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The purpose of this study was to evaluate trends in the incidence and mortality of early-onset CRC (age at diagnosis < 50), vs. late-onset CRC (age at diagnosis ≥ 50). A secondary objective is to compare characteristics and outcomes among Black and White Veterans among patients with early-and late-onset CRC. This study was a retrospective analysis of a national cohort of Veterans identified in the Veterans Administration (VA) Oncology database with a diagnosis of CRC between 2012 and 2017. The PRECEDE model was used to guide this study.

Descriptive statistics were used to compare characteristics among early-onset and late-onset patients and evaluate Black and White differences within both groups of CRC patients. Chi-square analyses, logistic regression, and Kaplan-Meier methods were the statistical analyses used to answer the research questions.

In this cohort of 13,940 patients, early-onset accounted for approximately 4% (*N*=604) and remained consistent each year, while late-onset represented approximately 96% (*N*=13336) of patients and remained stable over the years. The sample was majority male (96.06%). The females were majority early-onset (12.09%) compared to 3.01% late-onset. The Black-White race distribution was (28.48%/71.52%) in early-onset and (19.84%/80.16%) for late-onset. The following predisposing factors (age, race, marital status, tobacco history, health conditions, and BMI) and the enabling factors treatment and additional health insurance were statistically significant among early-versus late-onset CRC (all $p<0.0001$).

Findings from this study emphasize the importance of distinguishing between early-onset CRC and late-onset CRC to understand the unique characteristics of early-onset disease better, and factors contributing to racial differences in both early-and late-onset CRC.

EARLY-ONSET VS. LATE-ONSET COLORECTAL CANCER

TRENDS AMONG VETERANS

by

Monalesia Chapman

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Approved by

_____
Committee Chair

In loving memory of
my father Shelley James Harmon, and my brother Joe Nathan Harmon

In honor of
my mother Dorothy Harmon
my husband Ellis Chapman
my children Johnaustin, Christian, Christopher

APPROVAL PAGE

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CHAPTER I

INTRODUCTION

Colorectal cancer (CRC) is the third most commonly diagnosed cancer in men and women in the United States and the third leading cause of cancer-related deaths (Zullig et al., 2017). Over the last 10 years, the incidence and mortality rates of CRC have declined tremendously in the United States (Williams et al., 2016). While early detection is possible via screening, CRC incidence is decreasing due to increased screening and advanced treatment methods, the incidence among the subset of individuals diagnosed with early-onset CRC (age at diagnosis < 50) is increasing (Connell, Mota, Braghiroli, & Hoff, 2017). The increased incidence of early-onset CRC justifies the need to determine underlying causes and potential preventative methods.

According to the American Cancer Society (ACS, 2018), there will be an estimated 147,950 new CRC cases diagnosed in 2020 and 53,200 estimated deaths from CRC (ACS, 2020). Although there is a decrease in the incidence and mortality rate in all racial and ethnic groups, CRC is still a significant burden in the African American (AA) population (Augustus & Ellis, 2018; Williams et al., 2016). The increased burden of CRC in AAs led to the recommendation by the American College of Gastroenterology to screen AAs at age 45 years (Ashktorab et al., 2016). Screening is critical for CRC to be discovered at the early stages when treatment options have more favorable outcomes. According to the Centers for Disease Control and Prevention (CDC), 90% of people live

5 years or more if their CRC is diagnosed early through screening. Since the year 2000, the incidence and mortality rates of CRC in these younger individuals have been increasing, and additional research is needed to distinguish between early- versus late-onset CRC risk factors and outcomes.

There was a 13% increase in CRC death rates between 2000 and 2014 for those <50 years of age (Patel & Ahnen, 2018). Individuals diagnosed before age 50 are likely to present with advanced-stage disease, which affects health outcomes and survival. The increased incidence of early-onset CRC emphasizes the need to closely monitor individuals less than 50 years who present with warning signs such as hematochezia, change in bowel habits, anemia, and weight loss for no apparent reason.

Since the early 2000s, studies have been conducted to try to determine the patient demographics and tumor characteristics of this group (Jacobs et al., 2018). Further research is needed to understand factors unique to early-onset versus traditional or late-onset CRC so that appropriate measures can be taken to address the problem adequately. Early-onset CRC is a patient population where routine screening recommendations are limited and critical symptoms often go unrecognized (Connell et al., 2017). Overall, the research attributes early detection as the most significant reason for the decreased overall CRC incidence (Ahnen et al., 2014). Therefore, research is required to better understand factors related to early-onset CRC that may be different from traditional or late-onset CRC and understand factors that can assist in identifying at-risk persons who are younger than recommended screening ages.

Background

Colorectal cancer begins as a noncancerous polyp in the colon/rectum and develops into a cancerous tissue that metastasizes (ACS, 2018). The most common type of polyp is an adenomatous polyp, which accounts for approximately 96% of all CRC (ACS, 2018). According to the American Cancer Society, approximately 4.6% of men and 4.2% of women are diagnosed with CRC at some point in their lifetime (ACS, 2018). The lifetime risk is similar in men and women, although the incidence is higher in men because women have a longer life expectancy. Demographic factors that influence risk include age, sex, and race/ethnicity (ACS, 2018). The risk of developing CRC increases with age, with the median age for diagnosis being 66 years for men and 72 years for women (ACS, 2018). Currently, the incidence rate of CRC in men is 30% higher than in women, and the mortality rates are 40% higher in men. CRC incidence and mortality rates are highest in African Americans (AAs) and lowest in Asians/Pacific Islanders (APIs) (ACS, 2017, 2018, 2019). From 2009 to 2013, CRC incidence rates in AAs were about 20% higher than those in non-Hispanic whites (NHWs) and 50% higher than those in APIs (ACS, 2017). Colorectal Cancer deaths in AAs are 40% higher than NHWs and twice those in APIs. Socioeconomic status is one contributing factor to racial/ethnic disparities (ACS, 2018). The U.S. Census Bureau noted that 24% of AAs lived in poverty in 2015 compared to 11% of Asians and 9% of NHWs. Individuals with less than 12 years of education are 40% more likely to be diagnosed with CRC compared to individuals with post-graduate education (ACS, 2018).

However, among all racial and ethnic groups, CRC continues to be a significant burden among AAs (Williams et al., 2016). Studies have determined that AAs are at a higher risk for CRC, have the highest overall incidence, highest incidence of advanced stage at diagnosis, and lowest survival rate compared to all other racial or ethnic groups (Rahman et al., 2015; Williams et al., 2016). Colorectal cancer incidence rates are 27% higher in AA males compared to White males and 22% higher in AA women compared to White women. The mortality rates for AA men is 52% higher than White men, while mortality rates for AA women are 41% higher than White women (ACS, 2018). Between 2005 and 2014, CRC mortality rates declined approximately 2% per year in NHWs, Hispanics, and APIs, 3% in AAs, and stable in APIs/Alaska Natives (ANs). Five-year survival rates have improved among AAs over the last 20 years (45% to 59%), but the rates remain less than NHWs (50% to 67%, respectively) because CRC in AAs is at a more progressive stage at diagnosis (Griffin-Sobel, 2017).

Behavior or modifiable risk factors that affect the development of CRC include overweight and obesity, smoking, physical inactivity, and alcohol use (DeSantis et al., 2016; Griffin-Sobel, 2017). Additional risk factors include age, dietary factors, diabetes, personal history of colorectal polyps or CRC, history of chronic inflammatory bowel disease (IBD), family history of CRC, Lynch Syndrome, and other rare inherited syndromes (Connell et al., 2017; Crosbie et al., 2018; Patel & Ahnen, 2018).

A few studies have compared the difference in early-onset CRC vs. late-onset CRC. Preliminary results have shown that there are demographic, pathologic, and molecular differences between early-onset and late-onset CRC (Yeo et al., 2017).

Compared to late-onset CRC, early-onset CRC is characterized by a more advanced stage at diagnosis, more reduced cell differentiation, and left-sided tumor location (Patel & Ahnen, 2018). The most commonly reported symptoms individuals with early-onset present with include bleeding, abdominal pain, anemia, and change in bowel habits (Patel & Ahen, 2018). Many of the symptoms are often caused by other disorders (i.e., irritable bowel syndrome, bleeding hemorrhoids), which can lead to a delay in diagnosis. According to the Surveillance, Epidemiology, and End Results (SEER) database in the US, approximately 5% of the early-onset CRC diagnoses are in individuals <45 years and diagnosed at stage III or IV (Mauri et al., 2019). Another study reported more than 90% of late-onset CRC are diagnosed after the age of 50 years (Liang, Kalady, & Church, 2015).

Survival rates are increased through early detection and screening. Screening is a process of looking for pre-cancerous cells in individuals who have no symptoms of the disease. Routine CRC screening is one of the most effective ways to prevent CRC (Ahnen et al., 2014). Colorectal cancer screening helps detects precancerous polyps or abnormal growths in the colon or rectum before becoming cancerous, or diagnosis CRC at early stages when treatment is likely more successful and lead to increased survival rates (Gray et al., 2017). Colorectal cancer screening is also a cost-effective approach to reduce the prevalence of CRC in the general population (Carethers, 2015).

> The United States Preventive Services Task Force, American Cancer Society, American College of Gastroenterology and the American Society of Colon and Rectal Surgeons currently recommend CRC screening in asymptomatic and average-risk individuals to begin at age 50. (Williams et al., 2016, p. 2)

However, the American College of Gastroenterology (ACG) suggests African Americans (AA) begin screening for CRC at age 45 (Bromley, May, Federer, Spiegel, & van Oijen, 2015; Rex et al., 2017; Smith et al., 2018). Despite the recommendation that AAs screen at age 45, several studies have determined AAs are less likely to participate in CRC screening. The recommendation for early screening at age 45 is based on average trends in disease burden, demonstrating an increase in CRC incidence and mortality in individuals under age 50 years (Smith et al., 2018). Studies have shown that AAs are less likely to receive their CRC screening for various reasons, such as a lack of knowledge regarding CRC risk factors and the importance of CRC screening (Washington, Masadeh, Chao, & Shokar, 2014). Even within the Veteran Healthcare System, where there is equal access to health care, a study performed in the Greater Los Angeles VA system found that screening rates were lower among AAs than non-AAs (May et al., 2014). However, a more recent national study among Veterans that utilize the VA for their healthcare determined that Blacks were more likely than Whites to undergo CRC screening (May et al., 2019).

Regardless of the substantial amount of evidence that supports the effectiveness of CRC screening and the different screening options available, approximately one in three adults between the ages of 50 to 75 years old is not receiving CRC screening as recommended (Gray et al., 2017). The national CRC screening rates are around 65% nationwide, and 80% among the Veteran population (May, Whitman, Varlyguina, Bromley, & Spiegel, 2016). The participation of CRC screening in the United States remains less than the highest standard primarily among underserved populations, which

include racial and ethnic minority groups, the uninsured, and new immigrants (S. Gupta et al., 2014).

There are several different screening methods available for the early detection of CRC. Visual methods of screening such as colonoscopy, flexible sigmoidoscopy, computed tomographic colonography (CTC), and double-contrast barium enema are performed at a healthcare facility. The other screening options are stool-based tests that the patient can complete at home, such as the Guaiac-based fecal occult blood test (gFOBT), fecal immunochemical test (FIT), and the FIT-DNA (Cologuard). However, of the different screening methodologies, colonoscopy is considered the "gold standard" for CRC screening because it is a test with the capability of viewing the entire colon, detect polyps or tumors, and remove them during the procedure (American Society for Gastrointestinal Endoscopy [ASGE], 2017; Gray et al., 2017). Positive results from any of these screening methods require a colonoscopy for a complete diagnostic assessment (ACS, 2017). "Observational studies suggest that colonoscopy can help reduce CRC incidence by about 40% and mortality by about 50%" (ACS, 2017, p. 17). According to the recent ACS CRC screening guidelines, all the screening methods can help decrease CRC mortality if they are performed at the recommended time intervals and with the suggested follow-up. Although the ACS recommend CRC screening begin at age 45 years for average-risk individuals, the screening guidelines for VA remain at age 50 (ACS, 2018).

The Veteran Health Administration (VHA) is the largest integrated healthcare system that provides cancer care in the United States (Jackson et al., 2013). There are

approximately 50,000 new cancer cases diagnosed and/or treated in the VHA per year, and CRC accounts for 8% (Zullig et al., 2017). When comparing Veterans with CRC and non-Veterans with CRC, it was determined that Veterans are a unique population because Veterans who use the VA healthcare system are predominantly male, significantly older in comparison to the general population of survivors, and have more comorbidities such as diabetes, congestive heart failure (CHF), chronic obstructive pulmonary disease (COPD), lower health literacy, and a lower income than the general population of patients with CRC (Zullig, Williams, & Fortune-Britt, 2015). An analysis of VA CRC diagnoses indicated the 3-year CRC survival rates are approximately 70% in the general population as well as the Veteran population (Zullig et al., 2016).

In the United States, the incidence of early-onset CRC has been increasing by 2% to 3% per year since 2000 (Mauri et al., 2019). Because of the aging population, the increase in Veterans leaving active duty military, and more Veterans seeking VA healthcare, the cancer burden in the VA will increase (Zullig et al., 2015). Also, the VA will have to provide care for more early-onset CRC patients because of the increased increasing rate of younger Veterans receiving healthcare through the VA.

Purpose of the Study

The purpose of this study is to evaluate trends in the incidence and mortality of early-onset vs. late-onset CRC and compare characteristics among Black and White Veterans. Studies have shown that CRC screening is a required method that has decreased the incidence of CRC in individuals over age 50 (Ahnen et al., 2014). However, a better understanding of the underlying causes of CRC in early-onset allows

for opportunities to determine how to allow for early detection in this unique patient population of early-onset to improve health outcomes (Connell et al., 2017). Although the VA population is older, in general, the number of younger Veterans is increasing. Increased understanding of the factors related to and outcome differences among early-onset and late-onset CRC patients supports the Healthy People 2020's goal to reduce the CRC death rate and to increase the percentage of adults who receive CRC screening (HP 2020, 2018).

Significance of the Problem and Study Justification

There remains an increase in CRC incidence among adults who are below the recommended screening age of 50 continues. "From 2009 to 2013, CRC incidence rates decreased by 4.6% per year in individuals 65 years of age and older, by 1.4% per year in individuals 50-64, but increased by 1.6% per year in adults younger than 50" (ACS, 2017, p. 5). While there is limited information on the cause of this increased incidence (Crosbie et al., 2018; Kupfer, Carr, & Carethers, 2015), to decrease the burden of CRC, a focus on cancer prevention and early detection is essential. Although the ACS most recently recommended screening individuals' average risk for CRC at age 45 (ACS, 2018), the VA's screening recommendation for CRC remains at age 50 years.

Studies have determined that early-onset CRC accounts for 11% of all CRC in men and 10% of all CRC among women in the United States (Patel & Ahnen, 2018). "The median age of diagnosis of CRC in the overall group under age 50 is 44 with 75.2% of all early-onset CRC occurring between the age of 40-49" (Patel & Ahnen, 2018, p. 1867). Several studies (Connell et al., 2017; Patel & Ahnen, 2018; Rahman et al., 2015;

Yeo et al., 2017) have observed that CRC in this early-onset group are associated with more advanced stage at diagnosis with distinct clinical, pathologic, and molecular or tumor biology compared to individuals diagnosed over age 50 years.

Colorectal cancer screening is known to be a very cost-effective approach to reduce morbidity and mortality and the prevalence of CRC. Colorectal Cancer screening for individuals average-risk between 50-74 years has been known to decrease the CRC incidence and mortality (Connell et al., 2017). However, the increased incidence of CRC in individuals diagnosed under the age of 50 years has raised questions regarding screening recommendations. According to the literature, 10.9% to 15% of CRC cases are diagnosed in patients too young for average-risk screening; currently, there is not enough evidence to support a full range recommendation to screen individuals less than 50 years old (Connell et al., 2017). Associated cost and risk must be justified for earlier screening in individuals in this age group.

Early-onset CRC is usually diagnosed at advanced stage disease, therefore receiving a timely evaluation of symptoms is essential (Patel & Ahnen, 2018) .However, until there are universal recommendations for screening for early-onset CRC, other strategies must be implemented, such as primary care providers obtaining a more detailed family history from their patients to assess for CRC risk (Ahnen et al., 2014). Previous studies determined a delay in diagnosis was a potential problem for early-onset individuals and contributed to individuals being diagnosed at more advanced stages with less favorable outcomes. Educational strategies to improve increased awareness of early-onset CRC is an approach that can be beneficial to identify early-onset CRC rather than

screening asymptomatic individuals, which may not be cost-effective (Connell et al., 2017).

According to the literature, there is the need to increase awareness among patients and providers to raise awareness about CRC in the young to help promote early-stage diagnoses in younger adults who are symptomatic (Crosbie et al., 2018; Patel & Ahnen, 2018). Connell et al. (2017) define symptoms such as anemia without apparent cause, rectal bleeding, change in bowel habits, and weight loss as "red flag" symptoms that sufferers must report to their healthcare providers. Increasing symptom recognition through education and emphasizing the importance of early evaluation of the symptoms will help decrease the burden of CRC in younger individuals (Patel & Ahnen, 2018).

PRECEDE-PROCEED Model (PPM)

The PRECEDE-PROCEED Model (PPM) developed by Lawrence Green and Marshall Kreuter (Green & Kreuter, 1999) will guide this study (see Figure 1). The PRECEDE-PROCEED Model was developed in 1974 to improve health and change health-related behaviors. The PRECEDE model has been used in several studies for planning, implementing, and evaluating health promotion programs for different populations (Green & Kreuter, 1999). The initial framework was called PRECEDE. The PRECEDE model was tested in the field in the 1980s by practitioners and academics at local, state, federal, and national levels. Through collaboration in national efforts in support of health promotion objectives, disease prevention, and health initiatives in the community, limitations of the framework were noted, which led to the addition of PROCEED in 1991 (Green & Kreuter, 1999).

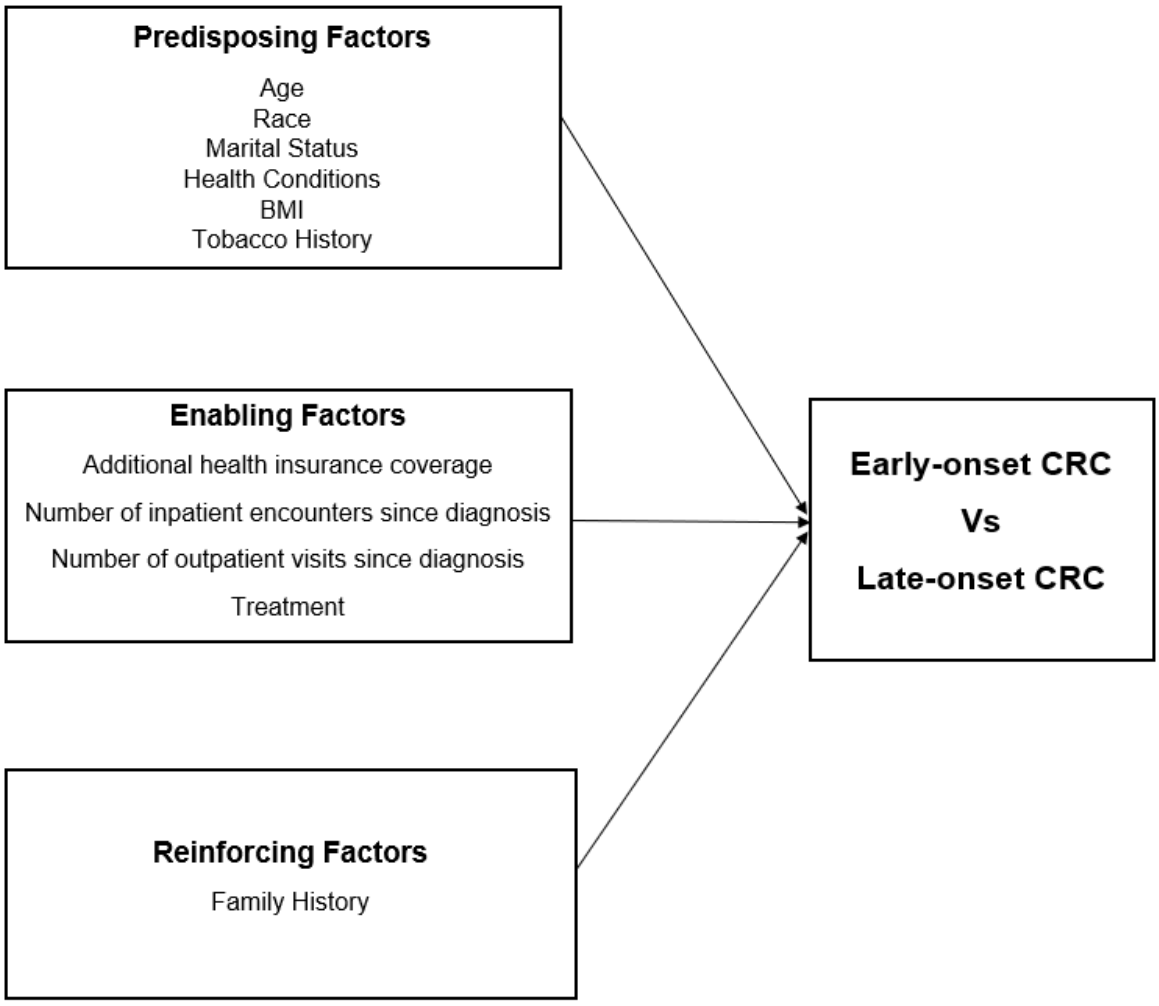


Figure 1. PRECEDE-PROCEED Model. Adapted from Green and Kreuter (1999).

PRECEDE stands for predisposing, reinforcing, and enabling constructs in educational diagnosis and evaluation. PROCEED stands for policy, regulatory, and organizational constructs in educational and environmental development (Green & Kreuter, 1999). The PRECEDE framework focuses directly on outcomes first, rather than the process. It is based on the principle that educational assessment should precede an intervention plan (Green & Kreuter, 1999). One usually looks at how they are going to plan a program or intervention before looking at outcomes. However, the PRECEDE

framework encourages one to ask why before how, by beginning with the desired outcome and determining what causes it.

The PRECEDE model was chosen because it remains one of the most comprehensive frameworks used to promote healthy behaviors and has been used in several cancer screening programs for early diagnosis (Green & Kreuter, 1999). Four constructs from the PRECEDE model will guide this study: Predisposing, Enabling, Reinforcing, and Health Outcomes (Green & Kreuter, 1999). The constructs from this model can help improve health outcomes through increased awareness of CRC. The predisposing factors include an individual's knowledge, attitude, beliefs, values, and perceptions that can hinder or facilitate motivation for change (Green & Kreuter, 1999). Other predisposing factors include sociodemographic factors such as age, race, and marital status (Green & Kreuter, 1999). For this study, the sociodemographic variables age, race, and marital status, time since diagnosis, comorbid health conditions, and specific behaviors are considered predisposing factors.

Enabling factors are antecedents to behavior that usually include environmental issues such as availability of health resources, accessibility of health resources, financial resources, referrals to appropriate providers, and barriers (Green & Kreuter, 1999). Enabling factors are antecedents to behavior that allows a motivation to be recognized, such as cost and other environmental issues like availability of transportation (Green & Kreuter, 1999).

Reinforcing factors provide feedback or incentives from others, which encourages the continuation of health behavior. The type of feedback the individual receives may

encourage or discourage the continuation of the behavior. Examples of reinforcing factors include social support from peers, family influence, and influence from healthcare providers (Green & Kreuter, 1999) and family history. Health Outcome identifies the specific health problem. The classic indicators of health problems are fertility rates, mortality or morbidity rates, and disability (Green & Kreuter, 1999). Health Outcomes of incidence and mortality can be examined for relation to the constructs of predisposing, enabling, and reinforcement factors.

The PRECEDE/PROCEED model has been used as a guide in several studies associated with screening behaviors (Hatcher, Studts, Dignan, Turner, & Schoenberg, 2011; Senore, Inadomi, Segnan, Bellisario, & Hassan, 2015). One study observed cervical cancer screening among Appalachian women using the PRECEDE/PROCEED model to identify and classify the causes of cancer screening, and to establish behavioral interventions which would increase cervical cancer screening (Hatcher et al., 2011). The purpose of the study was to examine the characteristics that predict cervical cancer screening for rarely- or never-screened rural Appalachian women who had not received a Pap test in the past 5 years or more, or ever. A survey was used to assess the predisposing, enabling, and reinforcing factors related to obtaining Pap tests. Thirty-four percent of the participants were rarely- or never- received their Pap test. Factors that increased the odds of these results included the belief that cervical cancer has symptoms and having regular access to medical care (Hatcher et al., 2011).

The study by Senore et al. (2015) examined the predisposing, enabling, and reinforcing factors of the PRECEDE/PROCEED model. The purpose of this study was to

review the available evidence of effective interventions utilized to increase CRC screening acceptance. A literature review of randomized trials designed to increase individual CRC screening was performed. The authors suggest that the PRECEDE/PROCEED model was a beneficial tool to use to assess the ways through which the predisposing, enabling, and reinforcing factors can affect screening behaviors (Senore et al., 2015).

The PRECEDE-PROCEED model has also been used in studies that utilized electronic health records (EHR) and screening. One study used the PRECEDE/ PROCEED model in planning public health screenings (i.e., oncological, mammography, cervical cancer screening, and chronic disease screening). It was determined this model provided an excellent framework for health intervention programs related to cancer screening to help improve the understanding of predisposing factors such as knowledge and the relationship between knowledge and screening (Sinopoli et al., 2018), whereas another study validated the use of EHR data to measure CRC screening rates at community health centers. The EHR was utilized to query screening methods. Results determined that the EHR data can provide a valid measure of CRC screening, but repeated assessments of programming accuracy are required. Among the 12 community centers, CRC screening rates ranged from 9.7% to 67.2% (median=30.6%), and adherence to FOBT ranged from 3.3% to 59%, (median=18.6%). However, most screenings were done by colonoscopy (Baker et al., 2015).

Another study used the PRECEDE/PROCEED model to evaluate the effectiveness of a self-management program to observe self-management behaviors of

individuals with type 2 diabetes (Nejhaddadgar, Darabi, Rohban, Solhi, & Kheire, 2019). An experimental study was conducted on 86 diabetic patients who were referred to a diabetes clinic. These 86 diabetic patients were recruited from a total of 326 diabetes medical records in those clinics. The participants were divided into two groups; control (n=43) and intervention (n=43). The intervention group received eight sessions of education based on the PRECEDE model-based management education, while the control group did not receive any of the education program. The mean time since the first diagnosis of diabetes was 8.6 years (SD=5.2), and the mean body mass index (BMI) was 31.63 (SD=4.20). The ages ranged from 32-86. At baseline, 35% of the patients had poor self-management behaviors (Nejhaddadgar et al., 2019). However, after the education program, all of the PRECEDE variables (predisposing, enabling, and reinforcing) and the self-management behaviors were significantly improved in the intervention group (Nejhaddadgar et al., 2019). The PRECEDE model is appropriate to use in this study because it guides the examination of trends in early-onset CRC and associated health.

Conceptional Definitions

Predisposing Factors

Predisposing factors are antecedents to behavior that motivate that behavior (Hatcher et al., 2011). Bringing awareness to individuals regarding early-onset CRC incidence and recognizing significant symptoms to report to healthcare providers is performed based on predisposing factors. These factors include knowledge, attitudes, and beliefs, as well as specific sociodemographic characteristics. Sociodemographic factors such as age, race, gender, and marital status predispose health-related behaviors (Green &

Kreuter, 1999). For this study, the sociodemographic variables age, race, gender, and marital status will define predisposing factors.

Enabling Factors

Enabling factors are defined as any characteristic of the environment that facilitates action and any skill or resource required to attain a specific behavior (Green & Kreuter, 1999). Enabling factors include the availability, accessibility, and affordability of resources such as healthcare insurance and financial income (Green & Kreuter, 1999).

Reinforcement Factors

Reinforcement factors are defined as any reward following or anticipated as a consequence of a behavior (Green & Kreuter,1999). Reinforcing factors include social support, positive peer influences, and advice or feedback from others, including healthcare providers. Reinforcing factors also consist of the different types of feedback or rewards received by an individual once changing their health behavior (Green & Kreuter, 1999). For this study family history will define the reinforcing factors.

Health Outcomes

Health outcomes are defined as any medically or epidemiologically defined characteristic of a patient or population that results from health promotion or care provided or required, as measured at one point in time. Health outcomes include morbidity or mortality rates. Morbidity rates can be measured by the incidence of CRC cases within a specific time.

Incidence is defined as a measure of the frequency of occurrence of a disease or health problem in a population based on the number of new cases over a given period

(Green & Kreuter, 1999). *Mortality rates* are defined as death rates. A mortality rate describes the frequency of occurrence of death, from any or a specific cause, in a given population during a certain time period.

Research Questions

This study aims to evaluate trends in the incidence and mortality of early-onset (age at diagnosis < 50) vs. late-onset (age at diagnosis ≥ 50) CRC and characteristics among Black and White Veterans. Therefore, this research study will answer the following questions:

1. What are the trends in incidence and mortality outcomes among Veterans with early-onset (age at diagnosis <50) versus late-onset (age at diagnosis ≥ 50) CRC?
2. Do predisposing, enabling, and reinforcing factors differ between early-onset CRC versus late-onset CRC?
3. Are there racial differences in predisposing, enabling, and reinforcing factors and mortality among those with early-onset vs. late-onset CRC?

Summary

Colorectal cancer is the third most commonly diagnosed cancer in the United States and the third leading cause of cancer-related death among men and women. The theoretical framework for the study is the PRECEDE/PROCEED model. This conceptual framework is a health promotion model that has been used to improve and promote behavior change. Four constructs of the PRECEDE/PROCEED model will guide the study: predisposing, enabling, reinforcement, and health outcomes. This study will

evaluate trends in the incidence, outcomes, and demographic differences in early-onset CRC vs. late-onset CRC among Veterans. Additionally, predisposing, enabling, and reinforcing factors related to health outcomes in early and late-onset CRC will be examined, as will racial differences among early-onset vs. late-onset CRC.

CHAPTER II

LITERATURE REVIEW

Over the last 20 years, there has been a decrease in the incidence and mortality of colorectal cancer (CRC) in individuals over the age of 50 in the United States. However, at the same time, there has been a steady increase in the incidence in individuals less than age 50 years (Austin, Henley, King, Richardson, & Eheman, 2014; Ballester, Rashtak, & Boardman, 2016; Bhandari, Woodhouse, & Gupta, 2017; Connell et al., 2017; Crosbie et al., 2018; Kupfer et al., 2015; Patel & Ahnen, 2018; Weinberg & Marshall, 2019; Wolbert et al., 2018; Yeo et al., 2017). The increasing trend in individuals less than age 50 was recognized in the early 2000s, and since then numerous studies have been performed to determine the contributing factors with no definitive explanation (Ballester et al., 2016; F. W. Chen, Sunsaram, Chew, & Ladabaum, 2017; Connell et al., 2017; Liang et al., 2015; Patel & Ahnen, 2018; Weinberg & Marshall, 2019).

The term “early-onset” is used to describe individuals diagnosed under the age of 50 (usually 20-49) and those diagnosed at or above age 50 are referred to as “late-onset CRC” or “traditional CRC” (Patel & Ahnen, 2018; Yeo et al., 2017). As is the case for most cancers, CRC has been known as a condition of the older population (Liang et al., 2015; Weinberg & Marshall, 2019) with the median age at diagnosis of 67 years, while the median age of individuals diagnosed with early-onset CRC is 44 (Patel & Ahnen, 2018). The increased incidence of early-onset CRC is not fully understood, and research

is needed to understand the biology of CRC in this group. Research has determined that early-onset CRC is usually diagnosed at advanced stage disease and have different molecular features when compared to individuals diagnosed at late-onset CRC (Patel & Ahnen, 2018).

This review of the literature will focus on health outcomes related to CRC screening, and trends in incidence and mortality related to early-onset vs. late-onset CRC regarding the general population as well as the Veteran population. These outcomes will be evaluated by examining the following constructs from the PRECEDE model: predisposing, enabling, and reinforcement factors. These factors were chosen for this study because of the belief that each factor influences the likelihood of behavioral and environmental changes.

The Veteran population is unique and has characteristics that make it different from the general U.S. population. The Veteran population is, on average, older than the general U.S. population and predominately male. However, the demographics are shifting, and women have become the fastest group of users in the VA healthcare system (Zullig et al., 2016). Furthermore, individuals that utilize VA healthcare services constitute a greater proportion of individuals of African American race, unemployed, and have a lower annual income, when compared to the U.S. general population. Veterans often have a higher comorbidity burden and are more likely to engage in health behaviors that increase cancer risk (i.e., smoking, a diet low in fruits and vegetables) (Zullig et al., 2017).

The Veterans Health Administration (VHA) is the largest integrated provider of cancer care in the United States and provides some portion of cancer care to approximately 3% of all cancer patients in the United States. There are approximately 50,000 cases per year in the VA and CRC accounts for about 8% of those cases (Zullig et al., 2017). Although the VA provides a high volume of cancer care to cancer patients in the United States, this review does not necessarily reference all Veterans but those Veterans that receive their healthcare in the VHA. All Veterans do not use VA healthcare. The VA makes every effort to provide equal access to all Veterans, yet there are still barriers that prevent some Veterans from receiving the care they need (May et al., 2014). Barriers include transportation issues to get to provider appointments and financial problems where Veterans do not have the income to make copays for CRC screenings such as a colonoscopy, or money to pay for transportation to appointments.

The three leading cancers, prostate, lung/bronchus, colon/rectum, occur within the VA and are the same as those observed among males in the general U.S. population (Zullig et al., 2017). However, as the number of female Veterans receiving VA healthcare continues to increase, there might be an increase in cancers common among females.

Predisposing Factors

Screening

In the ***general population***, the patient's perceptions, knowledge, attitudes, or beliefs were factors observed in the literature that facilitate motivation to receive CRC screening or noted as barriers to CRC screening. The literature also includes demographic characteristics as predisposing factors. This study will define the predisposing construct

as sociodemographic characteristics such as age, race, and marital status. These sociodemographic characteristics are also noted as predisposing factors related to screening in the Veteran population.

Patient's perceptions. Whether one is motivated to change behavior is based on an individual's perception of its importance. The literature discusses perception as a factor that influences an individual's decision to obtain CRC screening (Gwede et al., 2015). A study explored perceptions regarding CRC screening tests from patients at a federally qualified health center, as well as their preference for education received in the clinic (Gwede et al., 2015). Purposive sampling was used to recruit 53 mixed-gender patients, which was divided into eight focus groups. The participants were a racially diverse group (41.5% African American (AA), 35.8% Caucasian, 13.2% Hispanic, and 9.4% other) between the ages 50 and 75 years old who were average-risk individuals and asymptomatic for CRC. The mean age was 56.7, with approximately 51% females. The purpose of the focus groups was to assess the perception of what causes the delay or motivation to CRC screening, awareness of the importance of CRC screening, perceptions regarding the different screening options available, (specific to immunochemical fecal occult blood test (IFOBT) or colonoscopy), and preferences for receiving CRC screening education in the clinic. Findings determined that only 41.5% were current with their CRC screening (Gwede et al., 2015). The two most common delays for screening included the lack of knowledge regarding the perceived need to screen and provider recommendations to screen. However, the two motivating factors for CRC screening were the benefits of early detection and the importance of known risk

types such as family history. The preference for education was a video or DVD and informational pamphlets developed by providers (Gwede et al., 2015).

Another study assessed the relationship between CRC risk perception and screening behavior. According to the literature, to increase CRC screening rates, there is often a focus on increased perceptions of the risk for developing CRC (Atkinson, Salz, Touzam, & Hay, 2015). The results of the study indicated there was a small, positive, statistically significant relationship between risk perception and screening adherence (Atkinson et al., 2015).

Knowledge. Understanding the risks of CRC and knowledge about CRC screening is a significant factor that influences CRC screening. Several studies noted that knowledge had a significant impact on the utilization of CRC screening (Ballester et al., 2016; Brittain, Christy, & Rawl, 2016; C.C. Chen, Yamada, & Smith, 2014; Connell et al., 2017; Gwede et al., 2015). One study observed how the quality and quantity of health information obtained from the internet affect the number of individuals who receive CRC screening (C.C. Chen et al., 2014). The hypothesis was that if the internet information is reliable and trustworthy, individuals are more likely to consider screening. Findings showed that the quantity of cancer information from the Internet was one of the most significant factors that affected the decision to receive CRC screening (p=0.040). Approximately 83% of individuals who obtained cancer-related information from the internet received CRC screening. Patients less satisfied with the cancer information from the internet had a lower probability of receiving their CRC screening (p=0.018). Knowledge about CRC and CRC screening was found significant for predisposing factors

(p<0.0001). Other studies recommend educational endeavors intended for patients and providers to raise awareness about early-onset CRC and improve screening rates to help decrease the burden of early-onset CRC (Ballester et al., 2016; Connell et al., 2017; Patel & Ahnen, 2018).

Attitudes and beliefs. Attitudes or beliefs about CRC screening are considered factors that determine an individual's intent to obtain screening. One study reported how attitudes and beliefs were related to gender differences (Christy, Mosher, Rawl, & Haggstrom, 2017). Females believed that only males were at risk for CRC and did not see the need to obtain CRC screening, whereas males were hesitant about receiving screening such as a colonoscopy because of embarrassment and the procedure being invasive (Christy et al., 2017). For some male patients, the screening preference was the IFOBT (Immunochemical fecal occult blood tests) because it is not invasive, is more convenient and easier to use, and provides enhanced privacy. On the other hand, other male patients considered the IFOBT to be unsanitary.

Another study looked to determine the effect of knowledge and health beliefs related to CRC and how it impacted an individual's screening behavior (Taş, Kocaöz, & Çirpan, 2019). Findings determined individuals believed that the risk of developing CRC could be increased through modifiable behaviors such as smoking and alcohol use, diet, and obesity, as well as a family history of cancer. Some participants in the study were aware of symptoms of CRC such as rectal bleeding, change in bowel habits, and weight loss. However, over 31% did not know the symptoms of CRC, 11.9% did not know the age to start CRC screening, and 23% reported having information on CRC screening tests

(Taş et al., 2019). Study findings determined the reasons for not obtaining a CRC screening was the belief that individuals were not at risk (55%), the lack of knowledge about the screening tests (47.3%), and no provider recommendation for screening (34.5%) (Taş et al., 2019).

In the ***Veteran population***, age, and race are predisposing factors which impact CRC screening in an equal access healthcare system where all Veterans have similar access to services. The increase in screening is evident among Veterans who see their primary care provider at eligible screening age (Christy et al., 2017; May et al., 2014).

Age. The recommended screening age for Veterans who use the VA system is age 50-75. Several studies evaluated the screening rates among Veterans over the age of 50 who utilized the VA System for primary care. One study observed the association of masculinity beliefs and CRC screening among male Veterans (Christy et al., 2017). This study found that masculinity beliefs were unrelated to CRC screening adherence in male Veterans. However, increasing age, being married, higher income, access to health insurance, and education were overall predictors of CRC screening adherence. Another study examined the rates and predictors of CRC screening among African Americans (AA) and non-African Americans in a VA healthcare system. This study determined that 42% of AA were screened compared to 58% of non-African Americans (May et al., 2014). All of the Veterans were the age of screening eligibility ≥45 for AA and ≥50 for non-African Americans (May et al., 2014) Another study that observed the association between Veterans that utilized VA related health coverage versus Veterans that used non-VA healthcare coverage reported older age as a predictor of screening.

Race. Race or ethnicity is also considered a predictor of CRC screening among Veterans. One study examined the rates and predictors of CRC screening, as well as time-to-screening among AAs who utilized the VA system compared to non-AAs. Among a sample of 357 participants, findings reported that screening rates were lower among AAs than non-AAs (42% vs. 58%; OR=0.49, 95% CI=0.31-0.77) (May et al., 2014). In contrast, a cross-sectional study conducted by May et al. (2017) compared CRC screening rates among Veterans based on the type of healthcare coverage. The odds of CRC screening among Veterans with Veteran-status related coverage were higher among AAs than among Whites (OR=1.52, 95% CI=1.22-1.90).

Masculinity beliefs and provider recommendations. Studies performed in a federal facility and a VA healthcare system suggested masculinity would predict CRC screening rates. However, it was determined that although male patients were concerned about their masculinity and sexuality as the reasons they did not prefer a colonoscopy as the screening method of choice, masculinity beliefs did not predict CRC screening outcomes (Christy et al., 2017; Gwede et al., 2015). On the other hand, provider recommendations were considered a predictor of CRC screening and influenced an individual's attitude regarding screening behavior, and the benefits of screening (May et al., 2017). Veterans who had more contact with their healthcare providers had higher screening rates (May et al., 2017).

Incidence and Mortality

In the ***general population***, age, and race were predisposing factors related to CRC screening, which affect incidence and mortality. According to the literature, the incidence

and mortality of individuals over the age of 50 years has declined over the last decade. The decline is attributed to increased screening among adults over the age of 50 years (Ballester et al., 2016; Connell et al., 2017). One study focused on mortality alone and reported that demographic factors, such as age and marital status, were significant predictors of mortality (Tannenbaum, Hernandez, Zheng, Sussman, & Lee, 2014). This population-based study consisted of 47,872 CRC patients diagnosed between 2007 and 2011, in which 65.3% were 65 years and older, 72.9% White, and 52.1% male. Tannenbaum et al. (2014) determined that increased risks of mortality were discovered in individuals older than age 50 and who were unmarried.

Another study examined trends and annual percent change in incidence among individuals over age 50 years diagnosed with CRC from 2000 to 2014 (Ansa, Coughlin, Alema-Mensah, & Smith, 2018). In this study, it was determined overall that the incidence rate of CRC decreased from 54.5 per 100,000 to 38.6 per 100,000 in 2014, with an annual percentage change of -2.66 ($p<0.0001$). Individuals who were 60 years and older had higher incidence rates of CRC. Incidence rates were also higher in males (53.4 compared to 39.9 per 100,000 in females) and AAs (56.1 compared to 45.6 per 100,000 in Whites). The study suggests the increase in screening, preferably colonoscopy screening attributed to the decrease in CRC incidence among this group (Ansa et al., 2018).

Among the ***Veteran population***, few studies discussed the incidence and mortality related to CRC. However, in a 2010 update, CRC was identified as one of the three most frequently diagnosed cancers in the VA Healthcare system (Zullig et al., 2017). Another

study that observed CRC statistics in the VA from 2009 to 2012 reported an overall incidence rate decrease from 0.22-0.16 cases per 1,000 Veterans (Zullig et al., 2016). A study reviewed the evidence of 25 studies on racial/ethnic mortality disparities in the VHA across a variety of clinical settings (Peterson et al., 2018), and reported there was an increased risk of mortality among AA Veterans with CRC.

In comparison to Caucasian Veterans, AA Veterans with CRC had significantly increased rates of 3-year mortality. The findings from the review suggest that VHA's equal access health care system has reduced specific racial/ethnic mortality disparities when compared to the care delivered outside the VA.

Enabling Factors

Screening

Enabling factors in the ***general population*** focus on environmental issues such as accessibility of resources, availability of resources, and financial resources. Enabling factors noted in the literature that affect CRC screening included the availability of resources such as healthcare insurance and financial resources.

Lack of healthcare insurance. Studies determined that the lack of health insurance, lack of provider recommendations to screen for CRC, and the cost of screening were barriers to receiving CRC screening in individuals over the age of 50 (C. C. Chen et al., 2014; Gwede et al., 2015). It was suggested that more participants who had private health insurance received CRC screening compared to individuals who had government-financed Medicare health insurance for retirees (C.C. Chen et al., 2014).

Studies have also determined that AAs are less likely to obtain early CRC screening due to a lack of access to care (Washington et al., 2014).

Financial resources. Study findings determined that income was statistically significant (p=0.082) and positively affected CRC screening among individuals over age 55 (C. C. Chen et al., 2014). Other studies have observed lower screening rates among AAs due to lack of access to healthcare (Schlichting et al., 2014; Washington et al., 2014).

However, among the ***Veteran population***, individuals with Veteran-status-related coverage have higher screening rates due to the preventive health services use among Veterans (May et al., 2017). The Veteran population has a screening rate of 80% compared to the general population of 65% due to access to care (May et al., 2017). A cross-sectional study with a cohort of 22,138 Veterans compared the screening rates of Veterans that used the VA-status-related coverage versus non-VA-status-related coverage. Findings determined the screening rates were highest among Veterans that used the VA-status-related coverage (82.3%) (May et al., 2017). The odds of being up-to-date with CRC screening was higher among Veterans who used Veteran-status-related coverage (82.3%) than among those who used Medicaid (60.1%; $p< 0.01$), Medicare (80.2%; $p< 0.01$), and private insurance (74.5%; $p<0.01$). Additional access to healthcare, race/ethnicity and the increase in medical visits increased the odds of CRC screening (May et al., 2017). Although on a national level approximately 80% of Veterans who receive primary care at a VA healthcare facility are current with their CRC screening, Veterans who live in rural areas experience additional challenges to receiving their CRC

screening such as difficulty with transportation due to distance or travel time to a VA facility to receive a colonoscopy (Schlichting et al., 2014).

Incidence and Mortality

The most significant enabling factor discussed in the literature among the ***general population*** related to incidence and mortality was screening.

Screening. Incidence and mortality rates among individuals diagnosed with late-onset CRC have declined over the years due to access to screening (Austin et al., 2014; Crosbie et al., 2018; Murphy, 2019; Weinberg & Marshall, 2019). Studies suggest that colonoscopic screening has benefited older individuals and helped to improve health outcomes because this screening method detects CRC at an earlier stage and allows for the removal of pre-malignant polyps before becoming cancer (Weinberg & Marshall, 2019).

Among the ***Veteran population*** enabling factors are similar to the general population, such as accessibility of resources or financial resources. As mentioned, although the VA makes every effort to provide equal access to all Veterans enrolled in VA healthcare, all Veterans do not use VA healthcare services due to personal choice or barriers to care. There are also barriers such as financial problems and transportation issues may prevent an individual from getting to an appointment or having money to make the copay for individual screenings such as a colonoscopy (May et al., 2014).

Reinforcing Factors

Screening

Reinforcing factors discussed in the literature related to increased CRC screening in the ***general population*** included influence from providers, family, and peers. Studies observed how support from others influenced decisions such as screening.

Provider influence. Provider influence is a significant factor related to screening adherence. Studies have noted that provider recommendations for screening were predictors of increased screening rates (Gwede et al., 2015; May et al., 2017; Patel & Ahnen, 2018). Another study evaluated the association between patient-provider communication and compliance with CRC screening guidelines (Laiyemo et al., 2019). The study assessed whether individuals were more likely to be compliant with CRC screening guidelines if their healthcare provider discussed screening options with them and made specific recommendations regarding the choice of the screening method. The results of the study reported that individuals who had discussions with their providers regarding screening options and received recommendations for the specific screening modality were more likely to be compliant with screening guidelines (Laiyemo et al., 2019). Other studies reported that interpersonal trust and trust among providers were predictors of CRC screening (C. C. Chen et al., 2014; Washington et al., 2014).

Family and peer influence. Studies have determined that motivation from family or peers has been effective in increasing CRC screening (Gwede et al., 2015; Laiyemo et al., 2019). A study by Gwede et al. (2015) found that patients were motivated to screen if they received encouragement from their family, had close family or friends with CRC,

and received CRC screening recommendations from their providers, including information on the screening tests. The study by Laiyemo et al. (2019) evaluated whether a social contact person could effectively facilitate screening for a colonoscopy. The study consisted of 399 African-American participants (AAs) who were scheduled for a colonoscopy. The participant self-selected a social contact person to be a facilitator. The social contact person was given the participant's phone number to contact them and provide support and encourage compliance with the colonoscopy. Although results of the study indicated that there was no difference in the percentage of participants who received the colonoscopy (77.35 vs. 77.2%), however, having a social contact person involved did have a slight increase in the percentage with an adequate bowel preparation for the procedure (89.1% vs. 80.9%) (Laiyemo et al., 2019).

Among the ***Veteran population***, it was determined that screening rates were higher among Veterans who had more frequent contact with healthcare providers (May et al., 2017). Veterans who had appointments with providers near their screening age were more likely to receive their CRC screening recommendation.

Incidence and Mortality

Provider influence. The literature emphasized the critical role that primary care providers can contribute to decreasing the incidence and mortality of CRC. Studies performed recommend that providers change their approach in assessing and educating their patients about CRC (Ahnen et al., 2014; Connell et al., 2017). The recommendation is for primary care providers to utilize tools readily available to obtain a detailed family history before the age of 50 years, assess each patient's risk for CRC, and recommend

screening for individuals who meet high-risk family history of CRC or personal history standards according to the recommended screening guidelines (Ahnen et al., 2014).

Early-onset CRC Predisposing Factors

Screening

Age. As discussed in the literature, age influences the CRC screening guidelines. The American Cancer Society (ACS) updated the CRC screening guidelines May 2018, which recommend average-risk (those without a high-risk family history) CRC screening begin at age 45 due to the increased incidence of CRC incidence among individuals less than age 50 (N. Gupta, Kupter, & Davis, 2019; Murphy, 2019; Smith et al., 2018). Because of new or conflicting screening guidelines, studies looked at key factors to consider when recommending screening for CRC in younger adults. The studies reported there was limited empirical evidence of the effectiveness of screening younger individuals less than age 50 (Ballester et al., 2016; Murphy, 2019). The new guidelines recommended by the ACS has led to a debate about when to initiate CRC screening in average-risk individuals (Murphy, 2019). Most of the randomized trials of screening efficacy are limited to 50 years of age or higher (Murphy, 2019).

Additionally, screening recommendations from the American College of Gastroenterology (ACG) suggests AAs should begin screening for CRC at age 45 because of the increased incidence, increased prevalence of right-sided lesions, and lower mean age of onset of CRC in AAs (Bromley et al., 2015; N. Gupta et al., 2019; Rex et al., 2017; Smith et al., 2018).

Incidence and Mortality

Age. According to the evidence, there is a decreased incidence of CRC diagnosis in individuals age 50 years or older due to CRC screening, while there is an increased incidence in individuals less than age 50, which has limited screening recommendations (Ahnen et al., 2014; Austin et al., 2014; Ashktorab et al., 2016; Bhandari et al., 2017; Crosbie et al., 2018; Meester, Mannalithara, Lansdorp-Vogelaar, & Ladabaum, 2019; Rahman et al., 2015; Weinberg & Marshall, 2019; Yeo et al., 2017). According to the literature, even with the American Cancer Society's (ACS's) new recommendation to begin CRC screening at age 45 for average-risk individuals, it does not confirm these screening guidelines will address efforts to understand why there is an increased incidence in individuals less than age 45 (Weinberg & Marshall, 2019). A study performed by Murphy (2019) reported that incidence rates among individuals ages 20-49 increased from 8.6 per 100,000 in 1992, to 12.5 per 100,000 in 2015, with the most significant increase being among individuals 40 years of age (18.2-26.5 per 100,000), and a slight increase of (7.2-8.3 per 100,000) for individuals between age 45-49.

Knowledge. Other studies suggest that an increased awareness about CRC risk factors and symptom recognition of early-onset CRC, a better understanding of the molecular characteristics or biology of early-onset CRC, and efficient screening guidelines for individuals less than age 50 will decrease incidence and mortality rates of early-onset CRC (Crosbie et al., 2018; Yeo et al., 2017). One study reported that a lack of awareness regarding early symptoms of CRC or the increased incidence influenced the delay in diagnosis of CRC (Ahnen et al., 2014; Bhandari et al., 2017). The authors

believe that when individuals present with signs/symptoms of CRC, they are already at advanced stage disease.

Race. Several studies have compared the incidence among different races or ethnic groups (Ashktorab et al., 2016; Austin et al., 2014; Crosbie et al., 2018; Rahman et al., 2015). The two significant findings from the study performed by Rahman et al. (2015) include racial/ethnic groups diagnosed of early-onset CRC with advanced disease compared to NHWs. The authors propose that hereditary factors contribute to the increased incidence of CRC diagnosed as early-onset CRC among minority populations. Furthermore, it was reported that more individuals younger than age 50 were AAs (Austin et al., 2014; Crosbie et al., 2018). Austin et al. (2014) evaluated CRC trends from 1998 to 2009 in individuals less than age 50 among four racial/ethnic groups (non-Hispanic Whites (NHWs), AAs, Asians, Hispanic Whites). The study determined that the decrease in CRC incidence rates was highest among NHWs ($p<0.001$). In another study that observed incidence rates among individuals 20-44 years of age from 2000 to 2012, it was determined that AAs had the highest incidence of early-onset CRC (7.9/100,000) compared to NHWs and APIs (6.7 and 6.3/100,000, respectively) (Ashktorab et al., 2016).

Incidence and mortality are also affected by comorbidities related to CRC. The incidence of comorbid health conditions such as cardiovascular disease and diabetes increase with age. Therefore, studies suggest that as our population ages, the number of CRC patients with comorbidities at diagnosis will increase (Cuthbert, Hemmelgarn, Xu, & Cheung, 2018). In the Veteran population, Veterans are older, have a higher

comorbidity burden, and are known to engage in different health behaviors that impact cancer risk (Zullig et al., 2017).

One of the health behaviors that impacts CRC risk is smoking. The incidence of smoking is higher among Veterans than non-Veterans (Zullig et al., 2017). Cigarette smoking has been associated with an increased risk of CRC diagnosis and mortality. A higher proportion of individuals between the ages of 20-49 report current smoking behaviors than individuals 50 and above (18% vs. 12%, respectively; Crosbie et al., 2018).

Obesity is considered another reason for the increase in the incidence of CRC among individuals diagnosed at early-onset (Connell et al., 2017; Crosbie et al., 2018). Weight gain among individuals between early adulthood and mid-life has shown to be associated with a significantly increased risk for CRC. For each 5-unit increase in body mass index (BMI), there is an estimated 13% to 18% associated increase in the risk of CRC, whereas regular physical activity is associated with a 24% to 31% decrease in CRC risk (Connell et al., 2017). Obesity is similar among Veterans and non-Veterans; however, Veterans are more likely to consume a diet low in fruits and vegetables (Zullig et al., 2017).

Inflammatory Bowel Disease

Inflammatory bowel disease (IBD), including ulcerative colitis and Crohn's disease, is another clinical problem associated with an increased risk of CRC (Sebastian et al., 2014; Wang & Fang, 2014). Factors that have been found to increase the risk of CRC incidence among patients with IBD include extensive increase of disease, young

age at diagnosis, family history of CRC, and persistent inflammation of the colon (Wang & Fang, 2014).

Early-onset CRC Enabling Factors

Screening

The literature does not focus on enabling factors related to screening for early-onset CRC because there are currently no established guidelines for this group. In the absence of screening guidelines for patients diagnosed at early-onset CRC, accessibility to healthcare is essential to receiving prompt attention to evaluate CRC symptom recognition (Liang et al., 2015).

Incidence and Mortality

Lack of accessibility of resources. Enabling factors noted in the literature regarding CRC incidence in early-onset groups included the lack of accessibility of resources and access to healthcare. Studies determined that CRC incidence and mortality rates were affected by the lack of access to healthcare, socioeconomic status (SES), and stage of diagnosis (Tannenbaum et al., 2014). The study found that lack of access to healthcare, living in low SES neighborhoods, and late-stage diagnoses have a higher risk of mortality. In this study, a higher risk of mortality in younger individuals was associated with the cancer site and having Medicaid health services (Tannenbaum et al., 2014).

Early-onset CRC Reinforcing Factors

Screening

Provider influence. The literature discussed how primary care providers should take the opportunity to identify high-risk individuals under age 50 to receive CRC

screening (Ahnen et al., 2014). Providers' recommendation for early screening of high-risk individuals has been a strong predictor of CRC screening (May et al., 2017).

Incidence and Mortality

Provider influence. Several studies were performed to evaluate the increased incidence of early-onset CRC. One study addresses how primary care providers play a significant role in decreasing the incidence and mortality of early-onset CRC (Ahnen et al., 2014). Because of the steady increase of early-onset CRC, the authors recommend that primary care providers change their approach to evaluating and educating their younger patients. The authors suggest providers obtain a detailed family history before the age 50 years, to assess the risk for early-onset CRC so that earlier screening can be recommended to those with high-risk personal and family history (Ahnen et al., 2014; Ballester et al., 2016).

Current Knowledge and Gaps in the Literature

The increased incidence of early-onset CRC has received much attention over the last decade. Early-onset CRC accounts for 11% of all CRC patients, and is more prevalent in males, Hispanics, and AAs (Yeo et al., 2017). The research reports early-onset CRC presents with different clinical and molecular characteristics compared to late-onset (Patel & Ahnen, 2018). With the increased incidence of early-onset CRC, there are no established guidelines in the literature that support screening among this group of individuals. Several studies recommend new screening guidelines for early-onset CRC (e.g. ACS recommends screening at age 45), while others do not believe it is cost-effective to screen asymptomatic individuals. Evidence supports early detection through

screening as a method to decrease cancer incidence. However, there are no empirical data to determine if the current screening guidelines should be modified to identify early-onset CRC. One gap in the literature is the lack of evidence of the appropriate screening age and what should be done to support early-onset CRC screening.

The literature discusses race as a significant factor that influences screening, incidence, and mortality among minority groups. According to the literature, CRC is more prevalent in males, AAs, and Hispanics who are diagnosed at an earlier age with more advanced disease. Studies have determined that AAs are at a higher risk for CRC, have the highest overall incidence of early-onset CRC, highest incidence of advanced stage at diagnosis and worst outcomes compared to all other racial or ethnic groups (Rahman et al., 2015; Williams et al., 2016; Yeo et al., 2017). Colorectal cancer is the third leading cause of cancer death among AAs (Brittain et al., 2016). Several studies discussed how disparities affect the incidence of CRC. However, few studies address the issues related to disparities in the AA population or suggestions for the future. This gap in the literature requires attention to help decrease the disparities which exist among AAs.

Another gap in the literature is the lack of studies that reflect the Veteran population and early-onset CRC. Colorectal cancer is the third most commonly diagnosed cancer among Veterans. Colorectal cancer screening recommendations begin at age 50 within the VHA, which means Veterans might be diagnosed at advanced stage disease. Therefore, more studies are needed relating to early-onset CRC among the Veteran population to help prevent an increased incidence of early-onset CRC among the Veteran population. It will also be beneficial to perform studies that evaluate the screening

recommendations for Veterans that utilize VA healthcare services to help identify early-onset CRC.

Summary

This literature review provides evidence regarding the increased incidence of early-onset CRC and the challenges of addressing this issue. While there are continuous efforts to help determine the causes of early-onset CRC, strategies must be implemented to raise awareness. More research is needed to address the appropriate screening guidelines that will support early-onset CRC among the general population and the Veteran population. There is a need to increase awareness of the increased incidence of early-onset CRC and provide education on the early symptoms and risk factors of early-onset CRC. There is a need for further evaluation of the impact of early-onset CRC among minority populations. Four constructs of the PRECEDE model were used to guide the study to determine how to approach behaviors that will affect the health outcomes, incidence, and mortality as related to early-onset CRC. The health outcomes were evaluated by examining the predisposing enabling and reinforcing factors.

Novel educational strategies are likely necessary to help improve awareness of the increased incidence of early-onset CRC among patients, primary care providers (PCPs), and gastroenterologists (Connell et al., 2017). Providing education on symptom recognition may assist with identifying CRC risk factors and key symptoms, and encourage individuals to report to their provider, and subsequently trigger diagnostic investigations (Connell et al., 2017). This study will contribute to the gaps in the literature by comparing clinical and demographic characteristics of Veterans with early-

onset vs. late on-set CRC and assess racial differences in the clinical and demographic characteristics. Distinguishing between early-onset and late-onset will help identify unique factors associated with each, and how they might inform prevention and early detection efforts, to identify individuals high-risk for early-onset CRC that may benefit from early screening.

CHAPTER III

METHODOLOGY

Research Study Design

This study was an analysis of the Veterans Administration (VA) electronic health records (EHR) and other administrative data using a retrospective design. The retrospective design was chosen because it allows for comparison of outcomes for groups of individuals who differ on identified characteristics that occurred in the past (Zedeck, 2014). The retrospective design is an efficient way to acquire access to extensive amounts of data collected from year to year (Vogt, Gardner, & Haeffele, 2012). Large datasets such as those used in this study allow sample sizes that provide good predictability and trends in health conditions over time. This study focused on health outcomes related to trends in the incidence and mortality of early-onset vs. late-onset colorectal cancer (CRC) among Veterans. These outcomes were evaluated by examining the following constructs from the PRECEDE model: enabling and reinforcement, and factors.

Study Population

The VHA is the largest healthcare system in the United States and the largest integrated provider of cancer care in the United States. Approximately 3,500 CRC cases are diagnosed each year in the VA population. This study consisted of a cohort of all Veterans identified in the VA Oncology database as having a diagnosis of CRC based on ICD-0-3 (C180-C189, C260, C190-C219), between January 1, 2012, and December 31,

2017. The study consisted of 6 years of data for the CRC diagnoses and therefore expected to have adequate statistical power for data analyses. The inclusion criteria consisted of the following: age ≥ 18 years, Black or White race, Stage I-IV, and alive at least 30 days after diagnosis. Veterans with incomplete diagnosis dates or not diagnosed outside the specified timeframe, or no vital status information were excluded.

Data Sources

The study used existing data from the VA Corporate Data Warehouse (CDW) and the National Death Index. The CDW database is a national repository that consists of data from several clinical and administrative systems within VHA. The CDW merges multiple data sources, including demographics, patient encounters, vital signs, outpatient pharmacy, and vital status. The CDW Oncology database, inpatient and outpatient encounter files, and vital status data were used for this study. The VA Oncology Database is a national data source for all patients diagnosed and/or treated for cancer in the Veterans Health Administration (VHA) system. There are approximately 50,000 new cancer cases-reported-each year in the VA. The database included information on demographics, cancer diagnosis, stage, treatment course, recurrence, comorbidities, and outcomes. These data were used to identify CRC cases reported to the registry, along with information on demographic characteristics (i.e., age, race/ethnicity), clinical characteristics (i.e., stage, tumor location, family history), and treatment information.

The NDI is a centralized database of the cause of deaths in the United States. This database records information on file in state vital statistic offices. The CDC's National Center for Health Statistics (NCHS) established NDI as a resource to help

epidemiologists and other health and medical investigators determine the cause of death of study participants. NDI data are available to investigators only for statistical purposes in medical and health research. Access to NDI data within the VA is approved through a joint initiative with the Department of Defense, known as the Suicide Data Repository (SDR). The NDI database was used to assess the primary cause of death.

Measures

The leading independent variables in the study included demographic characteristics and health conditions that predispose health behaviors, enabling and reinforcing factors, and health outcomes (see Appendix A). The predisposing factors were defined in this study as demographic characteristics, health conditions, and tobacco history. The enabling factors include healthcare accessibility and treatment. The reinforcement indicator was family influence. Finally, health outcomes include early-onset CRC and mortality.

Predisposing factors measured include variables such as age, race, marital status, health conditions, and tobacco history. Studies determined age and race were predisposing factors noted as predictors of CRC screening among Veterans age 50 years or above, and CRC screening attributes to the decline in incidence and mortality (Christy et al., 2017; May et al., 2014). It was reported in the literature that demographic factors such as age and marital status, are significant predictors of mortality (Tannenbaum et al., 2014). Other predisposing factors include the presence of comorbid conditions occurring within one year before the CRC cancer diagnosis. The Charlson comorbidity index (CCI) was used and included the following health conditions; hypertension, congestive heart

failure, diabetes mellitus, and renal disease (Erichsen et al., 2013). Inflammatory bowel disease, which includes Crohn's disease and ulcerative colitis, is a health condition that was captured separately from the overall comorbidity index. Tobacco history was measured as never smoker, current/former smoker, or unknown status. Patient body mass index (BMI) was categorized as underweight, normal, and overweight or obese by the CDC measure levels.

Enabling factors identified in the literature include Veteran-status-related health insurance coverage. Individuals with Veteran-status-related health insurance coverage had higher screening rates compared to non-VA-status-related health coverage (May et al., 2017). Veterans who utilize VHA healthcare have access to healthcare and access to screening. Enabling factors for this study used several measures as a proxy for Veterans' access to and utilization of healthcare services. Additional health insurance coverage (ie in addition to VA healthcare benefits) was noted by a yes/no response or unknown indication. Also, enabling factors were measured based on the number of inpatient encounters (ie hospitalizations) or the number of outpatient encounters at a VA facility in the 1-year prior to the CRC diagnosis. The types of treatment received include chemotherapy, radiation therapy, surgery, or a combination of either treatment method. Data from the VA Oncology database indicated which type of CRC treatment received, or if the Veteran did not receive any CRC treatment.

Reinforcement factors were measured based on family influence (i.e., family history of cancer). According to the literature, patients were motivated to receive CRC screening if they had a family member with CRC. The family history of CRC is a

reinforcement characteristic, which indicates a significant likelihood of screening (Gwede et al., 2015). Veterans reported yes/no or unknown to family members diagnosed with any type of cancer not specific to CRC.

The dependent variables in this study are the primary health outcomes of early versus late-onset CRC, incidence, and mortality. The data were examined to determine the percentage of patients with early-onset CRC and late-onset CRC over time (2012-2017). Early-onset is defined as CRC diagnosis in persons younger than 50 years, and late-onset CRC defines a CRC diagnosis at age 50 or older. Analyses will determine if there has been an increased annual incidence of CRC. The mortality rates were determined by the vital status and date of death at 5 years after diagnosis, and the cause of death. Mortality rates were assessed from the date of diagnosis.

Reliability and Validity

The data used for this study were obtained from the VA Corporate Data Warehouse, which is widely used for several analyses regarding the population of Veterans using VA health care. The conceptual framework guided the selection of variables for the study. Specific indicators within each construct (predisposing, enabling, reinforcing, and health outcomes) are similar to health indicators and outcomes assessed in national databases such as the National Health and Nutrition Examination Survey (NHANES), and the Behavior Risk Factor Surveillance System (BRFSS) survey. For example, NHANES utilizes questionnaires to assess socioeconomic and health data (Obi et al., 2018), while BRFSS utilizes surveys to identify demographic variations in health-related behaviors such as race/ethnicity and healthcare characteristics such as access to

healthcare (Berkowitz et al., 2018). These variables are similar to those used by the Centers for Disease Control and Prevention (CDC) and the U.S. Department of Health and Human Services to evaluate Healthy People 2020 objectives and to assess trends.

Data Analysis Plan

Descriptive statistics were used to summarize predisposing factors defined as the demographic characteristics. Enabling and reinforcing factors were evaluated and categorized based on literature and feasibility in the current dataset. Health outcomes information was collected on all patients. Descriptive statistics were used to calculate measures of central tendency for all variables, and continuous variables were checked for outliers, normality, and missing data as a first level of data accuracy.

The goal of this statistical analysis was to explore the relationship between the health outcome of early-onset CRC (dependent variable) and the predisposing, reinforcing and enabling factors (independent variables). Missing data values were assessed and examined because the number and patterns of missing data can influence the results of the study (Boo & Froelicher, 2013). This study utilized an existing dataset; therefore, any patterns of missing data were examined to assess potential biases.

The first research question in this study was analyzed using descriptive statistics (frequencies and percentages). The incidence was calculated by dividing the number of CRC diagnoses of each category by the global denominator of VA users for the year they were diagnosed, and reported as a rate per 100,000 persons. Five-year overall mortality will be calculated from the diagnosis date to the date of death or five years post-

diagnosis. Five-year CRC-specific mortality will be calculated from the CRC cancer diagnosis date to death due to CRC diagnosis. Trends will be assessed graphically.

The second research question was analyzed using descriptive statistics to determine how enabling and reinforcing factors differentiate between early-onset CRC vs. late-onset CRC. Measures of central tendency were evaluated for all variables to determine outliers, distributions, and missing data. Means and SD were reported for continuous variables. Frequency and percentages were used to report categorical variables. Differences by categorical data were compared using chi-square tests, and differences in continuous variables were compared using a *t*-test or *F*-test. Nonparametric tests were used as needed based on data distributions. Logistic regression was utilized to compare the relationships between predisposing, enabling, and reinforcing factors the outcomes of early-onset CRC. Logistic regression was used to determine the relationship between one dichotomous dependent variable and several independent variables (Polit, 2010). Results were summarized with frequencies and percentages, Wald chi-square tests, *p*-values, and odds ratios.

The third research question was analyzed using a Chi-square test to compare racial differences. *t*-tests and *F* tests were used to determine differences in continuous variables with nonparametric tests used as required. Cox proportional hazards modeling was used to compare the association between predisposing, enabling, and reinforcing factors and overall survival among early versus late-onset CRC, and to estimate hazard ratios (HR) and their corresponding 95% confidence intervals (CI) for the associations between early-onset vs. late-onset CRC. Cox proportional hazards are useful to

investigate the association between the survival time (or time to any event) of patients and one or more predictor variables (Polit, 2010). Kaplan Meier survival methods were used to evaluate Black-White differences in overall and CRC survival, specifically in the early-onset group. The Kaplan Meier curves will display survival outcomes among both groups (early- vs. late-onset). All analyses were performed using SAS version 9.4 software (SAS Institute Inc., Cary North Carolina). Statistical significance for all analyses was set at $p<.05$. Appendix A displays all variables considered in the study.

Limitations

There are limitations to this study to be considered. The findings are limited to information that is available in the electronic health record. The data sources used only contained information on Veterans who use the VHA. The population of Veterans who use the VHA is different from the general Veteran population overall. On average, Veterans who use the VHA have a higher disease burden compared to the entire Veterans population (Zullig et al., 2016). Therefore, generalizability to the entire Veteran population, which includes more female Veterans who utilize the VA system and non-users may be limited. Also, there was limited control over what data are available to measure the constructs.

Protection of Human Subjects

Potential risks associated with retrospective secondary analysis were minimal since there was no involvement in direct patient contact. Confidentiality was maintained throughout the research process as required by the Institutional Review Board and the VA guidelines. The study was conducted in accordance with Health Insurance Portability

and Accountability Act (HIPAA) guidelines. There was a request for a waiver to be exempt from obtaining informed consent and authorization since the study used de-identified secondary data and a large number of patients represented in the dataset. Protected health information (PHI) was included in the dataset, such as social security numbers (real or scrambled), race, cancer diagnosis, diagnosis date, stage, surgery date. The CDW database resides in the VA informatics and Computing Infrastructure (VINCI). All data were managed and analyzed behind the VA firewall. The data were accessed along with tools for analysis and reporting in a secure, virtual working environment. To protect Veteran data, VINCI maintains compliance with the guidelines set forth by the Veterans Health Administration (VHA) Handbook 1200.12, Use of data and Data repositories in VHA Research, and all other applicable VA and VHA policies and regulations.

All data were securely stored behind the VA firewall and on password-protected computers. The study was approved by the Durham VA Institutional Review Board and the University of North Carolina at Greensboro Institutional Review Board. Dissemination will avoid deductive disclosure of any individual or small group of individuals by any characteristic or outcome.

CHAPTER IV

RESULTS

The results of the data analysis are presented in this chapter according to the research questions, which were guided by the PRECEDE conceptual model. The target population included all Veterans diagnosed at age ≥ 18 years. The median age at early-onset for both White-and Black was 45.58 years, while the median age at late-onset for White and Black was 67.69 years. There were 474 females in the dataset diagnosed with CRC compared to 13,466 males. Blacks and Whites were chosen because of the study interest and the small percentage of other race/ethnic groups identified in the CRC data. The demographic characteristics of the study sample are described, and key findings highlighted, followed by a chapter summary.

Study Sample

The study included a cohort of Veterans receiving care in the Veterans Health Administration and identified in the VA Oncology database with a diagnosis of colorectal cancer (CRC) between January 2012 to December 2017 (*N*=20,812). The study was further restricted to patients with invasive disease (i.e., stage I to stage IV CRC), while those with an unknown stage and stage 0/In Situ, were excluded. There were 15,666 male and female Veterans with stages I-IV CRC and at least 18 years old. A key objective of this work was to compare characteristics and outcomes by race, so the racial composition

was limited to Black and White Veterans (*N*=15,123). Patients who were missing vital status, and patients who died within 30 days after diagnosis were excluded (see Figure 2).

Figure 2. Flowchart of Inclusion and Exclusion Criteria for the Study Cohort.

The primary cancer sites indicated as appendix, colon overlaps, or not otherwise specified were excluded to retain only those with a definitive diagnosis of cancer in the colon and/or rectum ICD-0-3 codes (C180-C189, C260, C190-C219). Once patients were excluded who did not meet the eligibility criteria, the final study sample included 13,940 patients, of which (4.33%, *N*=604) were early-onset CRC and (95.67%, *N*=13,336) were late-onset (Figure 2). The sample was majority male (96.06%), which is characteristic of the U.S. Veteran population. The sample included a higher percentage of females (12.09%) in the early-onset group compared to 3.01% of females in the late-onset group (see Table 3 presented later in this chapter).

Results: Research Question 1

The first research question was to determine the trends in the incidence and mortality outcomes of early-onset (age at diagnosis < 50) versus late-onset (age at diagnosis ≥ 50) CRC. This study assessed trends over six years from 2012 to 2017 and observed that early-onset accounted for approximately 4% and was fairly consistent each year, while late-onset was approximately 96% and remained consistent over the years (Table 1).

Table 1

Trends in the Incidence of Early-onset CRC vs. Late-onset CRC

	Early-Onset *N*=604			Late-Onset *N*=13336		
Diagnosis Year	*N*	Incidence Rate/100,000	Percent of all CRC cases	N	Incidence Rate/100,000	Percent of all CRC cases
2012	105	1.87	(3.94%)	2563	45.69	(96.06%)
2013	101	1.77	(4.03%)	2404	42.04	(95.97%)
2014	105	1.79	(4.16%)	2419	41.32	(95.84%)
2015	104	1.75	(4.43%)	2241	37.63	(95.57%)
2016	110	1.82	(5.33%)	1952	32.37	(94.67%)
2017	79	----------	(4.30%)	1757	---------	(95.70%)

CRC=colorectal cancer. The 2017 incidence rate could not be calculated because 2017 VHA user information was not available for the denominator at the time of the analysis.

Incidence

The percent of early-onset CRC cases were lowest in 2012 (3.94%) and remained fairly consistent with rates between 4.03% to 4.43% between 2013-2015. In 2016, the proportion of early-onset slightly increased to 5.33%, followed by a decrease in 2017 to 4.30%. The percent of late-onset CRC cases remained consistent around 96% (Table 1), with small decreases across the years. The incidence rates from 2012 to 2016 ranged from 1.87 to 1.82 (per 100,000 persons) for early-onset and 45.69 to 32.37 (per 100,000 persons) among late-onset. Among early-onset, there was a decline in the incidence rates from 2012 to 2015; however, in 2016, the incidence rates increased. The late-onset CRC incidence rates declined steadily from 2012 through 2016.

Mortality

The 5-year mortality rates reflect patients who died within 5 years after diagnosis and describe patients who died of any cause (i.e., overall mortality) or due to CRC (i.e., CRC-specific mortality). The 5-year overall mortality rate was 27.65% for early-onset and 40.95% for late-onset. The 5-year CRC-specific mortality rate was 19.70% for early-onset and 21.03% for late-onset (Table 2). Among early-onset patients diagnosed 2012-2017, 5-year overall mortality was highest among those diagnosed in 2012 (36.19%), while the lowest rate of early-onset (17.27%) was observed for patients diagnosed in 2016. Among late-onset patients, the highest mortality rate (46.09%) was in 2013, and the lowest (28.46%) in 2017. Among early-onset patients diagnosed 2012-2017, 5-year CRC-specific mortality was highest among those diagnosed in 2012 (33.33%), while the lowest rate of early-onset (10.00%) was observed for patients diagnosed in 2016. Among late-onset patients, the highest mortality rate (28.09%) was in 2012, and the lowest (5.75) in 2017 (Table 2).

Table 2

Trends in Overall Mortality and CRC-specific Mortality of Early-onset CRC vs. Late-onset CRC

	Early-onset (*N*=604)		Late-onset (*N*=13336)	
Diagnosis Year	*N*	5-year mortality	*N*	5-year mortality
		Overall Mortality		
2012	105	36.19	2563	45.88
2013	101	30.69	2404	46.09

Table 2

Cont.

Diagnosis Year	Early-onset (*N*=604)		Late-onset (*N*=13336)	
	N	5-year mortality	*N*	5-year mortality
		Overall Mortality (cont.)		
2014	105	28.57	2419	44.40
2015	104	29.81	2241	40.52
2016	110	17.27	1952	35.60
2017	79	22.78	1757	28.46
2012-2017	604	27.65	13336	40.95
		CRC-specific Mortality		
2012	105	33.33	2563	28.09
2013	101	23.76	2404	27.04
2014	105	20.95	2419	24.60
2015	104	18.27	2241	20.04
2016	110	10.00	1952	14.81
2017	79	10.13	1757	5.75
2012-2017	604	19.70	1336	21.03

Note. CRC=colorectal cancer

Results: Research Question 2

The purpose of the second research question was to evaluate three constructs of the PRECEDE model (predisposing, enabling, and reinforcing factors) to determine the prevalence of these constructs between early-onset CRC versus late-onset CRC.

Predisposing Factors

The selected predisposing factors included age, race, marital status, tobacco history, body mass index (BMI), health conditions, and diagnosis period (Table 3). The

median age was 45.58 years for early-onset and 67.69 years for late-onset. There was a significantly higher percentage of Whites in the late-onset group compared to early-onset (80.16% and 71.52%, respectively, $p<0.0001$). The marital status between early- and late-onset CRC was statistically significant, with higher percentages of early-onset being unmarried (61.59%). When looking at tobacco history, the proportion of patients with current/former tobacco use was significantly higher among late-onset (68.27%) compared to early-onset (47.35%) ($p<0.0001$). Among early-onset, 43.54% of patients had a BMI ≥ 30, whereas 30.41% of late-onset patients had a BMI ≥ 30. When evaluating specific health conditions, the rate of hypertension was 31.13% in patients with early-onset CRC and 65.02% for late-onset. The percentages of patients with CHF, DM, and renal disease were at least two times greater in early-onset compared to that among late-onset patients. However, the proportion of IBD among early-onset (6.13%) was considerably higher compared to late-onset (2.65%). There were no significant differences in the proportion of patients with early-vs late CRC between the two diagnosis periods ($p=0.0598$).

Reinforcing Factors

Reinforcing factors were measured by assessing family history of cancer. The family history of cancer was statistically significantly different between early or late-onset CRC ($p=0.0002$). A higher percentage of early-onset (50.83%) had a family history of cancer, compared to 42.37% of late-onset (Table 3).

Additional Factors

There were additional clinically relevant factors evaluated in the study, which included tumor location, stage, and Charlson Comorbidity Index (Table 3). When

comparing tumor location, early-onset patients had more distal colon (37.09%) and rectal (36.42%) tumors, compared to late-onset, which had more proximal colon (42.05%) tumors. The early-onset patients presented with more advanced disease, stage III and IV, while late-onset patients presented with higher proportions at stage I (32.36%) and stage II (24.95%). Among the early-onset, 59.60% had no comorbidities, whereas 29.54% of late-onset had no comorbidities.

Table 3

Predisposing and Reinforcing and Additional Factors of Early-onset vs. Late-onset CRC (*N*=13940)

	Early-onset (age< 50) (*N*=604)	Late-onset (age ≥ 50) (*N*=13336)	*P* value
Predisposing Factors			
Age at diagnosis (years), Median	45.58	67.69	N/A
Age category, *n* (%)			N/A
18-29	20 (3.31%)	0 (0.0%)	
30-39	105 (17.38%)	0 (0.0%)	
40-49	479 (79.30%)	0 (0.0%)	
50-59	0 (0.0%)	2148 (16.11%)	
60-69	0 (0.0%)	6022 (45.16%)	
≥ 70	0 (0.0%)	5166 (38.74%)	
Sex, *n* (%)			<0.0001
Female	73 (12.09%)	401 (3.01%)	
Male	531(87.91%)	12935 (96.99%)	
Race, *n* (%)			<0.0001
White	432 (71.52%)	10690 (80.16)	
Black	172 (28.48%)	2646 (19.84)	

Table 3

Cont.

	Early-onset (age< 50) (*N*=604)	Late-onset (age ≥ 50) (*N*=13336)	*P* value
Predisposing Factors			
Marital status, *n* (%)			0.0028
Married	230 (38.08%)	5945 (44.58%)	
Unmarried	372 (61.59)	7294 (54.69%)	
Unknown	2 (0.33%)	97 (0.73%)	
Tobacco history, *n* (%)			<0.0001
Current/Former	286 (47.35%)	9105 (68.27%)	
Never	274 (45.36%)	3424 (25.67%)	
Unknown	44 (7.28%)	807 (6.05%)	
Health conditions, *n* (%)			
Hypertension	182 (30.13%)	8671 (65.02%)	<0.0001
CHF	3 (0.50%)	1019 (7.64%)	<0.0001
DM	27 (4.47%)	1424 (10.68%)	<0.0001
Renal disease	31 (5.13%)	1900 (14.25%)	<0.0001
IBD	37 (6.13%)	354 (2.65%)	<0.0001
Diagnosis time period, *n* (%)			0.0598
2012-2014	311 (51.49%)	7386 (55.38%)	
2015-2017	293 (48.51%)	5950 (44.62%)	
BMI (kg/ m²), *n* (%)			<0.0001
<18.5	24 (3.97%)	821 (6.16%)	
18.5-24.9	141 (23.34%)	4056 (30.41%)	
25.0-29.9	158 (26.16%)	4028 (30.20%)	
≥ 30	263 (43.54%)	4056 (30.41%)	
Reinforcing factors			
Family history of cancer, *n* (%)			0.0002
Yes	307 (50.83)	5650 (42.37)	
No	222 (36.75)	5698 (42.73)	
Unknown	75 (12.42)	1988 (14.91)	

Table 3

Cont.

	Early-onset (age< 50) (*N*=604)	Late-onset (age ≥ 50) (*N*=13336)	*P* value
Additional Clinical Factors			
Tumor location, *n* (%)			<0.0001
Proximal colon	160 (26.49%)	5608 (42.05%)	
Distal colon	224 (37.09%)	4217 (31.62%)	
Rectum	220 (36.42%)	3511 (26.33%)	
Stage, *n* (%)			<0.0001
I	171 (28.31%)	4315 (32.36%)	
II	102 (16.89%)	3327 (24.95%)	
III	182 (30.13%)	3146 (23.59%)	
IV	149 (24.67%)	2548 (19.11%)	
Charlson comorbidity index, *n* (%)			<0.0001
0	360 (59.60%)	3939 (29.54%)	
1-2	192 (31.79%)	4996 (37.46%)	
≥ 3	52 (8.61%)	4401 (33.00%)	

CRC, colorectal cancer; BMI, body mass index; CHF, congestive heart failure; DM, diabetes mellitus, IBD, Inflammatory bowel disease

Enabling Factors

The enabling factors included additional health insurance, number of inpatient encounters, the number of outpatient visits, and treatment (Table 4). When comparing patients who had additional health insurance, 17.88% of early-onset and 33.56% of late-onset reported no, to having additional health insurance. The mean number of inpatient encounters (i.e., hospitalizations) one-year pre-diagnosis was 0.76 (*SD*=2.10) for early-onset and 1.19 (*SD*=2.46) for late-onset. The mean outpatient visits one-year pre-

diagnosis was 99.84 (*SD*=141.14) for early-onset and 148.53 (*SD*=178.12) for late-onset. Regarding treatment, a higher proportion of late-onset received surgery only (36.79%) compared to early-onset (23.84%). However, a greater percentage of early-onset received radiation or chemotherapy compared to late-onset.

Table 4

Enabling Factors Related to Early-onset vs. Late-onset CRC Patients (*N*=13940)

	Early-onset (age< 50) (*N*=604)	Late-onset (age ≥ 50) (*N*=13336)	*P* value
Enabling factors			
Additional health insurance, *n* (%)			<0.0001
Yes	108 (17.88%)	4475 (33.56%)	
No	453 (75.00%)	8395 (62.95%)	
Unknown	43 (7.12%)	466 (3.49%)	
Number of inpatient encounters 1-year pre-diagnosis			N/A
Mean (SD)	0.76 (2.10)	1.19 (2.46)	
Median	0.0	0.0	
Range	0.0 - 31.0	0.0 – 33.0	
Number of outpatient visits 1-year pre-diagnosis			N/A
Mean (SD)	99.84 (141.14)	148.53 (178.12)	
Median	66.0	96.0	
Range	0.0 – 1594.0	0.0 - 3396.0	
Treatment, *n* (%)			<0.0001
Surgery only	144 (23.84%)	4906 (36.79%)	
Surgery +/- CT/RT	216 (35.76%)	2841 (21.30%)	
CT and/or RT	147 (24.34%)	2560 (19.20%)	
No treatment	97 (16.06%)	3029 (22.71%)	

CRC, colorectal cancer; CT, chemotherapy; RT, radiation therapy

Table 5 provides results from the logistic regression model to estimate the odds of having early-onset CRC based on the predisposing, reinforcing, and enabling factors. Here, the odds ratios (95% confidence intervals) are simultaneously adjusted for all factors in the table. In this cohort, Blacks were almost two times more likely than Whites to have early-onset CRC (OR 1.818, CI1.498-2.205) than Whites to have early-onset CRC. Patients that never used tobacco (OR 2.486, CI 2.079-2.973) and unknown tobacco users (OR 2.034, CI 1.387-2.983) were more than twice as likely than current/former tobacco users to have early-onset CRC. Patients that had IBD were three times more likely to have early-onset CRC. Patients that had a BMI of 25.0-29.9 (OR 1.367, CI 1.076-1.737) and a BMI ≥30 (OR 2.719, CI 2.178-3.394) were more than twice as likely to get early-onset CRC than patients with a BMI <18.5. Patients that had a family history of cancer were 1.443 (CI 1.199-1.736) times more likely to have early-onset CRC than patients that had no family history of cancer. Patients that were known to having additional health insurance were 60% less likely than patients with no additional health insurance to have early-onset CRC (OR 0.400, 0.320-0.500).

Table 5

Logistic Regression Analysis of the Relationship between Predisposing, Enabling, and Reinforcing Factors and the Likelihood of Having Early-onset CRC (*N*=13940)

Variable		OR	95% CI
Predisposing Factors			
Race, *n* (%)			
Black		1.818	1.498-2.205
White		reference	
Marital status, *n* (%)			
Married		reference	
Unmarried		1.193	0.999-1.424
Unknown		0.542	0.129-2.275
Tobacco history, n (%)			
Current/Former		reference	
Never		2.486	2.079-2.973
Unknown		2.034	1.387-2.983
Health Conditions, *n* (%)			
Hypertension	(reference=no)	0.249	0.206-0.301
CHF	(reference=no)	0.120	0.038-0.378
DM	(reference=no)	0.529	0.353-0.792
Renal disease	(reference=no)	0.619	0.422-0.909
IBD	(reference=no)	3.121	2.135-4.563
BMI (kg/ m²), *n* (%)			
<18.5		reference	
18.5-24.9		0.887	0.619-1.271
25.0-29.9		1.367	1.076-1.737
≥30		2.719	2.178-3.394

Table 5

Cont.

Variable	OR	95% CI
Enabling factors		
Additional health insurance *n*, (%)		
Yes	0.400	0.320-0.500
No	reference	
Unknown	1.533	1.086-2.165
Number of inpatient encounters 1-year pre-diagnosis, Median	0.993	0.934-1.055
Number of outpatient visits 1-year pre-diagnosis, Median	0.999	0.998-1.000
Reinforcing Factors		
Family history cancer, *n* (%)		
Yes	1.443	1.199-1.736
No	reference	
Unknown	0.931	0.683-1.269

CRC, colorectal cancer; BMI, body mass index; CHF, congestive heart failure; DM, diabetes mellitus, IBD, Inflammatory bowel disease; CT, chemotherapy; RT, radiation therapy; CI, confidence Interval; OR, odds ratio

Results: Research Question 3

Research Question 3 evaluates racial differences between predisposing, enabling, and reinforcing factors and mortality among those with early-onset versus late-onset CRC.

Early-onset CRC

Predisposing factors. When comparing the predisposing factors among early-onset CRC patients, the median age of diagnosis was 45.89 years for Blacks and 45.50 years for Whites (Table 6). A higher percentage of Blacks were unmarried than Whites.

Regarding tobacco history, the proportion of patients with current/former tobacco use was higher among Whites (50.93%) than Blacks (38.37%).

When evaluating specific health conditions among early-onset patients, the rate of hypertension was significantly higher among Blacks than Whites (43.02% and 25.00%, $p<0.0001$), respectively. There were no significant racial differences in the other conditions except renal disease, which was more common among Blacks (8.72%) than Whites (3.70%). The BMI among Blacks in the early-onset group was higher than Whites (Table 6). There were no significant racial differences in the diagnosis periods.

Reinforcing factors. When evaluating a family history of cancer, there were no significant differences, though a higher percentage of Whites had a family history of cancer (Table 6).

Additional clinical factors. Whites had higher proportions of distal and rectal tumors than Blacks, except for the late-onset group, where rectal tumor was slightly higher in Blacks (Table 6). When comparing stage, Whites had more advanced stage disease (III and IV) for early-onset compared to Blacks who had higher percentages for stage I. The proportion of Blacks with no comorbidities were lower than (54.07%) and Whites (61.81%, $p=0.04$).

Enabling factors. When evaluating additional health insurance in early-onset, there was no statistically significant difference, with similar rates between Blacks (16.28%) and Whites (18.52%) having additional health insurance (Table 7). When evaluating treatment, a higher proportion of Blacks (30.81%) received surgery only, compared to 21.06% of Whites. The mean number of inpatient encounters was similar for

both Blacks and Whites among early-onset. The mean number of outpatient visits one-year pre-diagnosis among Blacks and Whites was 106.42 and 97.22, respectively.

Late-onset CRC

Predisposing factors. When comparing predisposing factors among late-onset, the highest percentage of patients was between 60-69 years of age, with the proportion of Blacks and Whites within this age range being 44.14% and 45.41%, respectively (Table 6). There was a significantly higher proportion of Blacks unmarried at the time of diagnosis. A majority of late-onset patients were current/former tobacco users, with 65.04% of Blacks and 69.07% of Whites having that behavior. Regarding specific health conditions, there were significant racial differences observed for hypertension and renal disease, with higher proportions among Blacks (hypertension 70.71% and renal 16.93%) than Whites (63.61% and 13.58%) having these conditions. The BMI difference was statistically significant ($p<0.0001$) for late-onset with higher proportions among Whites with a BMI ≥ 30 (31.24%).

Reinforcing factors. The proportion of patients with a family history of cancer in late-onset were higher among Whites (44.10%) than Blacks (35.37%) (Table 6).

Additional factors. There were no significant differences in tumor location between Blacks and Whites in late-onset. Regarding stage, among both Blacks and Whites, the proportion for Stage I was 34.20 and 31.90, respectively. A slightly higher proportion of Blacks than Whites had no comorbidities.

Enabling factors. When evaluating the number of patients with additional health insurance in late-onset, there was a higher proportion of Whites with additional health

insurance (34.58%). The mean number of inpatient encounters was 1.36 among Blacks (*SD*=2.71) and 1.16 among Whites (*SD*=2.39). The mean outpatient visits among Blacks was 160.75 (*SD*=209.63) and 145.50 among Whites. When evaluating treatment in late-onset, there was a significant difference in the proportion of Blacks and Whites who received surgery (33.41%, 37.62%), respectively ($p<0.0001$). The group of patients that received no treatment was significantly higher among Blacks (26.64%) than Whites (21.74%) (Table 7).

Table 6

Predisposing and Reinforcing Factors of Early-onset vs. Late-onset CRC by Race (*N*=13940)

	Early-Onset			**Late-Onset**		
	Black (*N*=172)	White (*N*=432)	*P*-value	Black (*N*=2646)	White (*N*=10690)	*P*-value
Predisposing Factors						
Age at diagnosis (years), Median	45.89	45.40	N/A	65.16	68.22	N/A
Age category, *n* (%)			N/A			N/A
18-29	4 (2.33%)	16 (3.70%)		0 (0.0%)	0 (0.0%)	
30-39	25 (14.53%)	80 (18.52%)		0 (0.0%)	0 (0.0%)	
40-49	143 (83.14%)	336 (77.78%)		0 (0.0%)	0 (0.0%)	
50-59	0 (0.0%)	0 (0.0%)		726 (27.44%)	1422 (13.30%)	
60-69	0 (0.0%)	0 (0.0%)		1168 (44.14%)	4854 (45.41%)	
≥ 70	0 (0.0%)	0 (0.0%)		752 (28.42%)	4414 (41.29%)	
Sex, *n* (%)			0.1494			0.0019
Female	26 (15.12%)	47 (10.88%)		104 (3.93%)	297 (2.78%)	
Male	146 (84.88%)	38 (89.12%)		2542 (96.07%)	10393 (97.22%)	
Marital status at diagnosis, *n* (%)			0.0101			<0.0001
Unmarried	116 (67.44%)	256 (59.26%)		1696 (64.10%)	5598 (52.37%)	
Married	54 (31.40%)	176 (40.74%)		932 (35.22%)	5013 (46.89%)	
Unknown	2 (1.16%)	0 (0.0%)		18 (0.68%)	79 (0.74%)	

Table 6

Cont.

	Early-Onset			Late-Onset		
	Black (*N*=172)	White (*N*=432)	*P*-value	Black (*N*=2646)	White (*N*=10690)	*P*-value
Predisposing Factors (cont.)						
Tobacco History, *n* (%)			0.0100			0.0003
Current/Former	66(38.37%)	220 (50.93%)		1721 (65.04%)	7384 (69.07%)	
Never	88 (51.16%)	186 (43.06%)		744 (28.12%)	2680 (25.07%)	
Unknown	18 (10.47%)	26 (6.02%)		181 (6.84%)	626 (5.86%)	
Health Conditions, *n* (%)						
Hypertension	74 (43.02%)	108 (25.00%)	<0.0001	1871 (70.71%)	6800 (63.61%)	<0.0001
CHF	2 (1.16%)	1 (0.23%)	0.1417	199 (7.52%)	820 (7.67%)	0.7949
DM	9 (5.23%)	18 (4.17%)	0.5673	301 (11.38%)	1123 (10.51%)	0.1942
Renal disease	15 (8.72%)	16 (3.70%)	0.0117	448 (16.93%)	1452 (13.58%)	<0.0001
IBD	8 (4.65%)	29 (6.71%)	0.3403	62 (2.34%)	292 (2.73%)	0.2659
Diagnosis time period, *n* (%)			0.3267			0.7779
2012-2014	94 (54.65%)	217 (50.23%)		1459 (55.14%)	5927 (55.44%)	
2015-2017	78 (45.35%)	215 (49.77%)		1187 (44.86%)	4763 (44.56%)	

Table 6

Cont.

	Early-Onset			Late-Onset		
	Black (*N*=172)	White (*N*=432)	*P*-value	Black (*N*=2646)	White (*N*=10690)	*P*-value
Predisposing Factors (cont.)						
BMI (kg/ m²), *n* (%)			0.1423			<0.0001
< 18.5	4 (2.33%)	20 (4.63%)		232 (8.77%)	589 (5.51%)	
18.5-24.9	38 (22.09%)	103 (23.84%)		893 (33.75%)	3163(29.59)	
25.0-29.9	41 (23.84%)	117 (27.08%)		691 (26.11%)	3337(31.22%)	
≥ 30	80 (46.51%)	183 (42.36)		716 (27.06%)	3340 (31.24)	
Reinforcing Factors						
Family history of cancer, *n* (%)			0.1437			<0.0001
Yes	77 (44.77%)	230 (53.24%)		936 (35.37%)	4714 (44.10%)	
No	73 (42.44%)	149 (34.49%)		1248 (47.17%)	4450 (41.63%)	
Unknown	22 (12.79%)	53 (12.27%)		462 (17.46%)	1526 (14.28%)	
Additional Clinical Factors						
Tumor location, *n* (%)			0.2149			0.2876
Proximal colon	54 (31.40%)	106 (24.54%)		1122 (42.40%)	4486 (41.96%)	
Distal colon	58 (33.72%)	166 (38.43%)		805 (30.42%)	3412 (31.92%)	
Rectum	60 (34.88%)	160 (72.73%)		719 (27.17%)	2792 (26.12%)	

Table 6

Cont.

	Early-Onset			Late-Onset		
	Black (*N*=172)	White (*N*=432)	*P*-value	Black (*N*=2646)	White (*N*=10690)	*P*-value
Additional Clinical Factors (cont.)						
Stage, *n* (%)			0.0309			0.0049
I	62 (36.05%)	109 (25.23%)		905 (34.20%)	3410 (31.90%)	
II	29 (16.86%)	73 (16.90%)		600 (22.68%)	2727 (25.51%)	
III	49 (28.49%)	133 (30.79%)		607 (22.94%)	2539 (23.75%)	
IV	32 (18.60%)	117 (27.08%)		534 (20.18%)	2014 (18.84%)	
Charlson comorbidity index, *n* (%)			0.0438			0.0031
0	93 (54.07%)	267 (61.81%)		849 (32.09%)	3090 (28.91%)	
1-2	57 (33.14%)	135 (31.25%)		934 (35.30%)	4062 (38.00%)	
≥3	22 (12.79%)	30 (6.94%)		863 (32.62%)	3538 (33.10%)	

Note. CRC=colorectal cancer; BMI=body mass index; CHF=congestive heart failure; DM=diabetes, IBD=Inflammatory bowel disease

Table 7

Enabling Factors Related to Early-onset vs. Late-onset CRC by Race (*N*=13940)

	Early-Onset			**Late-Onset**		
	Black (*N*=172)	White (*N*=432)	*P*-value	Black (*N*=2646)	White (*N*=10690)	*P*-value
Enabling Factors						
Additional health insurance *n* (%)			0.7971			<0.0001
Yes	28 (16.28%)	80 (18.52%)		778 (29.40%)	3697 (34.58%)	
No	131 (76.16%)	322 (74.54%)		1765 (66.70%)	6630 (62.02%)	
Unknown	13 (7.56%)	30 (6.94%)		103 (3.89%)	363 (3.40%)	
Number of inpatient encounters 1-year pre-diagnosis			0.9998			0.0005
M (*SD*)	0.76 (1.85)	0.76 (2.19)		1.36 (2.71)	1.16 (2.39)	
Median	0.0	0.0		0.0	0.0	
Range	0.0 – 18.0	0.0 – 31.0		0.0 – 27.0	0.0 – 33.0	
Number of outpatient visits 1-year pre-diagnosis, Median			0.5084			0.0005
M (*SD*)	106.42 (161.87)	97.22 (132.10)		160.75 (209.63)	145.50 (169.29)	
Median	69.0	63.0		100.0	93.0	
Range	0.0 – 1594.0	0.0 – 1435.0		0.0 – 3396.0	0.0 – 2427.0	

Table 7

Cont.

	Early-Onset			Late-Onset		
	Black (*N*=172)	White (*N*=432)	*P*-value	Black (*N*=2646)	White (*N*=10690)	*P*-value
Enabling Factors (cont.)						
Treatment, *n* (%)			<0.0001			<0.0001
Surgery only	53 (30.81%)	91 (21.06%)		884 (33.41%)	4022 (37.62%)	
Surgery +/- CT/RT	45 (26.16%)	171 (39.58%)		513 (19.39%)	2328 (21.78%)	
CT and/or RT	33 (19.19%)	114 (26.39%)		544 (20.56%)	2016 (18.86%)	
No treatment	41 (23.84%)	56 (12.96%)		705 (26.64%)	2324 (21.74%)	

Note. CRC=colorectal cancer; CT=chemotherapy; RT=radiation therapy

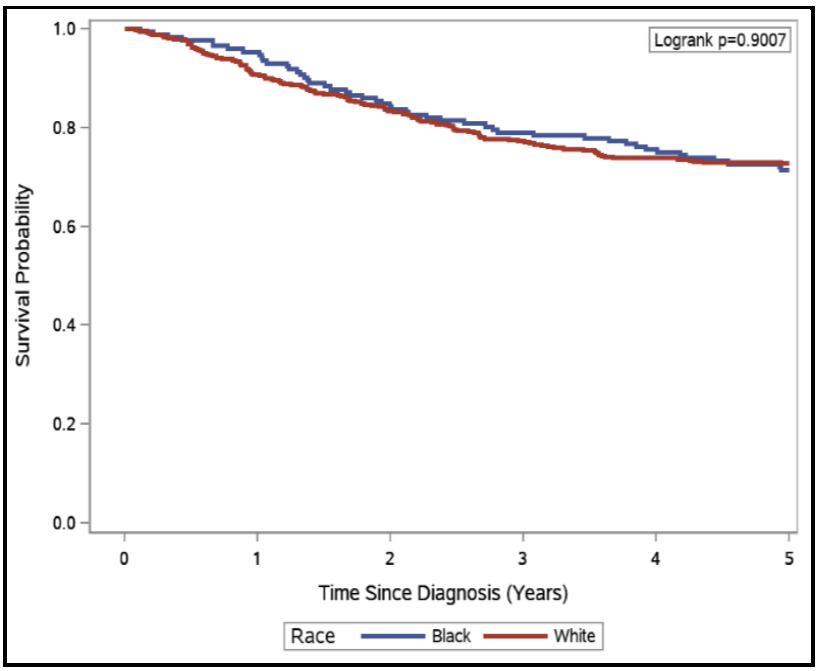
CRC Survival

We attempted to use the Cox model to estimate the hazards ratio comparing Blacks and Whites; however, the proportional hazards assumption was not met for the variables of interest. Therefore, the assessment of survival time was solely based on Kaplan Meier curves.

Early-onset. When evaluating overall survival (i.e., no death from any cause) among early-onset patients, Blacks appeared to have slightly longer overall survival times than Whites (Figure 3); however, this did not reach statistical significance. When comparing CRC-specific survival (i.e., no death due to CRC) for early-onset, survival time was also not significantly different between Blacks and Whites (p=0.7474).

Late-onset. Among *late-onset* CRC patients, there were no significant racial differences in overall survival (Figure 4), and there were no significant differences in CRC-specific survival (both p-values >0.05). Together these findings indicate that Blacks and Whites have similar survival outcomes among both early-onset and late-onset CRC patients.

Overall Survival



CRC-Specific Survival

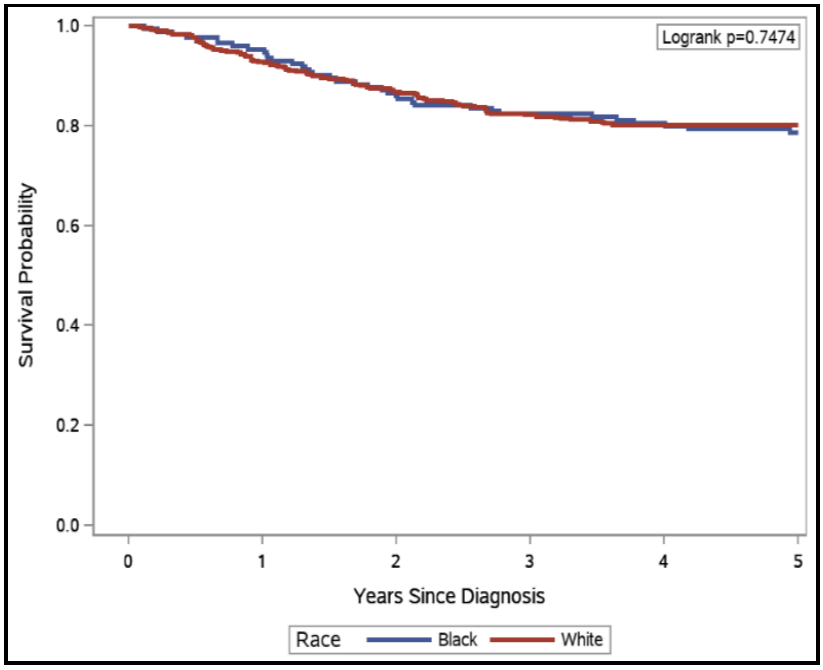
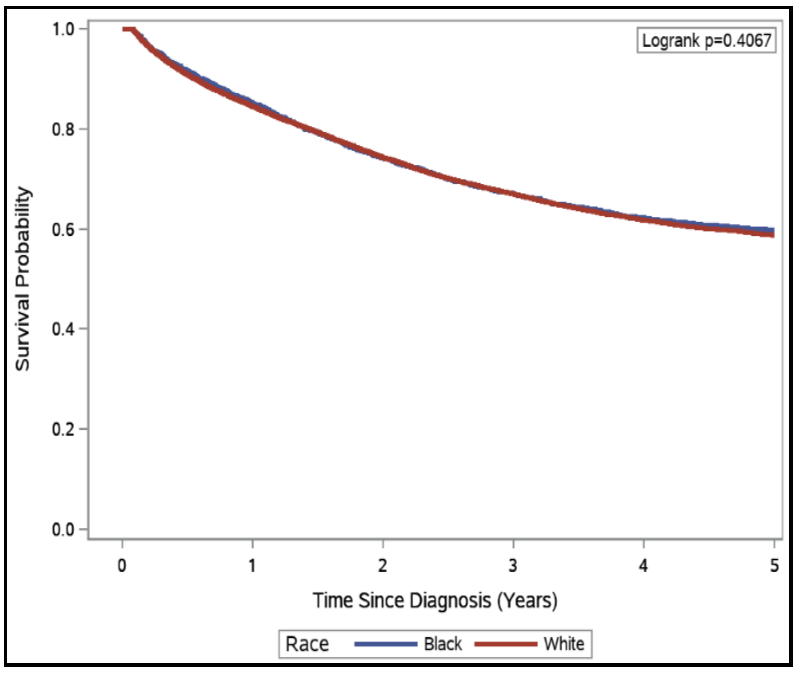


Figure 3. Kaplan-Meier Survival Curves to Show Survival by Race among Early-onset CRC.

Overall Survival



CRC-Specific Survival

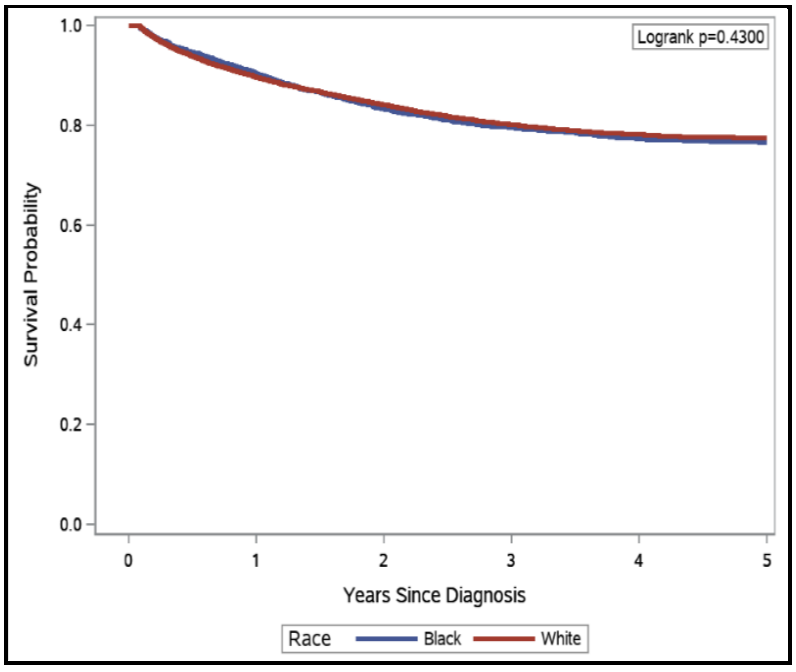


Figure 4. Kaplan-Meier Survival Curves to Show Survival by Race among the Late-onset CRC.

Chapter Summary

The study included 13,940 Veterans diagnosed with CRC between 2012 and 2017. The sample was predominantly White and majority male. There was a greater proportion of females in the early-onset CRC group than late-onset. The median age was 45.58 years for early-onset and 67.69 years for late-onset. This study assessed trends over six years from 2012-2017 and observed that early-onset accounted for approximately 4%, and late-onset was approximately 96% of all CRC patients. This distribution remained stable over time. There was a decline in incidence from 2012 to 2015 among early-onset, but an increase in 2016. There was a steady decline in incidence among late-onset CRC between 2012-2017. The 5-year overall mortality rate was higher among late-onset, as expected, while the overall mortality and the CRC-specific mortality rate was similar for early and late-onset.

When comparing constructs of the PRECEDE model (predisposing, enabling, and reinforcing factors) between early-onset and late-onset CRC patients, there were statistically significant differences between the predisposing factors (race, marital status, tobacco history, health conditions, and BMI). There were more persons in the late-onset group that had additional insurance compared to the early-onset group. A higher number of persons with late-onset CRC received surgery only than early-onset CRC patients, while the early-onset group had a higher percentage that had chemotherapy and/or radiation. A significantly greater proportion of early-onset patients had a family history of cancer ($p<0.0001$). The evaluation of additional clinically relevant factors (tumor location, stage, and Charlson Comorbidity Index) showed early-onset had more distal

colon and rectal tumors compared to late-onset, and early-onset patients had more advanced disease (ie stage III and IV). A higher proportion of the early-onset had fewer comorbidities.

Among early-onset when comparing racial differences between predisposing, reinforcing, and enabling factors, in the early-onset group, there were statistically significant differences in marital status, tobacco history, hypertension, and treatment among Blacks and Whites. A higher percentage of Blacks received surgery only compared to Whites. A higher percentage of Whites received chemotherapy and/or radiation. When comparing additional clinical factors between Blacks and Whites, Blacks had a higher percentage of comorbidities. Whites had more distal colon and rectal tumors, and advanced-stage disease among the early-onset group. There were no racial differences in overall or CRC-specific survival times within the early-onset CRC groups.

Among late-onset when comparing racial differences between predisposing, reinforcing, and enabling factors, in the late-onset group, there were statistically significant differences in marital status, tobacco history, hypertension and renal disease, BMI, and family history among Blacks and Whites. A higher percentage of Whites received surgery only, and the treatment groups that included chemotherapy and/or radiation was higher among Whites. When comparing additional clinical factors between Blacks and Whites, a higher percentage of Whites had one or more comorbidities compared to Blacks. Blacks had more proximal colon compared to Whites, and stage I CRC. There were no racial differences in overall or CRC-specific survival times within the early-onset CRC groups.

CHAPTER V

DISCUSSION

Introduction

The purpose of this study was to evaluate trends in the incidence and mortality of early-onset (age at diagnosis < 50) versus late-onset (age at diagnosis > 50) CRC among Veterans to determine the prevalence of constructs from the PRECEDE model (predisposing, enabling, and reinforcing factors) and evaluate racial differences between the constructs and mortality. An explanation of the study findings and conclusions are presented. Implications for practice, education, health policy, limitations, and recommendations for further research are discussed.

The sample characteristics in this study were similar to the characteristics reported in the literature. Most of the early-onset were between the ages of 40-49 years, and late-onset was 60-69 years. Earlier studies have reported that 75% of CRC patients diagnosed before the age of 50 occurs between the age of 40-49 years and late-onset between 60-69 years of age (Patel & Ahnen, 2018). The median age for this current study was 45.58 for early-onset and 67.69 for late-onset, which is similar to the literature, which reported 44 to 45 as the median age of early-onset and 67 for late-onset (Patel & Ahnen, 2018).

Over the last 20 years, there has been a decrease in incidence and mortality of CRC in individuals over the age of 50 in the United States (Connell et al., 2017; Crosbie et al., 2018). From 2009 to 2013, CRC incidence rates decreased by 4.6% per year in

individuals 65 years of age and older, by 1.4% per year in individuals 50-64, but increased by 1.6% per year in adults younger than 50 (American Cancer Society [ACS], 2017, p.5). According to the literature, although CRC incidence is decreasing due to increased screening and advanced treatment methods, the incidence among the subset of individuals diagnosed with early-onset CRC (age at diagnosis < 50) is increasing (Connell et al., 2017). In the United States, the incidence of early-onset CRC has been increasing by 2% to 3% per year since 2000 (Mauri et al., 2019). Studies have determined that early-onset CRC accounts for 11% of all CRC in men and 10% of all CRC among women in the United States (Patel & Ahnen, 2018).

There are approximately 50,000 new cancer cases treated in the VHA per year in which CRC accounts for 8% (Zullig et al., 2017). The trends in the incidence of early-onset CRC in the VA may have increased since 2017 because of the increase in younger Veterans receiving healthcare through the VA. In comparing Veterans with CRC and non-Veterans with CRC, Veterans are a unique population because Veterans who receive healthcare through the VA are predominantly male and significantly older in comparison to the general population. It will be important to continue to monitor patterns in early-onset CRC diagnosis and care among Veterans.

The first research question compared trends in the incidence and mortality of early-onset CRC versus late-onset CRC. The lower percentage of early-onset CRC cases in this study is likely because Veterans receiving care in the VA healthcare system (VHA) are older in general, so the VA might not experience as many early-onset cases as the general U.S. population. Considering all Veterans do not use the VHA for their

healthcare means all Veterans are not included. However, as increasing numbers of younger Veterans from more recent deployment eras, e.g. Operations Enduring Freedom/Operation Iraqi Freedom (OEF/OIF) use the VA for their healthcare, there may be an increase in early-onset CRC. Findings from this study determined that incidence rates over the 6-year study period declined each year among the late-onset group, which is similar to previous studies (Williams et al., 2016). Another study observed CRC statistics in the VA from 2009 to 2012 and reported an overall incidence rate decrease from 0.22-0.16 cases per 1,000 Veterans (Zullig et al., 2016). The decreased trend could be related to the robust CRC screening and quality improvement programs conducted in the VA. The VA has a nationwide CRC screening reminder integrated into the electronic health record, which alerts providers when the patient is due for their CRC screening. These quality improvement programs may have contributed to the early-stage detection and diagnosis, and the decrease in CRC incidence over time.

The mortality rates decreased over time in early-onset CRC patients, which contrasts with the literature that reports mortality rates in younger individuals have increased (Connell, Mota, Braghiroli, & Hoff, 2017). During the mid-1980s, there was evidence of a steady decline in CRC mortality rates overall, due to increased screening and improved treatment modalities. However, over the last decade, the evidence shows a steady increase in mortality in individuals under age 50 years (Weinberg & Marshall, 2019). The VA's screening rates may contribute to the decrease in CRC mortality in individuals over age 50, but there are limited screening recommendations for individuals under age 50 years (Connell et al., 2017). When comparing the trends in the 5-year

mortality rates, there were higher rates in the overall mortality and CRC-specific mortality rates among late-onset. This was expected given that these 2 groups are defined by age (ie a younger vs older groups of patients). Furthermore, there were studies performed in the general population that determined there were decreased trends in mortality in late-onset, which was attributed to the increased CRC screening in adults over age 50 (Ballester et al., 2016; Connell et al., 2017).

The second research question evaluated three constructs from the PRECEDE model (predisposing, enabling, and reinforcing factors) to determine if there were differences in early versus late-onset CRC. The *predisposing factors,* race, marital status, tobacco history, BMI, and health conditions were significantly related to having early-onset CRC.

In this current study, a higher percentage of late-onset persons were married. Previous studies have reported age and marital status as significant predictors of mortality (Tannenbaum et al., 2014). Tannenbaum et al. (2014) determined that increased risks of mortality were discovered in individuals older than age 50 years and unmarried. Also, there were significantly higher proportions of late-onset patients that were current/former tobacco users, which is similar to the literature. One study reported that the incidence of smoking is higher among Veterans compared to the general population (Zullig et al., 2017). Another study determined that current smokers had a higher proportion among individuals between the ages 20-49 (Crosbie et al., 2018).

When comparing the health conditions, there was a significantly higher percentage of patients that had hypertension in late-onset, which is similar to results

observed in another study that sought to determine the risk of cardiovascular (CVD) morbidity in older adults with stage I to III CRC. The study concluded that older patients with CRC are at increased risk of developing CVD and CHF, while diabetes and hypertension interact with chemotherapy to increase CVD morbidity (Kenzik et al., 2018). Inflammatory bowel disease (IBD) was significantly higher in early-onset than late-onset in our study. This finding correlates with the literature which determined IBD is usually diagnosed in individuals before age 35 and has symptoms similar to CRC, such as rectal bleeding, fatigue, and weight loss (CDC, 2018). A higher proportion of the early-onset persons were obese, with a BMI of ≥ 30 compared to late-onset. A previous study suggests that risk factors such as obesity, inactivity, dietary factors, diabetes, and family history could potentially influence the prevalence of CRC in young adults (Connell et al., 2017; Patel & Ahen, 2018). However, a more recent study that evaluated risk factors of CRC among Veterans receiving colonoscopy determined BMI and weight were associated with reduced odds of having early-onset CRC (Low et al., 2020).

There are a few studies that address early-onset CRC among Veterans. The most recent study was the study by Low et al. (2020). The purpose of this study was to observe risk factors associated with early-onset CRC which has not been studied widely. The study's finding determined that increased age and male sex was associated with increased risk of early-onset CRC. While the Low et al. (2020) study included patients receiving a colonoscoopy in which some had CRC while others did not, this current study was solely among those with an invasive CRC diagnosis.

The *reinforcing factor*, family history, had higher percentages among the early-onset group, which is similar to other studies that evaluated CRC and family history. Studies suggest CRC risk factors, hereditary factors, and family history could potentially influence the prevalence of CRC in young adults (Ahnen et al., 2016; Patel & Ahnen, 2018). Another retrospective study that evaluated factors related to early-onset CRC observed family history as a predictor of early-onset CRC (Gausman et al., 2019).

Additional clinical factors that were significant to outcomes included tumor location, stage, and the Charlson Comorbidity Index. Early-onset patients had a higher proportion of distal and rectal tumors and presented with more advanced stage disease, III or IV, which is similar to other studies. Similar studies have observed that early-onset CRC was associated with advanced-stage disease (stage III and IV) and rectal or left colon tumors compared to late-onset (Burnett-Hartman et al., 2019 & Connell et al., 2017).

According to the literature, more early-onset patients are characterized by more advanced stage disease at diagnosis, and likely to present with stage III or IV, compared to late-onset patients (Ahnen et al., 2014; Mauri et al., 2019). The late-onset group had more comorbidities than early-onset, which is expected among the Veteran population. Similar results from a previous study reported the Veteran population being older, in general, has higher comorbidity burdens (Zullig et al., 2017). The literature suggests that comorbid health conditions will increase as our population ages and that the number of CRC patients with comorbidities at diagnosis will increase (Cuthbert et al., 2018).

When evaluating the *enabling factors*, additional health insurance, and treatment were significant among early versus late-onset. A higher percentage of early-onset reported having no additional health insurance. Veterans that utilize the VHA for healthcare have access to health insurance. Having additional health insurance is not required and could contribute to why a significant number of Veterans do not have additional health insurance. Because most of the late-onset groups are Medicare-eligible, it was expected there would be a higher percentage of late-onset with additional health insurance.

Regarding treatment, a higher proportion of the late-onset had surgery only, which is similar to other studies. One study observed treatment patterns for CRC based on the age of onset and reported that older patients were less likely to receive chemotherapy or radiation therapy than younger patients (Burnett-Hartman et al., 2019). Prior studies had similar results in which younger patients were treated more aggressively with surgery, chemotherapy, and radiation, compared to the late-onset who received surgery only (Connell et al., 2017; Patel & Ahnen, 2018; Weinberg & Marshall, 2019). The higher proportion of early-onset patients who had surgery and chemotherapy or radiation may reflect that they are younger in general and can tolerate both surgery and chemotherapy or radiation, while comorbidities among older patients may preclude them from more aggressive therapies.

The third research question examined the racial differences between predisposing, enabling, reinforcing factors, and mortality among early-onset versus late-onset CRC. When comparing the *predisposing factors,* racial differences were relevant to the health

condition of hypertension, marital status, and tobacco history. Hypertension was significantly higher among Blacks than Whites, which is a finding similar to the literature. One community-based study performed a randomized control trial that compared the effect of a motivational interviewing tailored lifestyle intervention versus a culturally targeted intervention on improvement of blood pressure and CRC screening among Black men aged 50 or greater. The Black men were recruited from a barbershop in New York. The men had uncontrolled hypertension and were eligible for CRC screening. It was determined that Black men had the most significant burden of premature death from hypertension and the highest incidence and mortality from CRC (Ravenell et al., 2013). When evaluating selected *additional clinical factors*, Whites had a higher proportion of distal and rectal tumors and more advanced stage disease than Blacks. Another study found similar results where the increase in rectal cancer was larger in Whites (from 2.7 to 4.5 per 100,000) than in Blacks (from 3.4 to 4.0 per 100,000) during 2010-2014 (Murphy et al., 2019).. These findings are in contrast to other studies that report Blacks are diagnosed with CRC at more advanced stage disease than Whites (Crosbie et al., 2018; Patel & Ahnen, 2018; Yang et al., 2018). Potential factors contributing to this interesting finding include delayed diagnosis, risk factors such as tobacco use, or the study only included Veterans that use VHA for their healthcare. For example, the literature suggests individuals diagnosed at young-onset are more likely to be associated with delayed diagnosis and advanced-stage disease (Bhandari et al., 2017). According to the literature, many White Veterans only utilize the VA for their healthcare later in their illness after they have exhausted their health care options in the private

sector (Peterson et al., 2018). Smoking or tobacco use has also been reported as a known predictor of early-onset CRC. In this current study, Whites had a higher percentage of current/former tobacco users compared to Blacks. Another study that evaluated risk factors of advanced-stage CRC reported individuals that were less than age 50 were current/former smokers and were a significant predictor of presenting with advanced-stage disease (Moore et al., 2018). The findings pertain to characteristics available in the data, but there might be others related to this finding that we were not able to capture.

The *predisposing factors*, marital status, tobacco history, hypertension, and BMI were similar for Blacks and Whites in the late-onset CRC group. There was a higher proportion of Blacks unmarried at the time of diagnosis than Whites. Studies have reported marital status as a predictor of mortality (Tannenbaum et al., 2014). Another study that evaluated mortality observed that more Blacks who were unmarried had higher mortality rates (Wu et al., 2019). Regarding health conditions and late-onset, a higher proportion of Blacks had renal disease and hypertension compared to Whites, which is comparable to previous studies (Ravenell et al., 2013). The reinforcing factor of family history was higher among Whites, while other studies report that more Blacks had a family history of CRC in early-onset (Gausman et al., 2019).

When evaluating the *enabling factors*, there were statistically significant racial differences observed for treatment among early-onset and late-onset CRC. Among early-onset, more Blacks received surgery only, compared to Whites. Whereas in late-onset, more Whites received surgery only. Another study observed differences in CRC treatment patterns in early-onset and late-onset and reported clinically similar surgery rates between

AA and NHW (Alese et al., 2019). According to the literature, there is evidence that treatment options and access are unequal when comparing AA to NHWs (American Cancer Society [ACS], 2017). Although the VA makes every effort to provide equal access to all Veterans, all Veterans do not use VA healthcare services (May et al., 2014).

Overall survival among early-onset CRC was slightly longer in Blacks. Contrary to the findings in the current study, a previous study has reported increased cancer-related death with a 5-year survival being lower among AA (54.9%) than NHWs (68.1%) (Patel & Ahnen, 2018). A similar study was performed that compared mortality rates between AA and Caucasian Veterans in different settings and found that there was an increased risk for mortality among AA Veterans with CRC (Peterson et al., 2018).

Conclusions

This study assessed trends in early-onset versus late-onset CRC from 2012 to 2017 and determined that approximately 4% was early-onset compared to 96% late-onset. There was not an increased proportion or of early-onset CRC over time, as other studies report. When comparing the constructs of the PRECEDE model (predisposing, enabling, and reinforcing) factors, there were significant differences between race, marital status, tobacco history, health conditions, and BMI. There was a higher percentage of family history of cancer among the early-onset group. Among the relevant clinical factors, tumor location, stage, and Charlson comorbidity index were more common among the early-onset group. The enabling factors, additional health insurance was higher among late-onset while more early-onset received surgery, chemotherapy, and/or radiation. However,

more late-onset had additional health insurance. More of the early-onset had surgery, chemotherapy, and radiation, while more of the late-onset group had surgery only.

When comparing racial differences between the PRECEDE model (predisposing, enabling, and reinforcing factors), marital status, tobacco history, health conditions, and treatment were statistically significant between Blacks and Whites. A higher percentage of Blacks received surgery only in early-onset, compared to Whites.
However, a higher proportion of Whites received more aggressive treatment (i.e., chemotherapy, radiation) among early and late-onset CRC. Blacks had more comorbidities compared to Whites. When evaluating additional clinical factors, Whites had more distal colon and rectal tumors and more advanced-stage disease. There were no racial differences in the overall and CRC-specific survival times for early-onset or late-onset CRC groups.

Implications

Practice

Studies in the general population have noted an increased incidence of early-onset CRC. We did not see an increased incidence of CRC in early-onset in the VA, which might be related to national screening and quality improvement programs that have been conducted in the Veterans Affairs Healthcare System. For example, the VA has a nationwide CRC screening reminder integrated into the electronic health record, which identifies when individuals are due for CRC screening. However, increased awareness of the increased incidence of early-onset and late-onset and the risk factors related to CRC will prepare nurses and providers to be able to identify Veterans at the highest risk for

CRC. Given that many symptoms of early-onset CRC are similar to other disorders such as hemorrhoids and abdominal pain from inflammatory bowel disease (IBD), it is often diagnosed at advanced stage disease in the young (Patel & Ahnen, 2018). Therefore, it is important to know the signs and symptoms of early-onset CRC.

These study findings have identified important factors that may affect the incidence of early-onset CRC. Nurses are employed in different areas and settings of nursing practice, which allows them to inform Veterans about the increased risk of CRC and thorough assessment regarding family history. Access to various areas of practice allows nurses the opportunity to promote CRC screening practices, which can lessen incidence and mortality. Nurses should include assessment of patient reports of subtle signs and symptoms of CRC such as blood loss or changes in bowel habits, and weight loss. This should prompt nurses to provide additional education on CRC risks and signs or symptoms. Patients should be encouraged to report these symptoms to providers so persons can receive appropriate and timely screening and treatment recommendations.

Findings from this study determined that a higher percentage of early-onset patients were obese and had a BMI of ≥ 30. The increased BMI could be related to poor diets and inactivity. Nurses have the opportunity during inpatient visits or outpatient encounters with Veterans to encourage lifestyle modifications such as eating healthy, maintaining a healthy weight, being physically active, and participating in smoking cessation programs to reduce CRC related risk factors (Griffin-Sobel, 2017). By using a multidisciplinary approach, nurses can consult with other members of the health care

team, such as dieticians, or encourage patients to attend blood pressure or diabetes classes to improve diet and exercise behavior modifications.

Education

Although there are efforts to determine the causes of early-onset CRC, education is an essential factor that must be considered to ensure patients and families are screened and aware of early-onset CRC. Educational strategies should be developed to raise awareness of the increased incidence of early-onset CRC, risk factors, and critical symptoms of CRC of which patients should be aware (Patel & Ahnen, 2018). Providing education on symptom recognition will assist with identifying CRC risk factors and key symptoms, and encourage individuals to report to their provider, and subsequently trigger diagnostic investigations (Connell et al., 2017). Nurses can engage in face-to-face sessions with patients and their families and provide information and educational resources about CRC while considering the literacy level and using culturally appropriate language, which is a known disparity among AAs (Brittain et al., 2016).

Nurses can educate patients in vulnerable populations, rural and urban communities, public health campaigns, and telemedicine. Veterans who use the VA that live in rural areas are often unable to attend provider appointments or receive CRC screenings due to transportation or financial issues. Therefore, telemedicine, telehealth, mobile health, or video on demand is an option available to the Veterans to help manage their care and lifestyle behaviors. Oncology nurses and those working in cancer care should continue to increase their knowledge regarding incidence, prevalence, mortality,

risks, prevention, screening, and treatment options, so they are better prepared to educate patients and their families regarding CRC (Gray et al., 2017).

Research

This study evaluated several factors that had an association between early-onset versus late-onset CRC and racial differences. With the increasing incidence of early-onset CRC in the general U.S. population, there have been several studies that have evaluated different factors related to early-onset CRC. However, few studies have compared early-onset and late-onset CRC among the Veteran population. Findings from this study determined that early-onset CRC was observed in individuals between the ages of 40 and 49. The VA's recommendation for screening is currently age 50, which means there might be the omission of some of the early-onset patients who later present with advanced-stage CRC. More research is needed to understand better how to detect CRC at earlier stages in individuals under age 50 when the screening recommendation in the VA is age 50-75. Therefore, future research is required to understand factors that can assist in identifying at-risk persons who are younger than the recommended screening age. For example, assessment of signs and symptoms, family history, health status (comorbidities), and social determinants of health that are risk factors.

The clinical expertise and the daily interaction nurses have with patients is one of the essential reasons that nurses should be involved in cancer awareness, education, care, and research. Nurses can be competent in testing instruments, developing tools and measurement scales related to CRC, or the development of new detection methods to prevent early-onset CRC. More studies concerning early-onset CRC among the Veteran

population are needed. Although the unique health needs of minority populations were not significant in this study, because they do exist in the general US population, there is a need for more studies to address the health issues related to disparities of health among minorities in the general US population.

Policy

Policies related to screening and target goals of Healthy People 2020 are significant for early detection and to decrease the incidence and mortality of early-onset CRC. The American Cancer Society's most recent recommendation is to screen individuals with an average risk for CRC to age 45 (ACS, 2018). In 2017, the U.S. Multi-Society Task Force (USMTF) updated their CRC screening to recommend adults at average risk for CRC begin screening at age 50, but African Americans at age 45 (Smith et al., 2018). It is essential to ensure policies are in place regarding CRC screening because CRC screening is a known, cost-effective approach to reduce the incidence and mortality of CRC (S. Gupta et al., 2014). As mentioned, the VA's current policy recommends screening at age 50, which should be considered to contribute to the early-detection of early-onset CRC patients and may need to be revised.

The CRC objective for Healthy People 2020 is to reduce the number of CRC death rates. One of the leading health indicators of Healthy People 2020 is to increase the percentage of adults who receive colorectal cancer screening based on the most recent guidelines (Healthy People [HP] 2020, 2018). The goal to reduce the number of CRC deaths is an objective for Healthy People 2030, as well as increasing the proportion of

adults who receive a CRC screening based on the most recent guidelines (HP 2030, 2020).

Limitations

There were a few limitations of this study to note. Of the predisposing factors, patient knowledge, attitudes, and beliefs could not be measured. Research suggests knowledge and understanding of the awareness of the increased incidence of early-onset CRC, risk factors, and the importance of screening as essential factors that contribute to incidence and mortality rates. Patient's attitudes and beliefs were related to preventive measures such as patients receiving screening, which impacts incidence and mortality. According to the literature, Veterans who receive or have more contact with providers or receive recommendations for screening are more likely to receive their screening (May et al., 2017). This study's database did not include if there were provider recommendations for screening during inpatient encounters or outpatient visits. VHA administrative data do not capture patient attitudes and beliefs or provider recommendations for screening and were not available for this large-scale analysis.

Second, the findings are limited to information that is available in secondary analysis and use of the electronic health record. The VA Oncology database contains information on Veterans who use the Veterans Health Administration (VHA). Veterans who receive care in nonfederal systems or through multiple systems were not captured in this study. The population of Veterans who use the VHA is different from the general Veteran population overall. Therefore, this study's findings may not be generalizable to

the entire Veteran population who utilize the VA system, and non-user applications may be limited.

Another limitation to consider is the inability to evaluate gender differences. The majority of this study sample was males. The demographics in the VA are shifting due to females being the fastest growing population among Veterans, and females are more likely to be early-onset CRC patients. Therefore, evaluating gender differences was limited but it will be important for future research.

Another limitation to the study is we were not able to capture family history of CRC specifically, which is a key hereditary risk factor. We were only able to capture family history of any cancer. Another limitation is this study was limited to invasive CRC cases and excluded in situ cases.

Summary

The increase in early-onset CRC has been a topic of interest over the last twenty years. However, limited studies have been performed to compare the differences among the Veteran population. There is an increasing body of research being conducted to distinguish the differences in early-onset versus late-onset CRC. Results of previous studies in the general population have determined that Blacks have the highest incidence of early-onset, are diagnosed at advanced-stage, and have the worst outcomes.

The purpose of this retrospective study was to evaluate the trends of the incidence and mortality of early-onset versus late-onset CRC among Black and White Veterans. The framework that guided the study was the PRECEDE Model. There was an evaluation

of the differences between the predisposing, enabling, and reinforcing factors for early vs late-onset CRC, and racial differences in these constructs and mortality.

The findings of this study can promote practice change as necessary to assist in detecting early-onset CRC in the Veteran population. The development of novel education strategies will increase awareness of this incidence of early-onset CRC among Veterans, providers, and staff.

Overall, findings of this current study emphasize the importance of distinguishing between early-onset CRC and late-onset CRC to understand the unique characteristics of the early-onset disease and how those characteristics might inform prevention and early detection efforts.

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APPENDIX A

OVERVIEW OF CONSTRUCTS AND STUDY VARIABLES

Constructs	Study Variables
Predisposing factors	Age • Early-onset • Late-onset Race/Ethnicity • Black • White Marital Status • Married • Unmarried • Unknown Comorbidities/Health conditions • Hypertension • Congestive heart failure • Dementia • Diabetes • Renal disease • Inflammatory Bowel Disease (IBD) Modifiable health behaviors • BMI (kg/m^2) Standard Categories Underweight (<18.5) Normal (18.5-24.9) Overweight (25.0-29.9) Obese (≥30) • Tobacco History Never smoker Unknown smoker Current/Former smoker

Constructs	Study Variables
Enabling factors	Access to healthcare • Additional health insurance coverage (Yes/No/Unknown) • Number of inpatient encounters since diagnosis • Number of outpatient visits since diagnosis Treatment • Surgery only • Surgery ± CT/RT • CT and/or RT • No treatment
Reinforcing factors	• Family influence • Family history of cancer (Yes/No/Unknown)
Primary Health Outcomes	Incidence • Number of cases/100,000 person-years • CRC diagnosis ICD–0-3 Site (C18-C20) Early-onset CRC (CRC diagnosis < 50) Late-onset CRC (CRC diagnosis ≥ 50) Mortality • Overall 5-year mortality rate (calculated from the date of cancer diagnosis to date of death) • CRC-specific 5-year mortality rate (calculated from the date of diagnosis to date of death due to CRC)