (Feng et al., 2011; Meyerhardt et al., 2003b; Mills, Bellows, Hoffman, Kelly, & Gagliardi, 2013).

On the other hand, diabetes might increase mortality in general in association with death from diabetes-related diseases (e.g., stroke, ischemic heart disease, hypertension, chronic renal failure). For instance, in a study of multimorbidity and survival in persons with colorectal cancer, Gross et al. found that among CRC deaths, 9% were attributable to congestive heart failure and more than 5% were attributable to chronic obstructive pulmonary disease (Gross et al., 2006b). Another study using a large US cohort found a 2 fold increase of death from cardiovascular diseases among patients with self-reported diabetes and colorectal cancer (Dehal et al., 2011).

Some other plausible explanations may generate from more indirect influence of diabetes in terms of the cancer management and treatment. For instance, comorbid diabetes might influence treatment decisions, treatment response, and treatment-related side effects. Researchers found that patients with diabetes were less likely to start recommended colorectal cancer adjuvant chemotherapy (Gross, McAvay, Guo, & Tinetti, 2007) and less likely to receive

aggressive cancer treatment (van de Poll-Franse, Lonneke V et al., 2007). This might be due to increased cancer treatment related side-effects among diabetic patients compared to those without diabetes (Meyerhardt et al., 2003b).

Diabetes with complications and CRC prognosis

In this study, patients were more likely to die specifically of colorectal cancer if they had diabetes with complications. Reasons for this effect have not been fully explored. This study showed that, while diabetes in general or diabetes without complications is not associated with poorer colorectal cancer survival, when patients have diabetes with microvascular complications, they are more likely to die of colorectal cancer compared to non-diabetics. This might indicate that poor diabetes control is unfavorable for colorectal cancer patients and that controlling diabetes and preventing its complications might be beneficial for these patients.

Diabetes control is usually measured by glycosylated hemoglobin (HbA1c) where levels of HbA1c greater than 7.5% are considered unsatisfactory glycemic control and patients are referred to medication use to control diabetes (Woerle et al., 2007). A common medication used in diabetes control is Metformin which aids to decrease plasma glucose levels by increasing intracellular glucose uptake (Dodd et al., 2009). Researchers demonstrated that colorectal cancer patients who control their blood glucose using metformin experience a 30% improvement in overall survival compared to other agents (Garrett et al., 2012).

In our study we were not able to assess the effect of diabetes control on CRC outcomes as this information is not available; however, diabetes with complications can be considered a proxy to poor diabetes control as research shows that uncontrolled diabetes is an independent risk factor for diabetes complications (Stratton et al., 2006). Clinicians have a great role in aiding

their patients to manage their diabetes through regular HbA1c testing, education about lifestyle changes and medication. For instance, it has been demonstrated that cancer patients who receive diabetes education are less likely to visit emergency departments, have fewer hospital admissions and are more likely to manage their diabetes with more frequent HbA1c tests (Irizarry et al., 2013).

Effect of diabetes on CRC prognosis by stage

Colorectal cancer specific mortality was significantly affected by pre-existing diabetes with complications at localized, regional and distant stages compared to no diabetes but not when diabetes was present without complications. Consistent with this finding, previous literature reported that uncontrolled diabetes, an independent risk factor for diabetes complications, leads to diagnosis of CRC at later stages and poorer 5-year survival (Siddiqui et al., 2008; Stratton et al., 2006). Further, Huang and colleagues found that diabetic patients diagnosed at an advanced stage were particularly at significant higher risk of dying of colon cancer; although, they did not examine the relationship by diabetes complications status (Y. Huang, Lin, Chen, Lin, Yang, Jiang, Chang, Lan, Wang, & Liu, 2011). Our study shows that diabetes with complications is detrimental to CRC patients regardless of what stage they are diagnosed at. The exact mechanism for this finding is uncertain and further research is needed.

Effect of diabetes on CRC prognosis for Hispanics

Hispanics with colorectal cancer and pre-existing diabetes, particularly those who had diabetes with complications, were significantly more likely to die of overall causes compared to Hispanics without diabetes. The relationship was attenuated for mortality from colorectal cancer. The effect of diabetes on CRC mortality among Hispanics has not been examined in the

literature. In general, Hispanics have higher prevalence of diabetes with a substantial increase in the last decades (Geiss et al., 2014). Moreover, while mortality from diabetes is decreasing in other non-Hispanic racial/ethnic groups, it is on the rise for Hispanics (McBean, Li, Gilbertson, & Collins, 2004). Further, Hispanics have poorer survival from colorectal cancer compared to non-Hispanic Whites, especially when more precise follow-up procedures are used (Pinheiro et al., 2011).

Hispanics who suffered from diabetes complications were substantially more likely to die compared to patients without complications or no diabetes. Rising literature documents that Hispanics suffer disproportionately from diabetes complications which is likely to contribute to unfavorable cancer survival. Karter and colleagues reported that Hispanic members of Kiser Permanente were more likely to have diabetes complications compared to other groups, particularly, End Stage Renal Disease (ESRD) (Karter et al., 2002). Similarly, a systematic review observed an increased risk of ESRD and retinopathy among Hispanics in the US (Lanting, Joung, Mackenbach, Lamberts, & Bootsma, 2005). Other diabetes related complications that affect Hispanics disproportionately are amputations (Lavery et al., 1996).

Reasons for the higher proportions of diabetes complications among Hispanics is potentially due to less than optimal diabetes care and control. For instance, Hispanics are less likely to self-monitor their blood glucose as recommended by the American Diabetes Association (ADA) to monitor once daily when diabetes is treated with medications (Karter, Ferrara, Darbinian, Ackerson, & Selby, 2000). Compared to non-Hispanic Whites, Hispanics are less likely to treat their diabetes with diet and exercise (61% vs 36% respectively) and have lower proportions of annual eye examination (73% vs 49% respectively) (Coronado, Thompson, Tejeda, Godina, & Chen, 2007). Although health disparities among Hispanics are usually

attributed to poor access to care (Velasco-Mondragon, Jimenez, Palladino-Davis, Davis, & Escamilla-Cejudo, 2016), in our study all subjects were covered under Medicare and thus, access to care is unlikely a contributor to poor outcomes. Nevertheless, access to care is not always synonymous to quality of care. Disparities in quality of care among Medicare beneficiaries are not uncommon (Schneider, Zaslavsky, & Epstein, 2002). Moreover, lack of English language fluency plays a role in health care access and is likely a predictor for poor diabetes care for Hispanics. As it is documented that diabetes education is crucial to better diabetes management especially when diabetes is comorbid to cancer (Irizarry et al., 2013), it becomes imperative that Hispanics with CRC receive culturally competent diabetes education programs in order to improve their overall outcomes.

Section 4: Strengths and Limitations

Strengths

The strength of this study lies in the inclusion of large number of patients in the analysis from a nationally representative database. The SEER-Medicare data are widely used in research and offer a combination of clinical information from the cancer registries and diagnoses and procedures from the Medicare claims data. These data are population-based and allow authors to track patients longitudinally with the possibility to follow patients from their enrollment in the Medicare program until their death regardless of place of residency.

Limitations

Findings from this study have to be interpreted in light of certain limitations. Administrative and surveillance data are not inherently designed for research. Some important information lack and is likely to affect to some degree the magnitude of the effects. For example, many behavioral and patient characteristics such as obesity status, smoking, red meat and alcohol consumption, individual-level income brackets, physical activity level, and family history of CRC were missing. These factors are all related to diabetes and colorectal cancer outcomes. If patients who had diabetes also had heavy smoking and alcohol intake, had high BMI and other unfavorable characteristics, then the observed increased mortality associated with diabetes might be overestimated. Although we were unable to control for these factors, other studies that did control, did not observe a weakening in the association between diabetes and increased risk of overall and cancer specific death (Coughlin et al., 2004; Dehal et al., 2011). Moreover, since we controlled for comorbidities, most of the factors that were not included are covered in the comorbidities variable.

An important factor we were unable to account for is duration of diabetes; however, Dehal et al. did not find significant differences in CRC prognosis based on duration of diabetes (Dehal et al., 2011). Another limitation is related to the identification of diabetic patients from claims data. This limitation has two levels, first the accuracy of the algorithm used to identify pre-existing diabetes in the time frame set before CRC diagnosis. There is likelihood to miss some cases of diabetes if they did not have an encounter with their clinicians either at an outpatient or inpatient setting. To mitigate this limitation we allowed a long period of time of 24 months before CRC diagnosis and 3 month after to include previously undiagnosed diabetes (Yang et al., 2013), in addition, we used a validated algorithm with sensitivity of 74.4% and specificity of 97.5% (Hebert et al., 1999b) to identify patients with diabetes. Second, we do not have information on cases with prediabetes (impaired fasting glucose and/or impaired glucose tolerance) and our hazard ratios might be underestimated. This remains a concern as the prevalence of prediabetes is on the rise (Boyle, Thompson, Gregg, Barker, & Williamson, 2010).

Another concern is related to using Medicare data which tracks claims for patients 65 and older and previous medical history is unavailable for this patient population in addition to the restriction to non-HMO enrollees. This limitation affects the generalizability of the findings which are restricted to older persons aged 65 and older enrolled in Medicare Fee For Service plans. Nevertheless, the elderly population is the most affected by diabetes and CRC and the literature indicates that the elderly SEER population is similar in terms of demographic characteristics to the rest of the US elderly population (Warren et al., 2002).

Another clinical factor we have not controlled for is treatment. Reasons for this reside in unavailability of all the treatment variables in the dataset, only first course surgery and radiotherapy are recorded while chemotherapy is not. In addition, these variables are not reliable

as the data was missing for a large number of patients where the values are listed as “unknown whether surgery or radiation were performed”. Moreover, treatment is usually done according to guidelines based on cancer stage. Since one of the exposures in the study is the diabetes with complications, this would have a significant impact on the choice of therapy. It is not customary for surveillance data to contain detailed therapy information especially when other pathologies are present. Lastly, the findings did not take into consideration use of diabetes medication as this data was not available for the full study period. However, researchers found no difference in CRC deaths among those who have diabetes and use insulin compared to those with no reported diabetes (Dehal et al., 2011).

CHAPTER 6: CONCLUSION

This study contributes to the existing evidence about the association of pre-existing diabetes and mortality from colorectal cancer. It also adds to some knowledge gaps in terms of the relationship of diabetes complications and CRC survival; the relationship in terms of the association of pre-existing diabetes with advanced stage at diagnosis of CRC and the variation by race/ethnicity. In addition, the findings also underscore lack of understanding of the underlying mechanisms of how diabetes affects CRC outcomes.

In summary, this study used population-based data and the findings indicate that pre-existing diabetes contributes to poorer overall survival in patients with colorectal cancer and increased mortality from CRC in diabetes with complications. These results extended to the Hispanic group, a focus population in this study. Pre-existing diabetes is not associated with advanced stage at diagnosis in patients with colorectal cancer, however, diabetes with complications is unfavorable for survival from CRC for patients at all stages of diagnosis. These findings are relevant in the context of continuous increase in prevalence of diabetes among the aging US population. Because these diseases are more prevalent among the elderly, this group is more likely to have both diseases at the same time and more clinicians will need to develop care plans that are interdisciplinary and take into consideration the added burden of diabetes among CRC patients.

Particular attention is needed for patients with diabetes complications as they suffer from the worst outcomes. Increased focus on diabetes education, diabetes self-management and improved diabetes control are critical to improve survival in colorectal patients with comorbid diabetes. Diabetic patients may also benefit from earlier colorectal screening to reduce both the

incidence of CRC and improve CRC outcomes. New guidelines of CRC screening are warranted to take into account the added burden of diabetes.

APPENDIX A

Table 12. NCI Comorbidity Index Conditions and Codes

Condition	Definition/Codes
Acute Myocardial Infarction	ICD-9 Diagnosis: 410.xx with inpatient length of stay >2 days
History of Myocardial Infarction	ICD-9 Diagnosis: 412.bb
Congestive Heart Failure	ICD-9 Diagnosis: 398.91, 425.4x-425.5x, 425.7x-425.9x, 428.xx
Peripheral Vascular Disease	ICD-9 Diagnosis: 093.0x, 440.xx-441.xx, 442.0x-442.8x, 443.1x-443.9x, 447.70-447.73, 785.4x, V43.4x
	ICD-9 Procedure: 00.60, 38.13, 38.14, 38.15, 38.16, 38.18, 38.33, 38.34, 38.36, 38.38, 38.43, 38.44, 38.46, 38.48, 38.68, 39.25, 39.29
Cerebrovascular Disease (CVD)	ICD-9 Diagnosis: 430.xx- 438.xx
	ICD-9 Procedure: 00.61, 00.62, 00.63, 00.65, 38.12, 38.32, 38.42, 39.22, 39.28, 39.74
Chronic Obstructive Pulmonary Disease (COPD)	ICD-9 Diagnosis: 416.8x-416.9x, 490.xx-496.xx, 500.xx-505.xx, 506.4x, 519.1x
Dementia	ICD-9 Diagnosis: 290.xx, 291.0x-291.2x, 292.82, 294.1x, 331.0x-331.2x, 331.82
Paralysis (Hemiplegia or Paraplegia)	ICD-9 Diagnosis: 342.xx, 344.0x-344.6x, 344.9x
Renal Disease	ICD-9 Diagnosis: 403.01, 403.11, 403.91, 404.02, 404.03, 404.12, 404.13, 404.92, 404.93, 582.xx-583.xx, 585.xx-586.xx, 588.xx, V42.0x, V45.1x, V56.xx
	ICD-9 Procedure: 39.27, 39.42, 39.95, 54.98, 55.69
Mild Liver Disease	ICD-9 Diagnosis: 070.32-070.33, 070.54, 571.2x, 571.4x-571.6x
Moderate/Severe Liver Disease	ICD-9 Diagnosis: 070.22-070.23, 070.44, 456.0x-456.2x, 572.2x-572.8x, V42.7x
	ICD-9 Procedure: 39.1b, 42.91, 50.5x
Peptic Ulcer Disease	ICD-9 Diagnosis: 531.xx-534.xx
Rheumatologic Disease	ICD-9 Diagnosis: 710.0x, 710.1x, 710.4x, 714.0x-714.2x, 714.81, 725.bb
AIDS	ICD-9 Diagnosis: 042.xx-044.x, V08.bb, 795.71

NCI: National Cancer Institute
”b” denotes blank
”x” denotes any character including blank
Source: Healthcare Delivery Research Program, NCI

Table 13. The Association of Diabetes and Stage at Diagnosis for CRC

Model variables	Odds Ratio	95% Confidence Interval	
		Lower limit	Upper limit
Diabetes status			
No diabetes	Referent		
Diabetes without complications	0.98	0.94	1.01
Diabetes with complications	0.96	0.90	1.03
Age			
67-75	Referent		
76-85	0.94	0.91	0.97
86+	0.88	0.84	0.92
Comorbidities			
No comorbidity	Referent		
One comorbidity	0.91	0.88	0.94
Two or more comorbidities	0.72	0.67	0.76
Poverty level			
0%-<5% poverty	Referent		
5% to <10% poverty	1.05	1.01	1.09
10% to <20% poverty	1.06	1.02	1.10
20% to 100% poverty	1.16	1.10	1.23
Unknown	0.85	0.70	1.03
Sex			
Male	Referent		
Female	0.94	0.92	0.97
Marital status			
Single	Referent		
Married	0.93	0.89	0.98
Separated / divorced	1.05	0.98	1.13
Widowed	1.00	0.95	1.06
Unknown	0.72	0.66	0.78
Race/ethnicity			
Whites	Referent		
Black NH	1.13	1.07	1.19
Hispanic	1.14	1.07	1.21
American Indian/Alaska Native	1.13	0.87	1.46
Asian or Pacific Islander	1.15	1.07	1.23
Unknown	0.32	0.24	0.42
Histology			
Adenocarcinoma	Referent		
Carcinoma	1.51	1.45	1.58
Carcinoma NOS	2.44	2.15	2.77

Model variables	Odds Ratio	95% Confidence Interval	
		Lower limit	Upper limit
Cancer site			
Proximal	Referent		
Distal	0.99	0.95	1.02
Rectum	0.92	0.89	0.95
Colon, NOS	3.17	2.84	3.54
Grade			
Well differentiated	Referent		
Moderately differentiated	2.36	2.24	2.48
Poorly differentiated	5.27	4.96	5.59
Undifferentiated	5.29	4.65	6.02
Unknown	1.33	1.24	1.41

APPENDIX B

UNLV
UNIVERSITY OF NEVADA LAS VEGAS

Biomedical IRB – Exempt Review
Deemed Exempt

DATE: January 31, 2013

TO: **Dr. Paulo Pinheiro,** Community Health Sciences

FROM: Office of Research Integrity – Human Subjects

RE: Notification of IRB Action
Protocol Title: Is Diabetes a Predictor for Racial Differences in Stage at Diagnosis for Colorectal Cancer in Medicare Enrollees?
Protocol # 1301-4355M

This memorandum is notification that the project referenced above has been reviewed as indicated in Federal regulatory statutes 45CFR46 and deemed exempt under 45 CFR 46.101(b)4.

Any changes to the application may cause this project to require a different level of IRB review. Should any changes need to be made, please submit a **Modification Form**. When the above-referenced project has been completed, please submit a **Continuing Review/Progress Completion report** to notify ORI – HS of its closure.

If you have questions or require any assistance, please contact the Office of Research Integrity - Human Subjects at IRB@unlv.edu or call 895-2794.

Office of Research Integrity – Human Subjects
4505 Maryland Parkway • Box 451047 • Las Vegas, Nevada 89154-1047
(702) 895-2794 • FAX: (702) 895-0805

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CURRICULUM VITAE

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Education

2017 Ph.D. in Public Health - Epidemiology and Biostatistics

2013 Master in Public Health - Epidemiology and Biostatistics, University of Nevada, Las Vegas

2005 Master of Science in International Economics, University of Economics, Rabat, Morocco

2001 Bachelor of Science in Business Administration, University of Economics, Rabat, Morocco

Certification/Training

2016 Grant Writing Certificate (4.2 CEU), University of Nevada, Las Vegas Grant Academy Program

2015 Tableau Desktop III: Advanced, Tableau Software Solutions

2012 Biomedical CITI (Collaborative Institutional Training Initiative) certified

Professional Experience

2014-present Health Care Analyst & Tableau Lead, HealthInsight, Las Vegas, Nevada

- Lead analyst for HealtHIE Nevada, the only State-wide Health Information Exchange (HIE) dedicated to connecting healthcare organizations and exchanging timely and securely clinical information at the point of care to manage and improve patient outcomes. Responsibilities include managing the HIE internal and external datasets to create reports and dashboards critical to day-to-day operations and decision-making, improving marketing and outreach initiatives, increasing usage of the HIE products, evaluating progress towards achieving the HIE program and Board goals, and providing actionable data analyses to increase the value proposition to the community and stakeholders.
- Lead analyst for the Nevada Hospital Association (NHA) transparency website that aims to improve patient safety and quality of care by providing timely information on clinical and patient satisfaction measures such as infections, emergency care, adverse events and others. This aids patients in making informed-decisions about their care institutions options for their health care needs. Moreover, hospitals leverage the transparency data to evaluate their performance compared to other hospitals, state and national benchmarks. Responsibilities include data collection from disparate sources including, but not limited to, the Centers of Medicare and Medicaid Services (CMS) Hospital Compare and the Agency for Healthcare Research and Quality (AHRQ) MONAHRQ databases; cleaning; processing; summarizing, evaluating and submitting data for the website update.
- Lead analyst for the HealthInsight Comprehensive Resident Safety and Prevention program (CRiSP) funded by the Nevada Department of Health and Human Services, Division of Public and Behavioral Health. This program is an interdisciplinary quality improvement initiative that aims to prevent and reduce falls among nursing facilities (NF) residents. Responsibilities include periodic data collection about falls from participating NFs and summarizing the data

for quality improvement of fall-related care processes and outcomes and providing analytic summaries for program evaluation to gage progress towards falls-reduction goals.

- Lead analyst for HealthInsight Reducing Injury and Improving SafEty (RISE) Program to improve fall-related care processes and outcomes and minimize risk and harm to patients in acute care settings. This quality improvement initiative aims to reduce fall-related injuries by 20% in 24 months. Responsibilities include evaluating baseline falls rate per facility and evaluating program performance of fall rates by injury status.
- Lead analyst for the Strong Start program, a CMS initiative to support pregnant women within the Nevada Medicaid program to reduce pre-term births and low birth weight babies. Responsibilities included collecting data templates form participating facilities and auditing data accuracy and completeness, preparing the deliverables for CMS program evaluation, giving feedback to internal teams and facilities on program performance.
- Lead analyst for True North Dashboard evaluating the progress of the organization towards meeting the Ends Policies and mission set by the HealthInsight Board of Directors. Responsibilities include interacting with the CEO, the Executive Directors and various teams across the organization to evaluate the list of proposed measures to track HealthInsight's progress toward broad goals in terms of community-wide improvements in health care quality and costs. Build interactive visualizations as part of the True North dashboard to present clear and succinct data in the various domains and measures tracked under each domain, show trends, and display progress towards goals and benchmarks.
- Lead analyst for Tableau Use and Expansion. Internal role to improve usage of Tableau tools including desktop, reader, and Tableau server among analysts and across the organization. Responsibilities include evaluating usage efficiency, identifying best practices and facilitating

internal learning across existing users, providing technical support and managing software license purchases and allocations, and managing Tableau server among other tasks.

2012-2013 Intern, Office of Public Health Informatics & Epidemiology, Nevada Division of Public and Behavioral Health

- Evaluated the Infection Risk Assessment (IRA) survey data to examine whether this tool accurately and consistently reports the effectiveness of the Healthcare-Associated Infections (HAI) prevention and control initiatives
- Applied statistical programming to clean, organize, and prepare the dataset for analysis
- Assessed consistency of survey answers to related questions through frequency distributions
- Evaluated compliance of the healthcare facilities to the HAI modules (infection control program, employee health program, environmental infection control, etc.)
- Prepared detailed report of major findings including analysis tables
- Made recommendations about how to improve the survey tool to State Officers

2013 Intern, Exito! Cancer research internship, The Institute for Health Promotion Research, the UT Health Science Center, San Antonio TX

- Designed a research study to assess whether elderly diabetic Hispanic patients are at increased risk for colorectal cancer (CRC) and whether diabetes increases risk of advanced stage at diagnosis of CRC using the SEER-Medicare data bases
- Finalized research questions, hypotheses, and the study protocol
- Completed SEER-Medicare data request application form
- Developed Biomedical Institutional Review Board exempt application for research involving human subjects

- Reviewed SEER-Medicare databases and files documentation and training materials
- Conducted literature review of the diseases and risk factors under study
- Identified relevant variables to the study and established definition for cases and controls

2010-2014 Scholarship Counselor, Office of Financial Aid and Scholarships, UNLV

- Provided support and technical information to students and parents about scholarship resources
- Audited account balances and generate spending reports
- Responded and resolved State/Federal Aid and scholarships concerns
- Developed departmental protocols and procedure manuals
- Supervised and train student workers and graduate assistants

Selected Publications

No Differences in Cervical Cancer Stage at Diagnosis for Blacks and Whites in the Mountain West, Journal of Immigrant and Minority Health DOI: 10.1007/s10903-014-0149-x

The Effect of Marriage on Stage at Diagnosis and Survival in Women with Cervical Cancer, Journal of Psycho-Oncology. DOI: 10.1002/pon.4070

Peer-Reviewed Poster Abstracts and Presentations

Oral presentations

The 2013 American Public Health Association (APHA) meeting in Boston, MA.

The Health Sciences Brown Bag hosted by the UNLV Graduate and Professional Students Association

Poster presentations

The 2014 Nevada Public Health Association, Las Vegas NV

The 2014 Using Data Systems to Improve Hispanic Health Outcomes hosted by the Hispanic Serving Health Professions Schools, at the National Institutes of Health, Bethesda MD

The 2014 Nevada Cancer Coalition Summit, Las Vegas NV

The 2014 Graduate Research Forum, the UNLV Graduate College and the Graduate and Professional Student Association (2d prize) in Las Vegas, NV

The 2013 Nevada Public Health Association (NPHA) meeting in Reno, NV

The 2013 North American Association of Cancer Central Registries (NAACCR) Meeting (1st prize) in Austin, TX.

The 2013 American Society of Preventive Oncology (ASPO) Meeting in Memphis, TN.

The 2013 student internship poster presentation, School of Community Health Sciences, UNLV

The first annual UNLV Science, Technology, Engineering, and Mathematics (STEM) Summit

Honors, Awards & Scholarships

Jul 2015	Best visualization using Nevada public salaries, Las Vegas Tableau User Group
May 2015	Stacy Darling Scholarship, School of Community Health Science, UNLV
Mar 2015	UNLV Summer Session Scholarship, UNLV
Mar 2015	The Patricia Sastaunik Scholarship, UNLV

Mar 2015 UNLV Graduate Access Scholarship, UNLV

Aug 2014 GPSA Emergency Sponsorship, the Graduate and Professional Students Association

May 2014 Outstanding Thesis Award, School of Community Health Science, UNLV

May 2014 First recipient of the Mary Guinan & Shawn Gerstenberger Public Health Scholarship for dissertation project, School of Community Health Science, UNLV

Mar. 2014 Second Outstanding Poster Award at the Graduate and Professional Students Association Spring 2013 Research Forum

Nov. 2013 Selected as Outstanding Graduate Fall 2013 Commencement by UNLV President Neal Smatresk

Oct. 2013 Academic Scholarship; Western Users of SAS Software annual meeting

Sept. 2013 Academic Recognition; Multicultural Program for Engineering, Sciences, Allied Health Sciences, Community Health Sciences, and Nursing

Sept. 2013 Golden Key International Honor Society Graduate, UNLV Chapter

Aug. 2013 SCHS Travel Award; School of Community Health Sciences

July 2013 Nominated classified staff employee of the month

June 2013 Exito! Summer Institute in Latino cancer health disparities sponsored by the National Cancer Institute; Institute for Health Promotion Research, University of Texas, San Antonio.

June 2013 First Prize Student Poster Award; North American Association of Central Cancer Registries

May 2013 UNLV Graduate College Recruitment Scholarship; the UNLV Graduate College

May 2013 UNLV James F. Adams/GPSA Scholarship; the UNLV Graduate College

Apr. 2013 Outstanding Graduate Student Award; School of Community Health Sciences, UNLV

Apr. 2013 GPSA Summer 2013 Grant; the Graduate and Professional Students Association

Mar. 2013 Research Travel Award; School of Community Health Sciences, UNLV

Feb. 2013 Phi Kappa Phi Honors Graduate; Phi Kappa Phi UNLV Chapter 100

Feb. 2013 Senator Harry Reid Certificate of Commendation; Senator Harry Reid

Leadership

- Las Vegas Tableau User Group, active member, 2014-present
- Las Vegas SAS User Group, organizing committee, 2014-present
- UNLV Public Health Student Association, treasurer, 2014-2015
- The APHA Cancer Forum, membership chair, 2013-2015
- Advancement Committee Leader Member, The American Public Health Association (APHA) Student Assembly, 2013-2014
- Nevada Cancer Coalition, Active Member, 2013- present
- Nevada Public Health Association, active member, 2013- present