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Association between Metabolic Syndrome and Second Primary Cancer among Colorectal Cancer Patients

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Walden University
2020

Abstract

Association Between Metabolic Syndrome and Second Primary Cancers in Colorectal Cancer Patients

by

Olukayode Agbeyomi

MPH, Walden University, 2013

MB.BS, University of Ibadan,1998

Dissertation Submitted in Partial Fulfillment

of the Requirements for the Degree of

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Abstract

Colorectal cancer (CRC) is the third most common diagnosed cancer in both women and men in the United States. The gradual increase of incidence of second primary cancer (SPC) among CRC individuals has been a concern in recent times. Many CRC survivals have been forced back to be hospitalized for life-threatening cancers that are nonmetastatic cancers of CRC. Literature has suggested that there may be a relationship between metabolic syndrome (MetS) and CRC cases. The importance of early surveillance, detection, and treatment of SPC in CRC patients is significant to achieve better survival rates. The aim of this retrospective quantitative study was to investigate the association between MetS and its components (hypertension, obesity, diabetes, dyslipidemia, hypertriglyceridemia) and SPC among CRC patients, controlled for gender, age, and race/ethnicity. Social cognitive theory was the theoretical framework of the study. The 2011-2013 SEER-Medicare secondary data were used for this study and included 4,217 CRC patients. Bivariate and multivariable analyses were conducted to address this study's aim. Results revealed that CRC patients who were aged 65 to 75 years (*OR* = 2.9, 95% CI*:* 2.2-3.8) and obese (*OR* = 6.5*,* 95% CI: 5.2-8.3) had significantly more odds to develop SPC. This study promotes positive social change by enhancing clinicians' and public health policy makers' understanding of the relationship between age, obesity-induced MetS, and SPC in CRC patients. This study can also highlight the need for the early introduction of a surveillance program for the detection of SPC in CRC survivors by health care and public health professionals, and it demonstrates the importance of early intervention in mitigating SPC morbidity and mortality rates.

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Dedication

This dissertation is dedicated to the Almighty God who gave me grace and strength throughout the duration of this project. The inspiration of the Lord is the bedrock for the completion of this study in the midst of faceless forces of opposition. By the word of God, I laid the foundation, and by HIS Spirit I prevailed and finished (Zec4:9). And to HIM that called those things that be not as though they were be all honor, glory, power, might and dominion forever and ever. Amen.

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This dissertation would not have been possible without the unwavering encouragement and superlative expertise provided by my chair, Dr Vasileios Margaritis. My committee member, Dr Aaron Mendelsohn, as well as my URR, Dr Mountasser Kadrie, were instrumental in leading me to become a scholarly writer, researcher, and critical thinker. Thank you to my editor and the SEER-Medicare for supplying the dataset.

I would like to use this opportunity to appreciate some important people in my life who encouraged and supported me during this dissertation journey. First and foremost, I want to thank my beloved wife, Modupe, for her unreserved care and support every step of the way. I also want to thank my three sons, Glory, David and Toyan, for bearing with me throughout this journey. Thanks go to my friend Edward Irobi for his unrelenting support all the way and my best man Dike Ojji who never failed to ask for my progress in this study.

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Chapter 1: Introduction to the Study

In this study, I aimed to examine if there is any association between metabolic syndrome (MetS) and second primary cancers (SPCs) in colorectal cancer (CRC) individuals. Emerging evidence is showing that CRC survivors are at risk of developing SPCs (Lee et al., 2015; Raj, Taylor, Wray, Stamos, & Jason, 2011). SPCs cause remains unclear in the United States (Raj et al., 2014). Previous research has implicated MetS as the cause of CRC through different mechanisms in the literature like obesity, abnormal blood lipid, Type 2 diabetes mellitus, inflammation, and hypoxia (Braun, Bitton-Worm, & LeRoith, 2011). In this study, I explored the potential association of MetS with SPCs in CRC survivors to understand why CRC survivors may be at high risk of developing SPCs.

Previous researchers have found that there is high prevalence of MetS (mostly due to obesity) among women CRC survivors (Oritz-Mendoza & De la Fuente-Vera, 2014). Hence, there is need to study this association to have a more clear perspective of the risk CRC survivors are exposed to and advise policy makers accordingly.

This study can help clinicians, public health, and policy makers to decide if there is a significant risk among CRC survivors to develop SPC due to MetS. A high-risk association will require adopting new surveillance, and prompt screening of SPC for early detection and intervention can enhance survival and lead to social change.

The subsequent section includes the problem statement, which elucidates more about the problem and provides more literature in support; the research questions section,

which provides the independent and dependent variables in the study and the hypothesis; and the theoretical framework for the study.

Background

MetS is a combination of conditions that can enhance the development of chronic diseases. The mechanism of adipose tissue hypoxia in the obese individual is implicated in the significant relative risk of incidence of CRC in obese individuals, even after modifying for factors like smoking, body mass index (BMI), exercise, family history, smoking, hormonelike insulin and insulin growth factors, aspirin intake, and red meat consumption (Braun, Bitton-Worm, & LeRoith, 2011; Hu et al., 1999). Waist circumference was more significantly predictive for CRC than the BMI (Braun et al., 2011). Recently, the risk of development of SPCs after a CRC is rising among CRC survivors (Dasgupta, Youlden, & Baade, 2012). The risk of being diagnosed with SPCs was 33% higher (95% CI 1.12-1.56) for surgically treated patients and 45% higher (95% CI 1.29-1.64) in patients with proximal colon cancers than in patients with rectal cancers (Dasgupta et al., 2012). These SPCs are lung, bladder, kidney, stomach, and endometria cancers. The risk of SPCs after CRC differed by anatomic site of the CRC, and it was particularly pronounced in those whose CRC was in the transverse to descending colon (Phipps, Chan, & Ogino, 2013). There are limited studies on SPCs in the United States, and there is a need for patient education and effective surveillance programs for SPCs (Lee et al., 2015; Noura et al., 2009). There is a significant risk of MetS among obese CRC survivors with SPC (Oritz-Mendoza & De la Fuente-Vera, 2014). The present study

can help fill the gap in knowledge in public health and surgery on the association between MetS and SPC in CRC survivors in the United States.

The study is needed to allow policymakers and clinicians to have a new approach to SPC management in CRC survivors through intervention and surveillance that could reduce mortality of CRC survivors.

Problem Statement

CRC is the third most common cancer and the third highest cause of cancer mortality in the United States (Haggar & Boushey, 2009; Siegel, Desantis, & Jemal, 2014). Increasing incidence of SPC has been noted among CRC patients. A person diagnosed with CRC has an increased risk of developing SPC (SIR: 1.4; 95% CI: 1.3-1.5) in relation to the general population (Enblad, 1990; Lee et al., 2015; Raj et al., 2011). CRC has been associated with SPCs like lung (14%), bladder (11%), kidney (42%), stomach (28%), and endometrial cancers (26%; Phipps et al., 2013). Although the degree of risk is uncertain (Raj et al., 2011), the risk for SPCs has been found to increase among CRC patients irrespective of whether a curative surgery was done or not (Lee et al., 2015, Noura et al., 2009). The occurrence of SPCs in CRC patients is supported by the emerging hypothesis that there could be an association between MetS and some cancers (Esposito, Chiodini, Colao, Lenzi, & Giugliano, 2012). MetS and its component diseases are known as worldwide sources of health problems (Braun et al., 2011). MetS has five components: hypertension, obesity (abdominal), hypertriglyceridemia, dyslipidemia, and diabetes (Braun et al., 2011). The presence of any three of these components is confirmatory of MetS. The rise in SPCs affects men and women of different races mainly

in those 40 to 79 years of age. The individuals with the highest incidence of SPCs are those with CRC who are either undergoing treatment for CRC or are survivors of CRC. The increase in cancer has also been described in individuals without CRC but who have certain components of MetS in addition to other factors like inflammation and hypoxia (Braun et al., 2011). MetS currently affects one-third of U.S. adults (Kanagasabai, Nie, Mason, & Ardern, 2014). Obesity has been associated with CRC (Braun et al., 2011; Maet al. 2013). More than one-third (36.5%) of U.S. adults have obesity with age, gender, and race disparity, putting them at increased risk for CRC and SPCs (Centers for Disease Control and Prevention [CDC], 2016; Lee et al. 2015). Metabolic abnormality using obesity and diabetes for an independent assessment of obesity and diabetes has been described to have increased the incidence of CRC (Sturmer, Buring, Gaziano, & Glynn, 2006).

A study conducted in Australia showed that the length of survival for CRC patients with an SPC could be as little as 2 months (Dasqupta, Youlden, & Baade, 2012). MetS through its components (hypertension, abdominal obesity, diabetes, high serum triglycerides, low high-density lipoprotein [HDL] levels) is used as an index of predicting a long term chronic problem like CRC development due to the increasing acknowledgment of its role in enhancing not only cardiovascular disease but also chronic diseases like colorectal adenoma, gastric, and colorectal cancer (Pais et al., 2009; Pothiwala, Jain, & Yaturu, 2009; Trabulo et al., 2015). The component of MetS like waist circumference and waist to hip ratio, both regarded as abdominal obesity, has a CRC risk association (Trabulo et al., 2015) and the role of MetS in SPC development among

individuals with CRC needs further investigation. There are a limited number of studies in the United States on SPCs in CRC patients and on the association between MetS and SPCs in individuals with CRC. Most of the previous studies on SPCs in CRC patients have been done in Southeast England (Evans et al., 2002), Taiwan (Lee et al., 2015), Queensland, Australia (Dasgupta et al,, 2012), and Mexico (Ortiz-Mendoza & De la Fuente-Vera, 2014). Ortiz-Mendoza and De la Fuente-Vera (2014) discovered that there is an association between MetS and SPC among female CRC survivors. The authors studied 107 female participants between the age of 50 and 70 years, with a BMI of 25 to 37kg/m2. The mean glucose level for all the participants was 120 ± 58 mg/dL, cholesterol 228 ± 43 mg/dL, and triglycerides 207 ± 120 mg/dL. Fifty-five (51%) with glucose > 99 mg/dL, 85 (79%) with cholesterol > 199 mg/dL, and 67 (63%) with triglycerides > 149 mg/dL. Obesity (BMI = 30 kg/m2) occurred in 49 (46%) and metabolic syndrome in 27 (26%). The authors observed the high prevalence of obesity and concluded that it accounted for the several components of MetS found in the study participants (Ortiz-Mendoza & De la Fuente-Vera, 2014). In this study, I examined SPCs in CRC patients in the United States and thus helped to fill this gap.

Purpose of the Study

The purpose of this quantitative study was to determine whether there is an association between the components of MetS (increased blood pressure [greater than 130/85 mmHg], high blood sugar levels [insulin resistance], excess fat around the waist, high triglyceride levels, low levels of good cholesterol, or HDL; independent variables)

and SPCs (dependent variable) in CRC patients of different ages, gender, and ethnicity (age, gender, and ethnicity are also independent variables).

Research Questions and Hypotheses

Research Question (RQ)1: Is there an association between hypertension and SPCs in CRC patients?

$H_0$1: There is no association between hypertension and SPCs in CRC patients.

H_a1: There is an association between hypertension and SPCs in CRC patients.

RQ2: Is there an association between abdominal obesity and SPCs in CRC patients?

$H_0$2: There is no association between abdominal obesity and SPCs in CRC patients.

H_a2: There is an association between abdominal obesity and SPCs in CRC patients.

RQ3: Is there an association between dyslipidemia and SPCs in CRC patients?

$H_0$3: There is no association between dyslipidemia and SPCs in CRC patients.

H_a3: There is an association between dyslipidemia and SPCs in CRC patients.

RQ4: Is there an association between diabetes and SPCs in CRC patients?

$H_0$4: There is no association between diabetes and SPCs in CRC patients.

H_a4: There is an association between diabetes and SPCs in CRC patients.

RQ5: Is there an association between hypertriglyceridemia and SPCs in CRC patients?

$H_0$5: There is no association between hypertriglyceridemia and SPCs in CRC patients.

H_a5: There is an association between hypertriglyceridemia and SPCs in CRC patients.

RQ6: Is there an association between age, gender, and ethnicity with SPCs in CRC patients?

$H_0$6: There is no association between age, gender, and ethnicity and SPCs in CRC patients.

H_a6: There is an association between age, gender, and ethnicity and SPCs in CRC patients.

RQ7: Is there an association between MetS and SPCs in CRC patients?

$H_0$7: There is no association between MetS and SPCs in CRC patients.

H_a7: There is an association between MetS and SPCs in CRC patients.

Theoretical Foundation

Social cognitive theory (SCT) is a form of reciprocal determinism described by Bandura in 1960 as an interpersonal level theory that describes the triangular dynamic interrelationship between people (personal factors), their behavior, and their environments. This theory started as a social learning theory but gradually developed into SCT in 1986. SCT posits how people gain and keep some behavioral patterns while giving the basis for intervention strategies (Bandura, 1977). SCT deals more with social influence and external and internal social reinforcement (LaMorte, 2016). SCT examines how individuals get and keep behavior as well as the social environment where the

behavior is executed considering the individual's previous experience, which determines if a change will occur. It is this experience that affects reinforcements, expectations, and expectancies that together determine the reason and if the individual will perform the behavior (LaMorte, 2016). LaMorte (2016) explained that SCT started originally with five constructs before self-efficacy was added to become SCT and has the following constructs:

1. Reciprocal determinism: The core concept of SCT that refers to the triadic dynamic and mutual interaction existing between the person (learned experiences), environment (external system), and behavior (responses to stimuli to achieve goals).
2. Behavioral capability: Proficiency to be able to use knowledge and skill to perform a behavior after providing information on what to do. The individual should know how to do it and so learn from the action of their behavior that affects their environment.
3. Observational learning: The form of behavioral modeling that challenges the individual's ability to watch a behavior in others to reproduce the action.
4. Reinforcements: The reaction to a person's internal or external responses that determine if the action will be continued or not. Reinforcements are closely associated with the reciprocal relationship between behavior and environment and can be individually or environmentally initiated and can be positive or negative.

5. Expectations: Refers to the expected effect of an individual's behavior and can be outcome expectations that can or cannot be health related. This expected effect of an action can affect the completion of the behavior because people expect the result of their action.

Expectancy- put attention on the value of the outcome. It is subjective.

Both expectations and expectancies originate from previous experience.

6. Self-efficacy: This refers to individual's personal ability to carry out a behavior and is affected by the person's specific capabilities, other individual's factors, and the environmental factors.

SCT is useful in achieving successful behavior change, especially in obesity, which is the reason it is of importance in this study. There is an associated high relapse rate, and it requires motivation, self-efficacy, and self-regulation (Teixeira et al., 2015). In SCT, the individual is involved, the environment and the behavior. Using the construct of SCT, an individual has to have the behavioral capability to know how to use knowledge and skill to perform a behavior after providing information on what to do. This is followed by observational learning, where the watched behavior is copied and reproduced. If, for example, the exercise is skipping rope for 30 minutes every day while counting numbers to 100, the individual should be able to reproduce the behavior. It is after this that reinforcement reaction sets in as a response to the individual's personal internal or external response that decides whether the action will continue. This action can make or mar the theory. This phase is guided by the expectation of the individual, which is based on the prior action. The positive outcome means the individual can

continue without external regulation. The last construct is self-efficacy, which enables the individual to continue skipping daily every morning for 30 minutes in order to obtain the desired of health weight with subsequent improve weight, healthy heart, and better BMI. This is an example of how social cognitive theory can be used in this study.

Conceptual Framework

The conceptual framework of this study was based on previous empirical studies on how MetS is associated with colorectal cancer, which is a worldwide disease with varying geographical distribution. MetS has been identified among many cancer survivors, and its pathophysiology is described in the literature (De Haas et al., 2010). Obesity and other MetS components have been described in Mexican women cancer survivors (Ortiz-Mendoza & De la Fuente-Vera, 2014). The high prevalence of obesity among Mexican women has accounted for the components of MetS observed among cancer survivors in the study (Ortiz-Mendoza & De la Fuente-Vera, 2014). The influence of MetS on women's SPCs provides ample evidence supporting that MetS is a risk factor for many primary malignancies like CRC (Ortiz-Mendoza & De la Fuente-Vera, 2014). Obesity or excessive body weight gain (apple shape), a component of MetS, has been described in cancer pathogenesis. In the United States, 66% of the adult population is obese with a BMI > 25kg/m2, and half of them have a BMI > 30kg/m2 (Braun et al., 2011). Studies have revealed that fat tissue is a source of hormones like estrogen, testosterone, and growth factors that favor cancer growth by modulating the effects of diet and physical activity. The larger the effect of these factors, the higher the risk of developing CRC (Hemminki, Li, & Gong, 2001). Abdominal circumference has been

implicated as a better predictor of cancer than BMI in MetS patients. Obesity is a known risk factor for many cancers, including breast, endometrial, colorectal, uterine, kidney, pancreatic, and esophageal (Larsson & Wolk, 2007). It has been reported that obesity could cause Type 2 diabetes mellitus, which is another strong factor in the pathogenesis of certain cancers like CRC (Braun et al., 2011). The mechanism proposed has been the development of hypoxia by adipose tissue due to the combination of obesity, inflammation, and insulin resistance in patients with MetS due to adipose tissue hypoxemia (Brauns et al., 2011). Obese individuals have chronic inflamed adipose tissue due to high levels of inflammatory cytokines in plasma and adipose tissue, macrophage infiltration, and activation in the adipose tissue. Furthermore, inflammation through tumor necrotic factor can cause insulin resistance by mediating in the intracellular signaling cascade of insulin (Ye, 2009). The high free fatty acids and decreased adiponectin levels in the blood of obese people enhance insulin resistance (Braun et al., 2011). This accounts for the pathogenesis of MetS and reveals a high relative risk for colorectal cancer in obese people (Calle, Rodriguez, Walker-Thurmond, & Thun, 2003). The empirical data on the known mechanisms of obesity-related MetS carcinogenesis and the published differing impacts of MetS in different age groups, genders, as well as various ethnicities, provided the framework for the choice of variables and the research questions used in this study.

Nature of Study

This was a quantitative retrospective cohort study using secondary data. I used two cohorts. One cohort had CRC but not SPCs, and the second cohort had both. In this

study, the characteristics of the study population were described, and I attempted to identify risk factors for CRC and SPCs among CRC patients. The research questions were intended to identify the role played by age, gender, ethnicity, and MetS components (independent variables) in the pathogenesis of SPCs among CRC patients (dependent variable). The relationship between the dependent and independent variables was analyzed using bivariate and regression analysis via SPSS v25. Logistic regression helped to ascertain the odds ratios and the probabilities of association.

Types and Sources of Data

The secondary data derived from Surveillance, Epidemiology, and End Results (SEER) cancer registries 2011 to 2013. Patients with a history of CRC, aged > 65 years, with no history of cancer prior to their CRC diagnosis were eligible for the study. Patients who were followed < 1 year and/or had their SPCs diagnosed within the first year after diagnosis of CRC were not included due to difficulty in differentiating synchronous from metachronous SPCs in CRC patients. Moreover, patients with cancer of the small intestine were excluded to avoid misclassification due to difficulty in distinguishing it from SPCs in the first year (see Lee et al., 2015).

Operational Definitions

In this study, the following definitions apply:

Colorectal cancer (CRC): The primary cancer of this study with anatomical location in the colon (ascending, transverse, descending, and sigmoid) and rectum depending on where it starts.

Metabolic syndrome (MetS): Refers to a group of risk factors that when presented together in a person can cause cardiovascular disease, stroke, and chronic diseases. These risk factors include increased blood pressure (greater than 130/85 mmHg), high blood sugar levels (insulin resistance), excess fat around the waist, high triglyceride levels, and low levels of good cholesterol, or HDL (Braun et al., 2011).

Metachronous SPC: SPC detected after 6 months of the initial primary cancer diagnosis (Li-Chu et al., 2014; Lopez et al., 2009).

Second primary cancer (SPC): For this study, SPC represents the cancer that develops not as metastases of the primary cancer (CRC) but of a different histological cancer type arising after the diagnosis of primary cancer (CRC). SPCs for this study included lung, stomach, bladder, kidney and endometrial cancers (see Lee et al., 2015).

Synchronous SPC: SPC detected within 6 months of the initial primary cancer diagnosis (Li-Chu et al., 2014; Lopez et al., 2009).

Assumptions

An assumption was that the dataset contained correct diagnoses of SPCs in CRC, age, gender, and ethnicity. I assumed that the SPC dataset population was representative of the population, but results may not be generalizable to other populations. This is secondary dataset, which made it difficult to verify information in the dataset obtained from the study group.

Scope and Delimitations

The research problem was about if there is any association of MetS with the development of SPCs in CRC patients using various associated components of MetS and

age, gender, and ethnicity as independent variables. The study population included participants with CRC without SPCs and those with SPCs with CRC of ages above 40 years to exclude CRC of familial origin. The inclusion criteria were that of primary cancer histologically confirmed to be CRC, and metastatic lesion from elsewhere had to be excluded (Evans et al., 2002; Li-Chu et al., 2014). I excluded SPCs occurring within 6 months of diagnosis of CRC for lack of differentiation that can lead to misdiagnosis of metastases as SPCs (see Yen et al., 2015). There is a limitation based on the available data in the dataset because the study was limited by the number of the participants in the dataset who were eligible to be included in the study.

Limitations

The source of the sample population in a secondary data analysis may lead to bias in the study and, therefore, was limited to the data available in the dataset. The data were limited due to rare screening for SPC as described in the study and data availability. It was not possible to obtain additional information about the subjects in the cohorts. Consequently, analyses of relationships among variables were limited by what information was collected originally due to lack of access to additional information about the subjects in the cohorts. In other to address limitations, the source of the dataset was verified to be credible and reliable by checking where it was published(see Center for Public Education, 2017). The source of funding for the collection and analysis of data could be another method for checking for credible and reliable data sources, especially because it is possible that the organization that publishes the data may not have a particular bias, but the organization that funded the data collection could. Another way to

check for credible and reliable data source is to use the Stanford guidelines for web credibility (see Center for Public Education, 2017):

- Websites should have verifiable reference checks.
- The author should be identifiable as well as affiliates, credentials, and contact information.
- The site owner's or managing party physical address and contact information should be included.
- The site mission statement and identification of staff responsible for the site should be indicated
- Is there site advertisement? What is the source of funding even if its managed by a not-for-profit organization?
- What is the site quality and outlook? Is the site professional in appearance?
- How often is the site update? Are there typographical and grammatical errors?

Significance of the Study

The complex nature of cancer pathogenesis, including the detailed roles of oncogenes and tumor suppressors, suggests that many factors play a key role in cellular metabolism (Boroughs & DeBerardinis, 2015). The recent shift in thinking over the past 5 years is that cancer is a metabolic disorder rather than a genetic disease (Wishart, 2015). The authors in a study conducted in Mexico concluded that MetS may be a risk factor for a SPC in women (Ortiz-Mendoza, Pérez-Chávez, & De-la Fuente-Vera, 2016).

This study can provide insight as to the role MetS plays in SPCs associated with CRC. A combination of CRC with any of the SPCs creates a higher risk of mortality for the patient, thus necessitating closer surveillance for SPCs in all CRC patients. It is imperative to determine if there is an association between MetS and SPCs in CRC patients as this can help clinicians and policy makers to decide if there is need to adopt surveillance in CRC patients that can enhance the selection of individuals who may benefit from tertiary prevention and reinforce the importance of primary prevention.

Social Change Implications

This study can enhance clinicians and public health policy maker's understanding of the relationship between MetS and SPCs in CRC patients. This study can promote the need for an early introduction of a surveillance program for detection of SPCs in CRC survivors by clinicians and public health policy makers and show the importance of early intervention in mitigating morbidity and mortality rate, thereby enhancing survival.

The importance of early detection of these SPCs in CRC patients cannot be underestimated, as ignoring the presence and effect of SPCs can adversely affect the prognosis, treatment, and recovery. The results of the current study can be disseminated to clinicians and public health policy makers to promote screening for SPCs individuals with CRC.

Summary

CRC is the second common cause of death in the United States (Haggar & Boushey, 2009; Siegel et al., 2014). The discovery of MetS and its association with chronic diseases like CRC is a public health marker for more efficient screening and

preventive measures to detect at-risk individuals by controlling the components of MetS. MetS currently affects one-third of U.S. adults (Kanagasabai et al., 2014) and has been described to promote many cancers in obese cancer survivors (Ortiz-Mendoza & De La Fuente-Vera, 2014). A diagnosis of CRC puts the individual in jeopardy of developing SPCs like lung, bladder, stomach, kidney, and endometrial cancers (Lee et al., 2015; Raj et al., 2011). Some studies have described SPCs regarding a predisposition to the primary cancer sites and location of cancer in the colon (Phipps et al., 2013) while others have described SPCs about age and gender (Siegel et al., 2014). One study conducted in Mexico described a possible association between MetS and SPC in obese women who are cancer survivors (Ortiz-Mendoza & De la Fuente-Vera, 2014). To the best of my knowledge, no researcher has examined the association of MetS and ethnicity as a risk factor for developing a second primary lung, endometrial, kidney, stomach, and bladder cancer in patients previously diagnosed with CRC cancer using multivariable analysis.

Chapter 2 contains a review of the current literature on MetS and CRC cancer epidemiology SPCs and the pathology, diagnosis, and prognosis of lung, bladder, stomach, endometrial, and kidney cancers. In Chapter 2, studies supporting the conceptual framework and study design are presented. An in-depth revision of nonmodifiable risk factors of age, ethnicity, and gender are addressed as well as modifiable risk factors such as lifestyle (diet) and obesity.

Chapter 2: Literature Review

Introduction

The individuals diagnosed with CRC have an increased risk of developing SPC (SIR: 1.4; 95% CI: 1.3-1.5) compared to the general population (Enblad 1990; Lee et al., 2015; Raj et al., 2011). This risk is increasing among CRC survivors irrespective of the administration of the curative surgical therapy (Lee et al., 2015; Noura et al., 2009). An emerging hypothesis supports the existence of a possible association between MetS and certain cancers like CRC (Esposito et al., 2012). MetS affects one-third of U.S. adults (Kanagasabai et al., 2014). There are five components of MetS: hypertension, obesity (abdominal), hypertriglyceridemia, dyslipidemia, and diabetes, and only three are required for confirmation of MetS (Braun et al., 2011). This problem of SPC affects individuals of 40 to 79 years, both male and females of different races, with the highest incidence of SPCs among those with CRC on treatment or survivors of CRC (Lee et al., 2015, Noura et al., 2009). Obesity, a part of MetS, has been associated with increased incidence of CRC (Braun et al., 2011). Limited studies exist in the United States on SPC in CRC patients.

This study can fill the gap in the literature by examining the association between MetS and SPC among CRC survivors. A quantitative research methodology was applied using secondary data set to answer the research questions and hypotheses.

This chapter includes a description of the epidemiology of colorectal cancer in the United States. It also includes CRC risk factors, metastases, morphology and histological grading and classification, tumor marker and screening, staging, and treatment. Literature

on SPC with the risk factors and an in-depth update on metabolic syndrome with its components, and its role in the pathogenesis of cancer are also discussed.

The purpose of this quantitative study was to determine whether there is an association between the components of MetS and SPCs in CRC patients of different ages, gender, and ethnicity.

Literature Search Strategy

I employed MEDLINE, National Cancer Institute Comprehensive, CINAHL, PUBMED, GOOGLE SCHOLAR, and Walden University dissertation ProQuest to conduct this literature review. During the search, I used the following major terms: *metabolic syndrome, colorectal cancer, epidemiology, diagnosis, second primary cancers of colorectal cancer, colon cancer, endometrial cancer, lung cancer, kidney cancer, bladder cancer, colorectal cancer treatment, prognosis, age, gender, ethnicity,* and *CRP*. The above search method produced peer-reviewed articles from 2010 to 2020, among other articles.

Conceptual Framework

The conceptual framework chosen for this study was based on previous empirical studies on how MetS are associated with colorectal cancer and SPC. The incidence of CRC survivors is increasing, and so is the risk of developing SPC (Guan et al., 2015). MetS has been identified among many cancer survivors, and its pathophysiology is described in the literature (De Haas et al., 2010). Obesity and other MetS components have been described among Mexican women cancer survivors to be contributory to the risk of developing SPC (Ortiz-Mendoza & De la Fuente-Vera, 2014). The high

prevalence of obesity among Mexican women population has accounted for the MetS observed among cancer survivors in the study (Ortiz-Mendoza & De la Fuente-Vera, 2014). The influence of MetS on cancer survivors provides ample evidence supporting that MetS is a risk factor for many primary malignancies like CRC (Ortiz-Mendoza & De la Fuente-Vera, 2014).

Obesity has been described in cancer pathogenesis. In the United States, 66% of the adult population is obese, with a BMI > 25kg/m2, and half of them have a BMI > 30kg/m2 (Braun et al. 2011). Studies have shown that fat tissue is a source of hormones like estrogen, testosterone, and growth factors that favor cancer growth by modulating the effects of diet and physical activity. The larger the effect of these factors, the higher the risk of developing CRC (Hemminki et al., 2001). Abdominal circumference has been implicated as a better predictor of cancer than BMI in MetS patients. Obesity is a known risk factor for many cancers, including breast, endometrial, colorectal, uterine, kidney, pancreatic, and esophageal (Larsson & Wolk, 2007). It has been reported that obesity could cause Type 2 diabetes mellitus, which is another strong factor in the pathogenesis of certain cancers like CRC (Braun et al., 2011). The mechanism proposed has been the development of hypoxia by adipose tissue due to the combination of obesity, inflammation, and insulin resistance in patients with MetS due to adipose tissue hypoxemia (Brauns et al., 2011).

Obese individuals have chronic inflamed adipose tissue due to high levels of inflammatory cytokines in plasma and adipose tissue, macrophage infiltration, and activation in the adipose tissue. Furthermore, inflammation through tumor necrotic factor

can cause insulin resistance by mediating in the intracellular signaling cascade of insulin (Ye, 2009). The high free fatty acids and decreased adiponectin levels in the blood of obese people enhance insulin resistance (Braun et al., 2011). This account for the pathogenesis of MetS has revealed a high relative risk for colorectal cancer in obese people (Calle et al., 2003). Furthermore, obesity has been linked to MetS and insulin resistance in young adults with middle incomes (Madeira et al., 2013). The empirical data on the known mechanisms of obesity-related MetS carcinogenesis and the published differing impacts of MetS in different age groups, genders, as well as various ethnicities, provided the framework for the choice of variables and the research questions used in this study.

Recent study has revealed that the presence of obesity and MetS in early CRC is associated with worse survival prognosis (Cespedes-Feliciano et al., 2016).

Ortiz-Mendoza et al. (2016) observed from their study that obesity among Mexican women who have survived previous CRC is a predisposing risk factor for developing SPC. The study was a case-control study, using nine cases and 27 controls from a general hospital in Mexico City. The participants were women having second cancers (cases) age-matched with women with only one neoplasm as controls. Anthropometry measurements were taken for blood pressure, blood glucose, triglycerides, height, and weight to calculate the BMI and tumor type, and total cholesterol was obtained from their medical files. The criteria for selecting participants was the development of second cancer at least 6 months after the diagnosis of the first tumor. Diabetes mellitus was diagnosed if the individual was on insulin or an oral

hypoglycemic agent or if the fasting serum glucose was 126 mg/dl or greater. Hypertension was diagnosed using antihypertensive or having blood pressure 135/85mmhg or higher. Dyslipidemia was diagnosed using fibrates, statins, or having a cholesterol level greater than 199mg/dl or glyceride values greater than 149mg/dl. The diagnosis of the modified metabolic syndrome is made when three of the criteria are present, as previously highlighted. The sample size was calculated, and statistical analysis was done using Pearson "χ^2" and Fischer's test, and the odd ratio was used to study the association strength between variables using a 95% CI, and $p < 0.05$ was regarded as significant.

Lee et al. (2015) studied the features of second primary cancer in individuals with previous colorectal cancer among Taiwan's population. This was a multivariate retrospective cohort study conducted over a 16-year study period, using data from Taiwan's National Health Insurance research database. Out of 98,876 CRC patients in the study period, including 55,729 (56.4%) men and 43,147 (43.6%) women, with a median age of 67 years, 4,259 had developed SPCs after a median follow-up of 4.03 years. Data extraction and computing were done using Perl programming language (Version 5.12.2), the Microsoft SQL Server 2012 (Microsoft Corp., Redmond, WA) for data linkage and processing, and SAS 9.2 software for analysis. The standard incidence ratio (SIR) of the SPC was 1.13 (95% CI = 1.10-1,17) using a Poisson probability distribution. Univariate and multivariate Cox proportional hazards models were used to identify predictors of SPC occurrences among CRC patients.

When compared with the general population, colon cancer had a higher incidence of ovarian, thyroid, prostate, and hematologic cancers, whereas rectal cancer had a high risk of bone and soft tissue cancers (Lee et al., 2015). Colon and rectal cancer had a significantly higher risk for lung, kidney, breast, uterine, and bladder cancers than the general population (Lee et al., 2015). A reduced risk was noticed for liver and biliary tract cancers with rectal cancer (Lee et al., 2015). An independent risk factor from the study for SPC includes age of 70 and above, men, chronic obstructive pulmonary disease (COPD), cirrhosis, and dyslipidemia (Lee et al., 2015). CRC survivors, therefore, have increased risk of developing SPC.

Youlden and Baade (2011) studied the relative risk of developing any SPC in Queensland, Australia using a retrospective cohort study. The dataset was obtained from the Queensland Cancer Registry. The population included participants 15 years and older with a 2-month history of previous first primary invasive cancer. A total of 204,962 had first primary cancer, and 23,580 had SPC over a follow-up period of 5 to 25 years. The author excluded synchronous primary cancers within 2 months of the first primary cancer, and third cancers were also not included. The various cancers of the body sites were analyzed as cancers of head and neck, cancers of colon and rectum, and others body cancers were classified as "other." The SIR was calculated by dividing the total observed cases of second primary cancer by the expected number to estimate the risk of a cancer patient developing a second primary cancer relative to the incidence of cancer among the general population. The Poisson distribution was used to deduct the CIs used for the SIRs using 95% level of certainty, and SAS v9.2 for Windows was used for analysis. The

authors concluded that the highest percentage of second primary cancers occurred after an initial diagnosis of melanoma (21.6%), colorectal cancer (12.9%), prostate cancer (12.7%), or female breast cancer (12.6%). There are significantly increased relative risks of invasive cancer for males after the diagnosis of head and neck cancer, lung cancer, kidney cancer, esophageal cancer, melanoma, bladder cancer, non-Hodgkins lymphoma, thyroid cancer, lymphoid leukemia, or myeloid leukemia. However, males with the primary diagnosis of either prostate or stomach cancer had a significantly lower risk of cancer compared to the general population. The female cohort had a higher relative risk for second cancer for those diagnosed with head and neck cancer, colorectal cancer, cervical cancer, lung cancer, kidney cancer, melanoma, breast cancer, uterine cancer, bladder cancer, non-Hodgkins lymphoma, thyroid cancer, lymphoid leukemia, or myeloid leukemia. The female survivor had no significantly lower risk of developing a second invasive cancer in relation to the general population.

Literature Review

Colorectal cancer refers to any growth, lump or tumor of slowing growing in the colon and rectum. CRC is the second most common cancer after lung cancer (Li-Chu et al., 2014),). CRC affects men and women of all races and ethnic groups and mostly common in 50 years and older (CDC, 2017) and CRC remain a burden in the United States as 1,177,556 U.S. residents were estimated to be living with colorectal cancer in 2013 although the mortality rate has reduced as survival rate increases (Marley, & Nan, 2016).

CRC can be sporadic while 5–10% are from inherited syndromes like the hereditary non-polyposis colon cancer (HNPCC) and familial adenomatous polyposis (FAP). It is not unusual to have some overlap of genetic abnormalities involving both sporadic and inherited forms. The key mutation involved in colorectal carcinogenesis include APC, KRAS, and p53 genes. The individual with first degree relative with CRC has a risk of having colorectal cancer to be three times greater than one who has no family history (George & Rockall, 2017).

The most common histopathology form of colorectal cancer is adenocarcinoma which is postulated to have developed from the adenoma–carcinoma sequence which includes a natural progression from benign polyps into invasive cancerous lesions (George & Rockall, 2017).

CRC symptoms may not be detected on time for some time, and when it presents, the symptom can be easily confused with other diseases like hemorrhoids, anal fissure due to the similar characteristic presentation of blood in the stool (Eyvazzadeh & Reilly Colon and Rectal Center, N.D). Occasionally, the blood may not be obvious to the naked eye, and a test for occult blood on stool sample may be necessary. Another symptom could be changed in bowel habit with an alternate presentation of constipation and diarrhea. Other symptoms can appear as the disease advances. Symptoms may depend on the location of cancer, right-sided cancer tends to bleed and cause diarrhea while left sided cancer may not be detected early until it presents later with a bowel obstruction (Dragovich, 2014).

In advanced colon cancer cases, common clinical presentations include iron-deficiency anemia, rectal bleeding, abdominal pain, change in bowel habits, and intestinal obstruction or perforation (Toh, Griffiths & Farooq, 2012).

Abdominal symptoms like abdominal pain, vomiting, mucus discharge with stool and feeling of incomplete emptiness of the rectum (otherwise called Tenesmus) (Mayo Clinic, 2018). Other symptoms of CRC include fatigue, anemia, lack of appetite, rapid weight loss and bowel obstruction (Mayo Clinic, 2018). Colorectal cancer can spread by direct extension to adjacent structures and via lymphatics or blood (America Cancer Society, 2018). The most frequently involved metastatic sites are the liver, regional lymph nodes, lungs, and bones (Riihimaki, Hemminki, Sundquist & Hemminki 2016).

Epidemiology of CRC

The incidence rate is the most appropriate form of tracking the disease occurrence and is not affected by changes in treatment and survival, but CRC incidence has been affected by diagnostic techniques and screening program (Haggar & Boushey, 2009). CRC account for 9% of all cancer incidence (Haggar & Boushey, 2009). The incidence of CRC is decreasing in the United States and western countries due to improvement in early detection, supportive care and treatments giving rise to increasing in survivors who are developing second primary cancers (SPC) (Dasgupta, Youlden & Baade, 2012). CRC has a wide geographical variation with incident cases of 9.4% of cancer in men and 10.1% in women although the distribution is not uniform globally (Haggar & Boushey, 2009). This geographic variation is based on the understanding that CRC is a disease of developed western cultured countries although there could be under reporting of the

disease among the developing countries (Haggar & Boushey, 2009). The incidence rate of CRC between countries could varies up to 10 times from the highest rates to those with the lowest rates and could be from more than 40 per 100,000 people in the United States, Australia, New Zealand, and Western Europe to as low as below 5 per 100,000 in Africa and some parts of Asia (Haggar & Boushey, 2009). Marley and Han (2016) reported that only 2-8% of CRC was found in individual less than 40years in the United States and the European Union whereas Egypt, Saudi Arabia, the Philippines, and Iran has rates of 38%, 21%, 17%, and 15-35%, respectively.

CRC represents the third deadliest cancer and remains a heavy burden on the US population, as 1,177,556 U.S. residents were estimated to have been living with colorectal cancer in 2013 (Marley & Nan, 2016). Over some decades the burden of CRC has been reducing in both incidence and mortality rate while there is an improvement in the 5-year survival rate from low of 49.8% to a high of 66.2% (Marley & Nan, 2016).

CRC survival depends a lot on the disease stage at the time of diagnosis. The earlier the stage of cancer at diagnosis, the higher the chance of survival. The usual trend is for CRC detected at localized stage to have 90% 5-years survival rate, 70% for CRC at the regional stage and 10% for those with distance metastases (Haggar & Boushey, 2009).

Factors for CRC

There are 12 non-screening risk factors for CRC and these include family history of CRC, physical activity, inflammatory bowel disease, body mass index, hormone therapy in postmenopausal women, aspirin/nonsteroidal anti-inflammatory drug use, red

meat, fruit cigarette smoking, and consumption of processed meat, vegetables, and alcohol (Johnson et al., 2013).

Body Mass Index. There was found a significant association between BMI and CRC (*RR* = 1.10 per 8 kg/m2, 95% *CI*: 1.08–1.12). The association between BMI and CRC among males (for CRC, *RR* = 1.29 per 8 kg/m2, 95% *CI*: 1.26–1.34; for colon cancer, *RR* = 1.53 per 8 kg/m2, 95% *CI:* 1.32–1.77) was stronger than the association for females or the mixed population (for CRC, *RR* = 1.15 per 8 kg/m2, 95% *CI*: 0.98–1.34; for colon cancer, *RR* = 1.27 per 8 kg/m2, 95% *CI:* 1.07–1.51) (Johnson et al., 2013).

Physical activity. Physical activity has a significant negative correlation with CRC risk (*RR* = 0.88 per 2 standard scores, 95% *CI:* 0.86–0.91) but there was significant heterogeneity (Q=146, $p<0.0001$) which could be due to the changes in study type (cohort vs. case-control), cancer site (colon vs. CRC), and gender (female vs. male or mixed population) (Johnson et al., 2013)"

Tobacco (cigarette smoking). Using 1966 colon cancer cases and 7433 CRC cases in 15 studies to examine the association between tobacco use and CRC, there was a lack of proof to support nonlinearity between smoking and CRC ($p = 0.002$) (Johnson et al., 2013). Tobacco use was associated with the risk of development of CRC.

Alcohol. The author used data from 2469 colon cancer cases and 9717 CRC cases in 22 studies to examine the role of alcohol in the development of CRC and concluded that neither gender nor site of cancer was a significant source of variation. The overall linear trend between alcohol consumption and CRC was not significant (*RR* = 1.06 per 5

drinks/week, 95% *CI:* 0.91–1.23) and (*RR* = 1.26 per 20 drinks/week, 95% *CI*: 0.68–2.32) (Johnson et al., 2013).

Family history. The authors studied the association between a history of CRC in first-degree relatives and CRC risk using 8091 cases of CRC in 16 studies including family history data. Six of the articles reported risk estimates for females only, and the other ten articles reported risk estimates for a mixed population. The risk to develop CRC in individuals with family history was higher for compared to those with no family history of CRC (RR = 1.80, 95% CI: 1.61–2.02) (Johnson et al., 2013).

Inflammatory bowel disease (IBD). The author examined the association between IBD and CRC risk using data from 44799 patients with IBD and findings of 582 CRC cases and 14 colon cancer cases in 13 cohort studies,11 of which reported risk estimates for the male-female mixed population. Inflammatory bowel disease was identified as a risk factor for CRC if left untreated (Johnson et al., 2013).

Postmenopausal hormone therapy (HT). The authors observed significant heterogeneity ($p = 0.04$) and nonlinearity ($p < 0.001$) between current HT use and CRC, using 765 colon cancer cases and 1441 CRC cases among current HT users and never users, as reported in 7 studies. There may be reduced risk of CRC with HT because of the low *p* value (Johnson et al., 2013).

In a study about the correlation between CRC risk and aspirin/NSAID use, there was no statistical significance (Johnson, et al., 2013).

Processed meat. There was no statistically significant linear trend between processed consumption and CRC ($p = 0.28$) (Johnson et al., 2013).

Red meat. There was a significant positive correlation between CRC and red meat consumption (*RR*=1.13 per 5 servings/wk, 95% *CI*: 1.09–1.16). A significant linear dose-response relationship between the risk of colon cancer and red meat consumption (*p*=0.006) was detected (Johnson et al., 2013).

Fruit. Fruit consumption has some evidence of nonlinearity (*p*=0.02) association between fruit consumption and CRC (Johnson et al., 2013). There is a strong association of fruit intake with reduced risk of developing CRC in both men and women (Lee, Shin, Oh & Kim, 2017).

Vegetables. There is a significant inverse association between vegetable consumption and CRC (*RR* = 0.94 per 2 servings/day, 95% *CI*: 0.91–0.98) and (*RR* = 0.86 per 5 servings/day, 95% *CI*: 0.78–0.94) (Johnson et al., 2013). Lee, Shin, Oh & Kim, (2017), found that a high intake of vegetables reduces the risk of CRC.

Diagnosis of CRC. The diagnosis of CRC is done by colonoscopy examination, a form of endoscopic examination that allows a visual view of the colorectal segment of the large intestine and afford the clinician the opportunity to obtain suspected cancer biopsy for histological laboratory examination (George & Rockall, 2017). The computed tomography (CT) scan also be used for both diagnosis and evaluation of fistula and abscess formation which may locally complicate the CRC. The CT could be used to check for metastatic spread to organs like the liver or lungs (George & Rockall, 2017).

Metastases. CRC has the capability to metastases to extra intestinal sites like liver, lungs, and peritoneum and recurrence are seen in the brain, peripheral lymph nodes, bone, and thyroid gland (Augestad, Merok & Ignatovic, 2017). The mechanism by which

this occurs is not fully understood despite decades of research studies (Augestad, Merok & Ignatovic, 2017). There are metastases predictors such as sex, age, TNM stage, Tumor morphology, histologic grade, Carcinoembryonic antigen levels, Lymph node harvest, Tumor invasion in lymphatic and venous vessels, perineural invasion, and tumor location.

Sex. Male sex has a poor prognosis compared to the female sex. Also, men have higher incidence rate but lower survival rate after curative surgery (Augestad, Merok & Ignatovic, 2017).

Age. Age is regarded as an independent CRC risk factor with reduced survival rate after curative surgery as the age increases (Widdison, Barnett & Betambeau, 2011).

Morphology. CRC are histologically mainly adenocarcinomas in origin, arising from the glandular epithelium of the colon and rectum. Adenocarcinomas CRC has histologic subtypes like mucinous adenocarcinoma (5%-15%) and signet ring cell tumors (1%). Younger individual, advance stage cancer, poor outcome and lower survival rate commonly found in signet ring cell adenocarcinoma compared to non-signet adenocarcinoma CRC (Augestad, Merok & Ignatovic, 2017). However, its only in rectal cancer that the Mucinous adenocarcinoma is also associated with young age and lower survival rates, and there is no effect on survival in colon cancer (Augestad, Merok & Ignatovic, 2017).

Histologic grade. The histologic grade and tumor differentiation are described by TNM classification. The more differentiated a tumor, the slower growth and the spread (American Cancer Society, 2017). When a tumor is well-differentiated, it is designated as G1tumor, moderately differentiated tumors as G2 while a poorly and undifferentiated

tumors are designated G3 and G4, respectively. The higher the tumor's histologic grade, the worse the prognosis than G1 and G2 tumors (Augestad, Merok & Ignatovic, 2017).

Lymph node harvest. The more the harvested lymph node, the higher the risk of possible recurrence in both node positive and negative disease. There is associated improved survival with the number of lymph node recovered. Individuals with less than eight nodes have 62% for 5-year survival rate whereas those with more than 17 lymph nodes had a 76% 5-year survival (Augestad, Merok & Ignatovic, 2017).

Tumor invasion in lymphatic and venous vessel. This represents the main route of hematologic and lymphatic tumor metastases. This is dependent on the frequency of the spread, a number of tumor blocks. The author found a positive association between lymphatic invasion, tumor budding, depth of the tumor, poor differentiation, and lymph node metastases but inconclusive effect on the survival rate. Venous invasion is found to be associated with advanced T category and tumor depth and is regarded as an independent prognostic marker of extra intestinal metastases and reduced survival (Augestad, Merok & Ignatovic, 2017).

Perineural invasion. This is a new path, and it refers to the direct growth of cancer into the perineum of autonomic nerves inside of the superior and inferior mesenteric nerve plexus (Augestad, Merok & Ignatovic,2017).

Tumor location. Tumors of the right colon, left colon or rectum (Figure1) are the risk factor for metastases and better survival outcome. The left colon has 70% chance of having liver metastases while rectal cancer has over 200% of recurrence or develop lung

metastases when compared to the right colon cancer (Augestad, Merok & Ignatovic, 2017).

Carcinoembryonic antigen. Carcinoembryonic antigen (CEA) is associated with high preoperative levels which are indicative of risk of CRC recurrence. CEA has high specificity but low sensitivity to detect CRC recurrence in isolation and could only be used as a surveillance test (Augestad, Merok & Ignatovic, 2017).

Staging and imaging of colorectal cancer. The CRC cancer stage at diagnosis during the presentation is the determinant factor for the outcome. CRC staging is based on the international standard referred to as the TNM classification where T represents Tumor, N is for lymph node, and M is for extra-intestinal metastases (George & Rockall, 2017). The prognosis of CRC is dependent on the invasiveness of the tumor (T), the extent of regional lymph node (N) involvement and the presence of distant extra-intestinal metastases (M). Hideki et al., (2012) emphasized that the TNM classification is a reliable index for prognostic and better treatment plan for individuals having malignant tumors.

Clinical staging is based on findings from colonoscopy, computed tomography (CT) scan of the chest abdomen and pelvis and magnetic resonance imaging (MRI) scan of the pelvis for rectal tumors (George & Rockall, 2017). Conflicting liver lesions may need Ultrasound of MRI for assessment. Positron emission tomography (PET) scan may also be helpful in determining sites of disseminated disease. Diagnosis is usually by colonoscopy examination (George & Rockall, 2017).

Wolpin and Mayer, (2008) presented the TNM Staging System for Colorectal Cancer as follows:

Primary tumor (T)

Tx Primary tumor cannot be assessed

Tis Carcinoma in situ

T1 Tumor invades submucosa

T2 Tumor invades muscularis propia

T3 Tumor invades through the muscularis propria into the subserosa

T4 Tumor directly invades other organs or structures, or perforates visceral Peritoneum

Regional lymph nodes (N)

Nx Regional lymph nodes cannot be assessed

N0 No regional lymph node metastases

N1 Metastases in one to three regional lymph nodes

N2 Metastases in four or more regional lymph nodes

Distant metastases (M)

Mx Presence or absence of distant metastases cannot be determined

M0 No distant metastases detected

M1 Distant metastases detected

Stage Grouping and Five-year Survival

Stage TNM classification Five-year survival

I T1–2, N0, M0 > 90 %

IIA T3, N0, M0 80–85%

IIB T4, N0, M0 70–80%

IIIA T1–2, N1, M0 65–80 %

IIIB T3–4, N1, M0 50–65 %

IIIC T1–4, N2, M0 25–50 %

IV T1–4, N0–2, M1 5–8 %

Wolpin & Mayer, (2008) reported TNM classification as the most frequently used staging system based on three criteria: the depth of the bowel wall tumor intrusion, the extent of regional lymph node invasion, and extra intestinal metastases. The depth of tumor intrusion refers to the T stage and ranges from T1 (intrusion into the submucosa) to T4 (intrusion into the serosa or adjacent structures). The more the tumor intrusion increases, the higher the risk of spreading to the lymph nodes and to extra intestinal sites (Wolpin & Mayer, 2008). The pathologic review of immediate lymph nodes shows three N categories: N0 (no lymph nodes involvement), N1 (involve 1–3 lymph nodes), and N2 (involve more than three lymph nodes). Wolpin & Mayer (2008) emphasized the importance of adhering to the recommended guideline of identifying 12 or more lymph nodes in the resected specimen regional lymph nodes to prevent a poorer outcome in patients with node-negative and node-positive disease due to under- assessment, staging and consequently exclusion of effective adjuvant treatment.

Treatment

CRC treatment can be surgical and systemic using chemotherapy like fluoropyrimidines for example intravenous fluorouracil, oral fluoropyrimidines, adjuvant

therapy with fluoropyrimidines for stage III colon cancer, stage II colon cancer and adjuvant therapy with fluoropyrimidines for stage II and stage III rectal cancer, irinotecan, oxaliplatin, angiogenesis inhibitors, epidermal growth factor receptor inhibitors and combine targeted therapy (Wolpin & Mayer 2008).

Fluoropyrimidines: intravenous fluorouracil is the main stay of systemic chemotherapeutic treatment for CRC administered in combination with leucovorin and acts via the inhibition of the enzyme thymidylate synthetase found in pyrimidine nucleotide synthesis. Fluorouracil accounts for over 50% of tumor shrinkage accounting for overall survival outcome, and 20% of individual with metastatic colorectal cancer will have 50% tumor size reduction and survival rate improvement from 6months to 12 months (Wolpin & Mayer, 2008). It is pertinent to state that fluorouracil is not without side effect and these include neutropenia and stomatitis with five weeks every day bolus fluorouracil and leucovorin, diarrhea with bolus fluorouracil and leucovorin is given for six to eight weeks and hematologic, gastrointestinal effect with hand and foot syndrome and tender erythematous rash of the palm and soles when administer as continuous infusion (Wolpin & Mayer, 2008). Oral fluoropyrimidines was initially ineffective from poor gastrointestinal mucosa absorption until it was modified to undergo enzymatic transformation to fluorouracil and has a similar side effect of hand and foot syndrome (an example is Capecitabine). Tegafur is a more improved form that has better gastrointestinal mucosa absorption.

Adjuvant therapy with Fluoropyrimidines for stage III colon cancer: The use of adjuvant therapy in stage II colon cancer is not very clear for which it uses was not

recommended as routine in the stage II disease. However, the stage II disease with T4 tumor penetration, bowel perforation, or clinical bowel obstruction may benefit from its use (Wolpin & Mayer, 2008).

Irinotecan: this is a derivative of semi synthetic natural alkaloid camptothecin. It acts through the blockage of the enzyme topoisomerase I, which catalyzes the breakage and rejoining of DNA strands during DNA replication, SN-38 leading to the breakdown of DNA which enhances cell death. Side effect includes diarrhea, myelosuppression, alopecia and elevated serum bilirubin for which reason is never administered to patients with hyperbilirubinemia (Wolpin & Mayer, 2008).

Oxaliplatin: this is a product of diaminocyclohexane platinum compound that acts by producing DNA adducts that hinder DNA replication and cause cellular apoptosis. Its benefit is found when in combination with fluorouracil and leucovorin otherwise it is of limited benefit in metastatic colon cancer (Wolpin & Mayer, 2008).

Angiogenesis Inhibitors: they are blockers to the formation of new blood vessels by blocking the vascular endothelial growth factor (VEGF) responsible for blood vessel formation. Bevacizumab (Avastin) is an example used in combination treatment in advanced colorectal cancer, and the side effect includes reversible hypertension, proteinuria, bleeding episode, intestinal bowel perforation, arterial embolism, and reversible posterior leukoencephalopathy syndrome (Wolpin & Mayer, 2008).

Epidermal Growth Factor Receptor Inhibitors: they are agents that block epidermal growth factor receptor (EGFR) and prevent signaling pathway hindering

cellular growth, proliferation, and enhancing program cell death (Wolpin & Mayer, 2008).

Combined Targeted Therapy: the use of combined therapy in the treatment of CRC is ongoing to determine the efficacy of combining monoclonal antibodies with VEGR and EGFR in individuals with metastatic CRC (Wolpin & Mayer, 2008).

Screening: the screening for CRC has increased in the United States, but not enough people are getting screened for CRC (CDC, 2017). The screening process for CRC has been successful in detection due to the early detection of the pre-cancerous colorectal polyps or early-stage cancer prior to the symptoms manifestation, and before the disease grows, metastasized which allow easy to manage treatment that is not expensive, and has better chance of being successful (Marley & Nan, 2016). In 2014, 65.7% of U.S adults were current with CRC screening; 7% was screened but not current, and 27.3% were never screened (CDC, 2017).

It is recommended by the Centers for Disease Control and Prevention (CDC) and the U.S. Preventive Services Task Force that all men and women between the ages of 50 and 75 should be screened for colorectal cancer using fecal occult blood testing (FOBT), sigmoidoscopy, or colonoscopy (Marley & Nan, 2016). Nine out of every ten whose CRC is detected early and promptly treated tend to have five years survival time (CDC, 2017).

FOBT is an annual test that uses guaiac or antibodies to detect blood is a patient's stool sample to confirm colorectal cancer. The stool sample is collected in a specimen sample bottle test kit that returns for laboratory analysis (Marley & Nan, 2016). FOBT is

an inexpensive, easy to administer simple test which enables countries to adopt it as a better national screening test.

Sigmoidoscopy is an endoscopic procedure recommended every five years for direct visualization of the lower colon and rectum using a thin, flexible tube inserted into the rectum to visualize any pre-cancerous polyps or any existing cancer. This test is like colonoscopy except that a longer thin flexible tube is required since the whole length of the colon will be a scope. This procedure also includes polypectomy which is the removal of polyps during the scoping process and is recommended every 10years (Marley & Nan, 2016). Other screening methods include double-contrast barium enema, and the stool DNA test.

It has been shown that screening for a 50-year-old asymptomatic person should start due to the finding of exponential increase risk of colorectal pathogenesis and carcinogenesis (Marley &Nan, 2016). However, despite these recommendations and the successful outcome obtained from screening, certain issues kept the screening rate low in the United States (Marley & Nan, 2016). One of these issues includes the pattern noticed among African Americans which is a combination of enhancing risk and low screening and early presentation with CRC among African American population compared to Caucasian Americans (Marley & Nan, 2016). African American have a higher chance of dying from CRC. According to Marley and Nan, (2016), only 56% of African Americans above the age of 50 are compliant with the recommended screening guidelines, compared to 62% of Caucasians. This finding encouraged the advocacy for early screening age for African American population (Dagusta, Youlden & Baade, 2012).

Prevention and Control

There are many ways the prevention and control of colorectal cancer can be achieved. This includes dietary intake like the regular consumption of fish, fiber, vitamin D, and calcium, as well as aspirin intake and regular exercise, (Marley & Nan 2016). The intake of anti-inflammatory drugs with dietary change prevent the growth of new polyps and curb the growth of existing polyps (Marley & Nan, 2016).

Community /family interventions can be helpful in the prevention of colorectal cancer using family-based support for the person with colorectal cancer such as the use of encouraging words as a motivation measures during screening, exercising, and adopting a healthy diet, can be an effective learning tool to help with carcinogenesis prevention.

Surgical Treatment

Rectal cancer is surgically treated with total mesorectal excision with a high tie of the inferior mesentery artery to remove some lymph nodes with the specimen. It was also recommended that colonic surgery should follow a similar pattern mesocolic excision with dissection of the lymph nodes, but there is limited evidence-based information of the benefit to survival rate (Augestad, Merok & Ignatovic, 2017).

Surgical treatment is usually a radical intervention and include right or left hemicolectomy, segmental colectomy on the transverse or sigmoid colon, subtotal or total colectomy, with digestive continuity reestablished by ileocolic, colo-colic, colorectal or even ileorectal anastomosis or palliative (colostomy or colonic bypass in advanced non-resectable stages). Mastalier et al. (2012), assert that the tumors that have perforated nearby organs may lead to a block resection associated with distal splenopancreatectomy,

gastrectomy, etc. The tumor removal could end with the creation of colostomy for 3-6 months before reestablishing the digestive continuity by closing the colostomy.

Postoperative surveillance: It is reported that 40% of all CRC patients surgically cured will have a recurrence within five years after surgery. 80% of the recurrence will occur within 2years of the surgery, and this raises the issue of enrolling survivors in the post-operative surveillance program to ensure early detection of recurrence. According to Augestad, Merok & Ignatovic, (2017) the purpose of surveillance programs is to enhance early detection of recurrence and provide metastatic salvage surgery, ensure continuous monitoring of the effects of programs, and the social consequences of cancer survivorship. However, the success of this surveillance program although said to be 10% increase in survival, has been questionable by the findings in other studies (Augestad, Merok & Ignatovic, 2017).

Complications of CRC

These include intestinal occlusion by the tumor, localized or generalized peritonitis when the tumor perforates the colon, diastatic cecum perforation, the creation of fistula in a nearby organ like duodenum, small intestine, stomach, and finally death (Mastalier et al., 2012).

Second Primary Cancers

Individuals with CRC have been reported to be at risk of developing other cancers, and these second cancers may adversely affect the prognosis and survival time (Lee et al., 2015). Second cancer which develops after diagnosis with CRC could be either secondary or a second primary cancer. Secondary cancer is metastases of the same

histological cell type with primary cancer while the second primary cancer is of different histological cell type arising after primary cancer. Youlden and Baade, (2011) investigated the relative risk of cancer survivor developing second cancer in the Australian population and discovered that the relative risk of developing an SPC is higher compared to the population. Lee et al. (2015) demonstrated that the incidence of SPCs is higher in patients with CRC than in the general population (IR=1.13).

Secondary cancer occurs when the primary or initial cancer cells metastasize to another part of the body resulting in the formation of a new tumor of the same histological type with original cancer. CRC cells can metastasize from the primary cancer site through the lymphatic cells or the bloodstream to the liver, lung, bones, and other parts of the body (National Cancer Institute, 2017). Symptoms depend on the specific part of the body with the metastasis.

Lee et al. (2015) determined an increased risk of developing a second primary malignancy in a Taiwanese CRC population. Second cancers of the CRC were excluded to rule out the secondary cancer of the same histological origin. Results indicated excess risk for cancer of bladder, stomach, kidney, lung, prostate, ovarian, breast, thyroid and endometrium (Evans, et al. 2002, Ahmed et al.,2006, Youlden & Baade, 2011),

Lee et al. (2015) investigated the incidence of SPC among Taiwanese population and identified independent risk factor of SPC to include Age, men, COPD, cirrhosis, and dyslipidemia. The present percentage of SPC in the total number of cancers ranges from 0.73% to 11.70%, and the trend is increasing (Sun et al., 2015). Lee et al used Multivariate analysis to show that age ≥ 70 years (hazard ratio [*HR*]=1.40, 95%

CI=1.32–1.50; P<0.001), men (*HR*=1.44, 95% *CI*=1.35–1.53; *P*<0.001), liver cirrhosis (*HR*=2.05, 95% *CI*=1.77–2.39; *P*<0.001), COPD (*HR*=1.21, 95% *CI*=1.12–1.30; *P*<0.001), and dyslipidemia (*HR*=1.16, 95% *CI*=1.07–1.26; *P*=0.001) remained significant independent predictors of cancer development (Lee et al., 2015). Oritz-Mendoza et al. (2016) in a study done in Mexico showed that obese females are more significantly affected than males raising the question of the impact/roll of the obesity induced metabolic syndrome in causing SPC among female CRC survivors. Dasgupta, Youlden & Baade showed that CRC survivors in their cohort had a significantly higher risk of developing subsequent colorectal (*SIR* = 1.47, 95% *CI* 1.30-1.66) or non-colorectal cancers (*SIR* = 1.24, 95% *CI* 1.18-1.31) and the risks were significantly higher for both male and female when compared to population of the same age in Queensland population.

Examples of SPC (Lung, Bladder, Kidney, Gastric, and Endometria Cancers)

Lung cancer: Lung cancer is the leading cause of cancer death and the second most common cancer among both men and women in the United States (CDC, 2017). Cancer starts in the lung and can spread to lymph node or other organs like the brain and other parts of the body as metastases. Lung cancer has two main types, the small cell and non-small cell lung cancer which is more common (CDC, 2017).

Smoking cigarette is the most important risk factor that is linked to 80-90% of lung cancer and can cause cancer in any part of the body (mouth, throat, esophagus, stomach, colon, rectum, liver, pancreas, larynx, trachea, bronchus, kidney, and renal pelvis, bladder and cervix and acute myeloid leukemia). Smoking is a cause of CRC

(American Cancer Society, 2017). The cigarette has 7000 toxic chemicals that are mainly poisonous (CDC, 2017). Smokers are 15 to 30 times likely develop lung cancer or be killed by lung cancer than individuals that are non-smokers.

Second-hand smoke from other people's cigarette, pipe, or cigars is also a risk factor for lung cancer. Radon gas that cannot be seen, smell or taste naturally trapped in houses and dirt can cause lung cancer. Other work-related exposures like asbestos, arsenic, diesel exhaust, silica, and chromium are associated with lung cancer (CDC, 2017). Personal of family history of lung cancer could be a risk factor. Having a relative brother, sister, parent, or children that have had lung cancer is a risk factor. Radiation to the chest in a cancer survivor can predispose the patient to develop. The role of diet is still ongoing but drinking arsenic in water clear as a risk factor for lung cancer.

Jian et al (2013) conducted a study in Taiwan and found an association between lung adenocarcinoma and CRC in both sexes in cross-township but not in the cross country. The author found a significant correlation between colorectal cancer and lung adenocarcinoma in men (r=0.526, P=0.021), but not in women.

Endometrial Cancer: Endometrial cancer is the cancer of the endometrium that originates from cells lining the inner part of the uterus (the endometrium). Endometrial cancer represents the most common cancer found in the female reproductive system and accounts for 6% of all female cancers in the United States [National Cancer Institute (NCI), 2014]. Endometrial cancer can be squamous cell carcinoma, adenocarcinoma, and undifferentiated carcinoma, based on the histologic cell type seen under the microscope (American Cancer Society, 2015). There are risk factors associated with increased risk of

endometrial cancer such as genetics, obesity, early menarche, postmenopausal estrogen therapy, tamoxifen use, and late menopause (NCI, 2014). The incidence rate of Endometrial cancer among the African American women is higher compared to White women, and the mortality rate is twice other ethnic/racial population (NCI, 2014). Oliver et al. (2001) shows that African American women are likely to present late with advanced stage cancer and more likely to have non-endometrioid, high-grade tumors at the time of diagnosis compared to Caucasian women who have similar demographics. Menopausal women account for most individuals diagnosed with endometrial cancer, with an average age of diagnosis of 60. Oncolink, (2015) reveal that Endometrial cancer is less common in women less than 40 years of age (5-10%). Patients with an initial diagnosis of CRC may have an increased risk of developing a type of endometrial cancer later (Singh, Singh, Miller, Strum & Coyle, 2012). CRC is associated with endometrial cancer, and 10% of endometrial cancer could be due to hereditary none- polyposis CRC while the majority is not genetic. Singh et al.(2012) conducted a CRC screening study involving 267 women with endometrial cancer, 39% were less than 60years at diagnosis, median age was 66, and 25 (9.4) of endometrial cancer patients has family history of CRC, 125 women had CRC screening with 12 (9.6%) being screened for CRC within 1 year of diagnosis and 33 (26.4%) screened for CRC before endometrial cancer diagnosis. 142 women (53.2%) did not have CRC screening reported, and of those women screened, ten had adenomatous polyps with one having polyps that are greater than 1cm, four had tubulovillous histology, and three had CRC. This reinforces the association between CRC and endometrial cancer.

Gastric cancer: Gastric cancer is a slowly growing tumor that arises from the inner lining of the stomach and may not be detected. Cancer can start in the different part of the stomach like gastro esophageal junction, cardia and can metastasize in different ways. These cancers are capable of growing and invading surrounding organs and spreading to distance organ through the invasion of lymph vessels and surrounding lymph nodes and blood stream in advance case spreading to the liver, lungs, and bones (American Cancer Society, 2017). Symptoms include weight loss due partly to poor appetite, abdominal pain, nausea, vomiting with or without blood, vague abdominal discomfort, heart burn, feeling of fullness on eating small meal, swelling or fluid accumulation, anemia (American Cancer Society, 2017). Gastric cancer has different histological cell types like adenocarcinoma, lymphoma, gastrointestinal stromal tumor (GIST), Carcinoid tumor and others like squamous cell carcinoma, small cell carcinoma, and leiomyosarcoma. Early detection is possible using upper endoscopy to detect cancer, and a biopsy can be obtained for histological cell type analysis. There is a place for imaging test using x-ray, magnetic fields, sound waves, or radioactive substances to create pictures of the body. This will help detect the lesion and its location, assess its spread and what treatment option will be effective. Surgical intervention is the main stay of treatment supported by adjunct treatment like chemotherapy, targeted therapy, and radiation therapy. Jian et al. (2013) in a study in Taiwan reported that significant cross-country correlations in colorectal cancer (r=0.918, P<0.001), gastric cancer (r=0.985, P<0.001) and lung adenocarcinoma (r=0.685, P=0.001) were observed between men and

women. There were links of lung adenocarcinoma and gastric cancer (r=0.122, P=0.024) and colorectal cancer (r=0.128, P=0.018) in women.

Bladder cancer: Each year in the United States, about 55,000 men and 17,000 women get bladder cancer (CDC, 2017). Men are three times likely to have bladder cancer than women, with the white Caucasian having the highest rate of getting bladder cancer (36.4 per 100,000 men), followed by black men (19.0), Hispanic men (18.6), American Indian/Alaska Native men (14.8), and Asian/Pacific Islander men (14.0) (CDC, 2017). Among the women, white women had the highest rates of getting bladder cancer (9.0 per 100,000 women), followed by black women (6.4), Hispanic women (4.8), Asian/Pacific Islander women (3.7), and American Indian/Alaska Native women (3.4) (CDC, 2017). According to 2014 statistic, 15,775 (11,291 men and 4,484 women) died from bladder cancer (CDC, 2017).

The primary risk factor associated with bladder cancer development is smoking and other risk factors include chronic urinary tract infection, gene mutation, family history of bladder cancer, exposure to chemicals like dye, metal, and petroleum at work, use of chemotherapy drugs, ingestion of good water contaminated by arsenic and use of chines herbal preparation known as Aristolochia fangchi (CDC, 2017). The risk for bladder cancer can be reduced by not smoking.

The common symptom is blood in the urine, frequent urination and pain while urinating. There could be back pain and pelvic pain. In a study conducted by Calderwood, Huo, & Rubin (2008) the risk for developing urologic cancer increased after a diagnosis of CRC (SIR, 1.24; 95% CI, 1.20-1.28) but the highest risk is for subsequent

renal pelvis and ureteral cancers in patients with a CRC diagnosis before the ages of 50 to 60 years or with multiple primary CRCs.

Kidney cancer: The most common kidney cancer is the renal cell carcinoma account responsible for 90% of all kidney cancer cases, 2.4% of all adult cancer cases and mortality of 140,000 death annually (Emory Winship Cancer Institute, 2016). Renal cell carcinoma (RCC) is common in males than females and varies in geographic variation with a higher rate in Europe and North America than Asia and South America (Emory Winship Cancer Institute, 2016). The direct cause of kidney cancer is unknown, but there are risk factors like smoking, obesity, genetic predisposition, and hypertension. Men who smoke have 50% more risk of developing RCC than non-smokers. Obesity increases the risk of developing RCC by 24% in men and 34% for women (Emory Winship Cancer Institute, 2016).

RCC is detected on physical examination and using CT scans, Ultrasound, PETscan and blood test. Thompson et al. (2006) in their study 2,188 (80.4%) participants had a clear cell, 378 (13.9%) had papillary, and 128 (4.7%) had chromophobe renal cell carcinoma. Patients with papillary renal cell carcinoma were significantly more likely to have colon cancer ($p = 0.041$). This shows there is a possible association between colon cancer and RCC.

Metabolic Syndrome (MetS)

Also, known many names such as syndrome X, metabolic disease, insulin resistance syndrome or dysmetabolic syndrome. MetS is a combination of conditions that when taken together can increase the risk of development of heart disease, stroke,

diabetes, stroke, and other chronic health problems like cancer. Moore, Chaudhary & Akinyemiju, (2017) state that the diagnosis of MetS is made when any three of the following five components are present:

- Abdominal obesity (apple-shaped).
- Hypertension
- Dyslipidemia- Low levels of HDL cholesterol in the blood
- Dyslipidemia- High levels of triglycerides in the blood
- Diabetes mellitus type 2.

Metabolic syndrome is not a diagnosis but serious health condition (America Heart Association, 2015). MetS affect 30% of the U.S population. MetS affect 4 out of 10 Americans as they get to 60 and 70 years. This syndrome is becoming more common in the United States. Over 30 percent of adult Americans are estimated to have MetS (Moore, Chaudhary & Akinyemiju, 2017). The prevalence of MetS has gradually increased since 2007 from 25.3% to 34.2% in 2012 (Moore, Chaudhary & Akinyemiju, 2017). The prevalence of MetS was higher in women compared to men between 2003 to 2012 and considering race/ethnicity, the highest prevalence was seen in Hispanics, followed by non-Hispanic whites and blacks (Jong, 2015). MetS increasing prevalence has been reported among Chinese elderly (Liu et al., 2013) and is fast becoming a serious global challenge.

According to Weil (2017), there is no physical symptom for MetS but the symptoms of its components. Thus, there is obesity, hypertension, the clinical symptom of diabetes resistance, etc. There is high level of insulin which will cause chronic

inflammation, damage thickening of the blood and arterial wall damage (Weil 2017). Some studies have found sex differences in risk predictors of MetS, which could suggest possible role of sex hormone levels and androgen/estrogen balance in determining MetS (Hadaegh et al., 2017; Kim HA, Lee SY, Kwon HS, Lee SH, Jung MH et al. 2013). MetS is a chronic problem which develops if not corrected.

The National Cholesterol Education Program's Adult Treatment Panel III report (ATP III) was used by WHO and provided the criteria for diagnosis of MetS based on the following criteria:

- A waist circumference of more than 40 inches for men and over 35 inches for women).
- Fasting glucose of 100 mg/dL or more or on medication high blood glucose
- Fasting blood triglycerides of more than 150 mg/dL or on medication for high triglycerides treatment.
- Low HDL cholesterol levels or on medication for low HDL cholesterol treatment: 40 mg/dL for men and < 50 mg/dL in women.
- High blood pressure >140/90 mmHg or taking medication for hypertension.

Abdominal obesity is the increased waist circumference and the form of obesity that is most frequently associated with MetS (American Heart Association, 2004).

Dyslipidemia is characterized by raised triglycerides and low concentrations of HDL cholesterol obtained through Lipoprotein analysis (AHA, 2004). Abnormal lipoprotein analysis obtained are atherogenic and include low HDL level, increased remnant lipoproteins, elevated apolipoprotein B, and small LDL level (AHA, 2004).

Elevated blood pressure is commonly found in insulin-resistant individuals and it is strongly associated with obesity due especially to its contribution to the arterial thickness in older individuals (AHA, 2004).

Insulin resistance is common among many people with metabolic syndrome, and it strongly associates with other metabolic risk factors. Chronic insulin resistance enhances the development of glucose intolerance, another emerging risk factor.

Another important contribution to MetS is the proinflammatory state, clinically described by the elevations of an acute-phase protein like C-reactive protein (CRP) which is characteristically found in individuals with metabolic syndrome (AHA, 2004; Chen, Yen, Huang, Lee, Hsia & Lin 2012). Obesity is a cause of elevated CRP level among other causes due to the release of inflammatory cytokines from the numerous obese individual's adipose tissues (AHA, 2004).

MetS are also associated with a prothrombotic state, characterized by increased plasma plasminogen activator inhibitor (PAI)-1 and fibrinogen. The levels of Fibrinogen and CRP rises in response to a high-cytokine state to establish the possible metabolic connection between prothrombotic and proinflammatory states (AHA, 2004).

Measuring levels of CRP is useful as a marker in some disease to determine progress or effectiveness or treatment and an increased basal level of CRP predisposes to increase the risk of diabetes, hypertension, and cardiovascular disease (Jain, Gautam & Naseem, 2011). CRP (CRP rs1205 AA genotype) is associated with the increased risk of development of colon and rectal cancer (Slatter et al., 2011).

MetS component causes cells to lose sensitivity to insulin accounting for the insulin resistance and causing a buildup of glucose in the blood. The pancreas repeatedly compensates by producing more insulin causing the characteristic effect that is responsible for MetS (Weil, 2017). The high insulin level triggers a stress response that causes the release of cortisol, the body's long-acting stress hormone. This, in turn, trigger an inflammatory reaction that damage healthy tissue if left unchecked (Weil, 2017).

Foods enhancing obesity and insulin resistance may enhance MetS. These include sodas, ice cream, jams, jellies, salad dressing ketch up, etc. (Weil, 2017). Sleep apnea also contributes to the development of MetS (Weil, 2017).

The cause of MetS is unknown, but certain factors have been implicated in the etiology of MetS including factors such as dietary intake and lifestyle.

There are three known sources of origin of MetS: obesity and disorders of adipose tissue; insulin resistance; and groups of independent factors like molecules of hepatic, vascular, and immunological in origin which arbitrates for some component of MetS. There are other contributing factors like age, proinflammatory condition and hormonal changes (AHA, 2004).

The increasing incidence of obesity is considered to be responsible for the increasing prevalence of MetS (AHA, 2004). Obesity is known to enhance high serum cholesterol, hypertension, hyperglycemia and low HDL and is consistent with metabolic risk factor (AHA, 2004). In obesity, there are lots of adipose tissue that produce different products like adiponectin, cytokines, non-esterified fatty acids (NEFA), and PAI-1 which further aggravate the risk factors. Insulin resistance is enhanced by the high level of

NEFA which fills the liver and the muscle with lipid. Obesity is usually accompanied by high CRP levels which encourage increase cytokine and proinflammatory state (AHA, 2004). A high PAI-1 promotes the prothrombotic state, whereas low adiponectin levels in association with obesity further worsening metabolic risk factors (AHA, 2004).

Insulin resistance increases as the body fat level increases. Obesity (BMI ≥30 kg/m2) predisposes to postprandial hyperinsulinemia with a comparative low insulin sensitivity, although this sensitivity varies among the obese population (AHA, 2004).

Role of Independent Factors in Metabolic Syndrome

There are independent factors that mediate each risk factors of MetS such as genetic and acquired factors which introduce some variability in the expression of these risk factors (Roberts, Hevener & Barnard, 2013). Blood pressure and lipoprotein metabolism are regulated by genetic differences while glucose levels depend on the insulin-secretory ability and insulin sensitivity (Hardy, Czech & Corvera, 2012). This variation constitutes an important factor in the etiology and pathogenesis of metabolic syndrome.

Another contributing factor to the pathogenesis of MetS is the increasing age which provides answers to why MetS prevalence increases with advancing age (AHA, 2004). A proinflammatory state has been directly associated with the etiology of insulin resistance, and atherogenesis. Endocrine factors have also been linked to abnormalities in distribution of the body-fat and its indirectly association to metabolic syndrome shows the composite nature of MetS pathogenesis (AHA, 2004).

The aim of the treatment is to eliminate the risk factors: stop smoking, treat diabetes, control the blood pressure, treat blood lipid abnormality, start exercise and ensure healthy dietary intake (America Heart Association, 2015). Elevated blood pressure should be treated using lifestyle modification therapy. The use of antihypertensive drugs in the guidelines for hypertension is recommended as there is no specific type of antihypertensive that is specific for treatment of individuals with MetS (Moran et al., 2015; AHA, 2004).

Dyslipidemia should be treated using LDL-lowering drugs like statins to reduce apolipoprotein B containing lipoproteins which is beneficial in MetS individual due to reduced risk of cardiovascular disease (CVD) event (AHA, 2004). Treatment with fibrates combined with statin gives a better outcome in treating abnormal lipoprotein level (Agouridis, Rizos, Elisaf & Filippatos 2013; AHA, 2004).

There is no drug treatment that targets PAI-1 and fibrinogen. The use of antiplatelet therapy like low-dose aspirin has been described for primary prevention of CVD in MetS (Stegeman, Bossuyt, Yu, Boyd & Puhan 2015; AHA, 2004).

Hyperglycemia predisposes individuals with MetS to high risk for CVD. Hypoglycemic agents should be used to reduce the A1c to levels below stipulated normal value in addition to using lifestyle modification (AHA, 2004, American Diabetes Association, 2013).

The use of lipid-lowering drugs like statin or fibrates reduces the proinflammatory state and reduce CRP levels (AHA, 2004, Chen, et al., 2012).

Summary and Conclusion

The incidence of CRC is increasing while the mortality is reducing due to the screening test and better treatment approach which now is predisposing them to a higher risk of developing SPC (Guan et al., 2015). SPC among CRC survivors is a new cancer challenge that is threatening CRC survivors especially with the first five years after primary cancer (Yang et al 2017). A lot is much yet to be learned about the pathogenesis of the origin of SPC and the factors that trigger the malignancies. In this chapter the current state of knowledge for the variables that were used in this study was reviewed, including the component of MetS (abdominal obesity, hypertension, hyperglycemia, hyperglyceridemia, dyslipidemia), age, gender, and ethnicity as risk factors for second primary cancers among CRC survivor's population.

MetS have been implicated in association with many diseases which include CRC and its association with SPC. The site of the SPC has been influenced by the anatomic site of primary cancer as shown in figure1 below (Raj et al., 2011). The common high-risk sites for SPC are those with origin from the embryonic endoderm (Yang et al., 2017). A right-sided colon cancer (ascending colon in figure1) was linked with SPC of the stomach, small intestine, pancreas, ureter, pelvis, renal, breast, and thyroid. The left-sided primary colon cancer (descending colon in figure1) was linked with secondary CRC, whereas rectal cancer was linked with SPC of the lungs, vagina, and urinary bladder (Yang et al., 2017).

The tumor site was important as the risk for developing an SPC was higher only among those whose initial tumor was in the descending colon (SIR=1.6; 95% CI: 1.3 to 2.0) compared to the proximal colon (SIR=1.4; 95% CI: 1.3 to 1.6) (Raj, et al., 2011).

The large intestine is the site where inflammation takes place and influences carcinogenesis through a complex mechanism (Slattery et al., 2011). One of the mechanisms highlighted is via the activity of the CRP an inflammation biomarker triggered by an increase in plasma cytokine level IL6 which increases the level of CRP associated with high risk of CRC whose strong determinant is BMI (Slattery et al., 2011).

Obesity has numerous adipose tissue which predisposes to having both high CRP and promote high hyperglycemia, hypertension, low HDL and serum cholesterol, which is compatible with metabolic risk factor (AHA, 2004; Kaur, 2014). Obesity in conjunction with MetS has been implicated as index of worse survival in early stage CRC (Cespedes-Feliciano et al., 2016).

Gender plays a role in SPC among CRC survivors as the incidence of SPC among CRC survivor was higher in females (SIR=1.5; 95% CI: 1.3 to 1.6). In Europe, both age and gender has been found to influence the prevalence and prognostic significance of MetS (Vishram et al., 2015).

The enormous risk of developing SPC among CRC survivors associated with obesity, insulin resistance or independent factors induced MetS. The poorer prognosis for individuals with SPC, particularly those with endometrial, kidney, lung, stomach, and bladder cancer, necessitate a better understanding of the risk factors associated and adoption of surveillance in the CRC survivor population. The results obtained from this

study will aid clinicians in determining appropriate screening and importance of timely treatment and interventions to reduce mortality and improve health outcomes.

Chapter 3 will focus on the choice of the appropriate research design for the study and the rationale for the design, the power analysis engaged and sample size estimate, the target population, the sampling and sampling methods, instrumentation used and materials, secondary data collection and process of analysis using the dependent variable, independent variables, and the research questions. The chapter ends with quality assurance and how human subjects are protected.

Chapter 3: Research Method

Introduction

Colorectal cancer survivors are known to have other health issues, but the major concern is to have to deal with another cancer (American Cancer Society, 2017; Raj et al., 2009). Science has achieved some progress in the management of CRC by the introduction of early screening intervention, which has enhanced survival rate. However, the euphoria of this success due to declining mortality but increasing incidence hardly ended before researchers started detecting the emergence of lethal and life-threatening cancer types among these survivors (Guan et al., 2015). These emerging cancers are the SPC associated with CRC from the bladder, kidney, stomach, lungs, and endometrium. Individuals with previous colorectal cancer are subject to the same risk of cancers types that other people get (American Cancer Society, 2017). The incidence of the SPC among CRC is on the increase (Guan et al., 2015; Lee et al., 2015). The probability of developing SPC was 33% higher (95% CI; 1.12–1.56) for CRC that received surgical treatment and 45% higher (95% CI; 1.29–1.64) after proximal colon cancers relative to rectal cancer (Dasgupta et al., 2012).

MetS has been associated with etiology CRC in the literature due to its complex components (high blood pressure, abdominal obesity, diabetes mellitus, hypertriglyceridemia, hypercholesterolemia), which are health risk factors that act either independently or complimentary in action and effect to cause acute stroke, cerebrovascular accidents, heart attack, and chronic diseases like CRC that can lead to morbidity and mortality (Cespedes-Feliciano et al., 2016). One recent study has revealed

that the more MetS components that are present, the higher the risk of death, even in the absence of obesity (Cespedes-Feliciano, et al., 2016). Individual MetS components show adverse and protective relationships that depend on how they are defined and measured and affect their influence on survival and outcomes due to paradoxical associations with each component, which has led to conflicting survival results (Cespedes-Feliciano et al., 2016). However, there is an existing relationship between obesity associated MetS and CRC as both obesity and MetS have been implicated with worse survival prognosis among early stage (I-III) CRC Patients (Cespedes-Feliciano et al., 2016). MetS is associated with an increased incidence and mortality as well as the risk of colorectal cancer in both sexes, and the risk expressed by the full MetS is not higher to the sum of the MetS components (Esposito et al., 2013). Moreover, obesity associated MetS in a Mexican study has been shown to be associated with SPC, especially in obese Mexican women (Oritz-Mendoza et al., 2016).

Guan et al. (2015) reported an increased incidence of SPC among CRC survivors aged 20 to 40 years, American Indian/Alaska Native due intensive treatments for initial CRC, normal aging, and continuous exposure to carcinogens.

The incidence of SPCRC was found to be higher in females (SIR = 1.5; 95% CI: 1.3 to 1.6) and Hispanics (SIR = 2.0; 95% CI: 1.7 to 2.4) with primary colon cancer to confirm that the risk of SPC among CRC survivors is higher with gender (female) and ethnicity (Hispanic) than the general population (Raj et al., 2009). A similar study done in Mexico found an association between obese female Hispanics and the development of SPC among CRC survivors (Ortiz-Mendoza & De la Fuente-Vera, 2014). The

identification of incidence characteristics of SPCs is essential for continuous cancer surveillance among CRC survivors (Guan et al., 2015).

The purpose of this study was to fill the gap in the literature by demonstrating the existence of an association between MetS and SPC among colorectal cancer survivors/deceased. I used a quantitative research method and selected participants with SPC after CRC into a cohort group and a control group with CRC treatment but no second primary cancer as another cohort. I investigated the association between MetS with both groups and compared the results.

In this chapter, I describe the research design as well as the rationale with an in-depth description of the study methodology, including population, sampling, and sampling procedures of the secondary data. I also include the operationalization of constructs, instrumentation, data analysis plan, as well as the threats to internal and external validity and ethical procedures.

Research Design and Rationale

The purpose of this study was to fill the gap in the literature by demonstrating any existing association between MetS and/or its components and SPC among CRC survivors/deceased. I studied three main areas that included MetS and SPC in CRC survivors/deceased. The independent variables were hypertension, abdominal obesity, diabetes, dyslipidemia, and hypertriglyceridemia, and the dependent variable was SPC among CRC survivors/deceased.

Research Questions

RQ1: Is there an association between hypertension and SPCs in CRC patients?

Hypotheses

H01: There is no association between hypertension and SPCs in CRC patients.

Ha1: There is an association between hypertension and SPCs in CRC patients.

Research Question 2

RQ2: Is there an association between abdominal obesity and SPCs in CRC patients?

Hypotheses

H02: There is no association between abdominal obesity and SPCs in CRC patients.

Ha2: There is an association between abdominal obesity and SPCs in CRC patients.

Research Question 3

RQ3: Is there an association between dyslipidemia and SPCs in CRC patients?

Hypotheses

H03: There is no association between dyslipidemia and SPCs in CRC patients.

Ha3: There is an association between dyslipidemia and SPCs in CRC patients.

Research Question 4

RQ4: Is there an association between diabetes and SPCs in CRC patients?

Hypotheses

H04: There is no association between diabetes and SPCs in CRC patients.

Ha4: There is an association between diabetes and SPCs in CRC patients.

Research Question 5

RQ5: Is there an association between hypertriglyceridemia and SPCs in CRC patients?

Hypotheses

H05: There is no association between hypertriglyceridemia and SPCs in CRC patients.

Ha5: There is an association between hypertriglyceridemia and SPCs in CRC patients.

Research 6

RQ6: Is there an association between age, gender, and ethnicity with SPCs in CRC patients?

Hypotheses

H06: There is no association between age, gender, and ethnicity and SPCs in CRC patients.

Ha6: There is an association between age, gender, and ethnicity and SPCs in CRC patients.

RQ7: Is there an association between MetS and SPCs in CRC patients?

Hypotheses

H07: There is no association between MetS and SPCs in CRC patients.

Ha7: There is an association between MetS and SPCs in CRC patients.

The aim of the study was to assess the variables at a particular time, over 6 months after treatment of CRC, and to compare them with CRC survivors with SPC. The first cohort consisted of men and women with a diagnosis and treatment of colorectal cancer without SPC. The second cohort included both men and women with a diagnosis of SPC among CRC survivor/deceased. The variables under study are described in Table 1.

I did not expect any time or resource constraints for this study design choice. However, there was a delay in getting the appropriate dataset for the study. The study was a quantitative retrospective cohort study using secondary data collected over 3 years by the

SEER- Medicare (2011-2013). These data were accessible at a cost to use by researchers after signing a collaboration agreement form

I selected a quantitative cohort study design for this study due to its use in similar studies (see Houser, 2012). The quantitative cohort study design is good at determining relationships between a risk and an outcome, with causality inferred based on varying criteria. The relationship between MetS component risk factors and SPC among CRC disease cannot be tested using an experimental design due to the unethical reason of exposing individuals to risk factors they would otherwise not experience.

The choice of a quantitative study design did not give the opportunity to control some extraneous, modifiable variables; this served as a limitation to this study. Examples of extraneous variables that were not controlled for are genetically induced CRC conditions like familial adenomatous polyposis, hereditary nonpolyposis colorectal cancer, Lynch syndrome, Turcot syndrome, Peutz-Jeghers syndrome, smoking, and alcohol-related CRC.

Table 1

Research Questions (RQ), Independent Variables and Cohort

Research question	Independent variables	Cohort
RQ1	Hypertension	Group of CRC survivors/ deceased Men and women without SPC.
RQ2	Abdominal obesity	
RQ3	Dyslipidemia	
RQ4	Diabetes	Group of CRC survivors/ deceased Men and women with SPC.
RQ5	Hypertriglyceridemia	

RQ6	Age, gender, and ethnicity
RQ7	MetS

Note. In each case, the dependent variable is the diagnosis of second primary cancer (SPC).

Methodology

Study Population

In this study, I used secondary data from the (SEER-Medicare. The SEER-Medicare contains data on the general population as well as clinic-based data. The SEER-Medicare database is used for doing population-based case-control studies to show the causes of cancer among the U.S. elderly (Engels et al., 2011). This database is the product of the electronic merger of SEER and Medicare data (http://healthservices.cancer.gov/seermedicare/). The linkage incorporates name, Social Security number, sex, and date of birth to create a match that is 94% successful to SEER cancer cases for those over the age of 65 with Medicare coverage, while 3% of the elderly are without Medicare coverage, and another 3% lack sufficient information for the merger (Engels et al., 2011). The SEER-Medicare linkage is upgraded every 2 years, and identifiers are removed from the resulting merged files (Engels et al., 2011). The study population was obtained from the dataset of CRC cases reported from 2011 to 2013 of both genders, totaling 58,171 cases (National Institute of Health, 2017).

The SEER-Medicare collects health data from persons across a wide spectrum of CRC risk. These data are from colorectal cancer persons through population-based cancer registries, clinical settings, and community covering 26% of the U.S population.

The study population from the dataset included male and female patients diagnosed with colorectal cancer for over a five-year period from 2011-2013 in the dataset. The dataset provides information on colorectal cancer, age, gender, ethnicity, and any diagnosis of second primary cancer of colorectal cancer like lung, stomach, endometrial, kidney and bladder after an initial diagnosis of colorectal cancer.

Sampling Procedures

The sampling procedure include random selection of participants from 58,171 cases of CRC reported by SEER-Medicare from 2011-2013 period into two cohorts. Cases were compared with a subset (a sample) of the "risk set". The cohort members who initially are at risk could be included in the subset when such member becomes a case especially in cases of SPC. The choice of this method allowed cases that occur later during the follow-up to be eligible for inclusion in the controls for earlier cases (Szklo & Nieto, 2014). For this study, all cases were drawn from the same cohort, and then the correct number of subjects with second primary cancers were selected and then matched with those without second primary cancers.

The study sample was made of adults male and female participants diagnosed with colorectal cancer based on the inclusion criteria which include presence of CRC subjects must have been diagnosed with a colorectal or colorectal cancer-related second primary cancer, lung, endometrium, kidney, bladder, and stomach during the study period.

Sample Size and Power

The sample sizes for the secondary analyses of colorectal cancer and second primary cancers (lung, stomach, kidney, bladder, and endometrial cancers) were restricted by the size of the data set. The population set of CRC cases in the SEER-Medicare are 58,171 cases of both genders reported between 2011-2013 (NIH, 2017). The study was conducted using adequate effect size and statistical power to prevent type 1 and type II errors and to achieve a well representative study that will make the study attain statistical significance. Since I used secondary data, my sample size was all the valid cases in the dataset, therefore a priori power analysis is not needed. After the data analysis, I conducted post hoc power analysis using G*Power calculator (Faul, Erdfelder, Lang & Buchner, 2007) to confirm that the obtained sample size is adequate.

Instrumentation and Materials

This study used archival data from the Surveillance, Epidemiology, and End Results (SEER)-Medicare. The SEER- Medicare dataset is the Program of the National Cancer Institute which provides information on cancer statistics with the intention to ameliorate the cancer problem in the U.S. SEER-Medicare is a secondary data set collected using Health Measures, Multidisciplinary Treatment planning (MTP) questionnaire and Patient-Reported outcomes version of the common terminology criteria for adverse events (PRO-CTCAE) (National Institute of Health, 2017). Health Measures also known as the Person-Centered Assessment Resource (PCAR) is created and validated by National institute of Health (NIH) as an online resource that use four person-centered measurement systems. The Multidisciplinary Treatment Planning (MTP)

questionnaire is used to provide insight into the different ways on how it's used for different kinds of cancers in care delivery organizations to enhance the quality of care (NIH, 2017).

Reliability of Data

The generalizability of research study to the population hinges on reliability and validity among researchers using quantitative study (Houser, 2012). SEER-Medicare ensures the data are reliable by providing a detailed description of research methods, researcher journal, peer examination of procedures and results, and measures of instrument reliability (accuracy and consistency of test instrument and results). The SEER-Medicare database improves data quality and consistency by the centralized system to manage the data which provides support for all main cancer registry functions, including data import, linkage, editing, consolidation, and reporting. (Sun & Trinh, 2015).

Validity of Data

Construct validity is to ensure that the study measures that which researchers said it was intended to measure, or originate the truthfulness of the result (Golafshani, 2003, Bashir, Tanveer & Azeem 2008). The linkage of the SEER-Medicare data is a joint effort of the NCI, the SEER registries, and the Centers for Medicare and Medicaid Services (CMS). The linkage of persons in the SEER data to the Medicare claims was done by NCI and CMS and not by individual researchers to ensure accuracy and reliable of data for the appropriate research. The SEER collects 28% of the US. Population's cancer incidence and survival data from population-based cancer registries (Sun & Trinh, 2015).

Quality improvement represents an integral part of the SEER program through routine audits conducted on many data received from hospitals and external sources (Sun & Trinh, 2015). The SEER-Medicare administrator reported that the following are how quality and validity are maintained through numerous checks performed at each step of the linkage and file preparation; some of the checks include the followin:

1. Compare list of patients received for linkage with Medicare with patients in SEER file.
2. Compare gender, date of death in SEER and Medicare and remove linked patients that don't match on gender or have more than 6 months difference in date of death.
3. Compare counts between linkages, and check that all old patients are in the new linkage. Investigate missing cases.
4. Track number of claim records received to the number of output records from each step of the claims processing and to the final records.
5. Calculate rate of claims per patient by claim type and compare the rates produced for each calendar year.
6. Run sample analysis programs and compare between linkages.
7. Test all extract programs and confirm that patients and their claims from prior linkages are included in new linkage files.

SEER's most up to date file has diagnoses from 1973 to 2012, an approximate 8.6 million cases including 7.8 million malignant cases. The SEER-Medicare contain patient entitlement and diagnosis summary file (PEDSF) contains Cancer files from SEER that

include detail like site, morphology, grade, stage and those that matched Medicare records, including demographic data, Medicare eligibility and coverage, and socioeconomic data that was gathered by the US Census for the census tract where the patient lives (Engels et al., 2011). The summarized denominator (SUMDENOM) file has similar demographic but only 5% of sample Medicare beneficiaries residing in the SEER areas, chosen randomly using the last 2 digits of their Social Security number (Engels et al., 2011).

Data Analysis Plan

This study used only secondary data for analysis. There is HIPAA protection for Data obtained from cancer patients due to confidentiality, and permission was received before accessing SEER-Medicare data after answering series of questionnaires about the study over a period of nine months. The dataset was free of the identification of the patients to prevent compromise of confidentiality. The proposed secondary data for this study was electronically extracted, cleaned to address miscoded, missing data before analysis using SPSS (PASW version 25) (Frankfort-Nachmias & Nachmias, 2008). The reason for using SPSS is due to its ability to handle the analysis of large datasets as well as provide relevant analysis of statistical tests. The independent variables that I proposed to use in this study are presented in Table 2:

Table 2

Variables, Research Questions, and Level of Measurement

Variable name	Research Question(s)	Role	Level of Measurement
Second primary cancers Lung, Stomach, Kidney, Bladder, Endometrial	1, 2, 3, 4, 5	Dependent	Categorical
Age	6	Independent	Continuous
Gender	6	Independent	Dichotomous
Ethnicity	6	Independent	Categorical
Alcohol		Mediating	Dichotomous
Smoking		Mediating	Dichotomous
Genetic/Familiar		Mediating	Categorical
Metabolic syndrome:			
Hypertension	1	Independent	Continuous
Abdominal obesity	2	Independent	Continuous
Dyslipidemia	3	Independent	Continuous
Diabetes	4	Independent	Continuous
Hypertriglyceridemia	5	Independent	Continuous
Metabolic Syndrome	7	Independent	Dichotomous

Descriptive statistics were calculated for each of the study variables in table 3. I used frequencies to describe the dichotomous and categorical variables, while the mean and standard deviation was used for the continuous variables, such as age.

The dependent variable (existence of SPC) was categorical variable with two levels (yes/no). Binomial logistic regression analysis (BLR) is a statistical technique that is used to predict the possibility of categorical or binary or dichotomous outcome variables (Mala, Ravichandran, Raghavan, & Rajmohan, 2010). The independent variables can be either dichotomous (binary) or continuous (interval or ratio in scale).

Multicollinearity was evaluated using simple correlations among the independent variables, and multivariate diagnostics (i.e., standard multiple regression) was used to assess for multivariate outliers and to exclude of outliers or influential cases (Starkweather & Moske, 2011).

BLR was the choice for analysis because there is no need for the assumption of normality, linearity, or homoscedasticity (Starkweather & Moske, 2011). BLR has some assumptions, like the assumption of independence among the dependent variable choices which says that a difference exists between the choice of or membership in one category to another category (dependent variable) (Starkweather & Moske, 2011).

Threats to Internal and External Validity

It is imperative to maintain balance in the control of threats to internal validity with the need to maximize external validity. The need for research studies to be generalizable is an important issue, but when the research study has too much external control, it becomes limited in applicability to the real-world populations (House, 2012). It is imperative that the research balance every component that gives strength to internal validity while maintaining a sizeable external validity as possible (Houser, 2012).

SEER-Medicare database is known for standard quality research through the quality assurance that helps maintain and minimizes threats to internal validity by ensuring regular quality improvement routine audit (Sun & Trinh, 2015). Also, the threats to external validity are minimized through the centralized control system (Sun & Trinh, 2015). The SEER site is evaluated pre- and post-implementation of a current redesign. Also, The SEER-Medicare linked database represent an important national research

resource that supports studies on cancer patterns of care, quality of cancer care, and costs of cancer care (National Cancer Institute, 2005). Also, SEER-Medicare ensure quality data through a three-year cycle for updating the data link in conjunction with extensive and detailed technical support on SEER-Medicare web page as well as organizing occasional conferences, workshops, presentations; and publications in the professional literature (National Cancer Institute, 2005).

In this study, the generalization of the results (external validity) should be done with caution and it is partly confirmed by the control of confounding using multivariable analysis.

Ethical Considerations

Ethical consideration is guided by Institutional Review Board (IRB) that reviews the study protocol, administered questionnaires, discover problems and concerns, and works with the investigators as needed to improve the study. The IRB guides the researchers as well as ensure the participant's confidentiality is maintained. I received approvals from Walden University IRB (#12-04-18-0249165) and the SEER-Medicare which is source of the dataset.

Summary

In this chapter, I presented the methodology for the proposed study. I used secondary data analyses using a retrospective study design. The study population included male and female patients diagnosed with CRC and later develop SPC. The study intended to involve the use of binomial logistic regression to look for associations to test the associations between the MetS, its components and SPC among CRC patients,

controlled for age, gender and race/ethnicity. The results of this study will be presented in Chapter 4.

Chapter 4: Results

Introduction

The purpose of this quantitative study was to investigate the association between MetS, MetS components, gender, race, and age and SPC among patients diagnosed with CRC. I used 2011 to 2013 secondary data from the SEER-Medicare, obtained from the study of cancer among the U.S. elderly population (65 years and over; National Institute of Health, 2017). The SEER-Medicare CRC dataset represents health data collected from people across a wide spectrum of CRC risk and cover 26% of the U.S population. The information obtained from SEER-Medicare data included age, gender, race-ethnicity, MetS components, and any diagnosis of SPC (lung, stomach, endometrial, kidney, and bladder) among CRC patients over a 5-year period.

The ethical approval to conduct this study was received from Walden University IRB (approval # 12-04-18-0249165) and the SEER-Medicare (contract # SRMEDIC/003027), which was the source of the dataset. Approval was received from SEER-Medicare after about 9 months of scrutiny of the study proposal by SEER-Medicare. The complexity of the dataset delayed initiation of study analysis as there was a need to retrieve and merge several large complex dataset folders of the numerous study variables.

A change from the initial data analysis plan was necessary. The mediating variables of smoking, alcohol, and family history of MetS were unavailable or with many missing cases in the dataset and therefore were not included in the analysis. Also, age

was changed to a categorical variable from the previously proposed use as a continuous variable to have a better distribution of the sample by age category.

This chapter includes the presentation of the descriptive statistics for all variables and the demographic characteristics of the sample. The chapter continues with the presentation and description of the results of the bivariate analysis between each predictor and the dependent variable and multivariable analysis between the predictors and the dependent variable.

Descriptive Analysis of the Sample Population

The epidemiological data included the following independent variables: MetS and its components (hypertension, obesity, diabetes, hypertriglyceridemia, dyslipidemia), age, gender, and race. The dependent variable was SPC in CRC (yes/no). The descriptive statistics are shown in Table 3.

The total study population N =4,217 was characterized by approximate equal male (50.3%) and female (49.7%) participants. Individuals aged 65 to 75 years-old (68.8%) were more than participants aged above 75 years (31.2%). Whites (41.7%) were the predominant race, followed by African Americans (20.1%), Hispanic/Latinos (10.3%), Asians (8.6%), American Indians/Alaskan natives (7.8%), and Native Hawaiian/other pacific islanders (6.5%), and 5.0% were unknown. Among the study population, 25.2% demonstrated MetS, 31.6% had hypertriglyceridemia, 46.6% had dyslipidemia, 21% had hypertension, and 42.5% of the study population were recorded as obese. In addition, 11.1% of the study population had SPC, and 10.8% were reported to have Type 2 diabetes mellitus.

Table 3

Descriptive Statistics of the Variables Under Study (N=417)

Variable	Frequency	Percent %
Gender		
Males	2120	50.3
Females	2097	49.7
Age (in years)		
65-75	2900	68.8
>75	1317	31.2
Race		
White	1759	41.7
Black/African American	847	20.1
American Indian/Alaska Native	331	7.8
Asian	361	8.6
Hispanic/Latino	436	10.3
Native Hawaiian/other pacific islander	272	6.5
Unknown	211	5.0
SPC		
Yes	468	11.1
No	3749	88.9
MetS		
Yes	1062	25.2
No	3155	74.8
Obesity		
Yes	1794	42.5
No	2423	57.5
Diabetes Mellitus		
Yes	457	10.8
No	3760	89.2
Hypertension		
Yes	884	21.0
No	3333	79.0
Dyslipidemia		
Yes	1964	46.6
No	2253	53.4
Hypertriglyceridemia		
Yes	1332	31.6
No	2885	68.4

The RQs and hypotheses of this study are the following:

RQ_1: Is there an association between hypertension and SPCs in CRC patients?

Hypotheses

$H0_1$: There is no association between hypertension and SPCs in CRC patients.

Ha_1: There is an association between hypertension and SPCs in CRC patients.

Research Question 2

RQ_2: Is there an association between abdominal obesity and SPCs in CRC patients?

Hypotheses

$H0_2$: There is no association between abdominal obesity and SPCs in CRC patients.

Ha_2: There is an association between abdominal obesity and SPCs in CRC patients.

Research Question 3

RQ_3: Is there an association between dyslipidemia and SPCs in CRC patients?

Hypotheses

$H0_3$: There is no association between dyslipidemia and SPCs in CRC patients.

Ha_3: There is an association between dyslipidemia and SPCs in CRC patients.

Research Question 4

RQ_4: Is there an association between diabetes and SPCs in CRC patients?

Hypotheses

$H0_4$: There is no association between diabetes and SPCs in CRC patients.

Ha_4: There is an association between diabetes and SPCs in CRC patients.

Research Question 5

RQ_5: Is there an association between hypertriglyceridemia and SPCs in CRC patients?

Hypotheses

$H0_5$: There is no association between hypertriglyceridemia and SPCs in CRC patients.

Ha_5: There is an association between hypertriglyceridemia and SPCs in CRC patients.

Research 6

RQ_6: Is there an association between age, gender, and ethnicity with SPCs in CRC patients?

$H0_6$: There is no association between age, gender, and ethnicity with SPCs in CRC

patients

Ha_6: There is an association between age, gender, and ethnicity with SPCs in CRC

patients

RQ_7: Is there an association between MetS and SPCs in CRC patients?

Hypotheses

$H0_7$: There is no association between MetS and SPCs in CRC patients.

Ha_7: There is an association between MetS and SPCs in CRC patients.

Results

In order to address these RQs, inferential analyses were conducted in two phases. First, bivariate analysis (chi-square) was conducted for each independent variable and the outcome variable (SPC; yes/no).

Bivariate Analysis

The results of this analysis are presented in the chi-square Table 4.

Research Question 1. As can be seen in Table 4, out of the total of 468 participants with SPC, 47 (10%) had hypertension compared to 421 participants with no hypertension but with SPC (90%). There is a significant relationship between no hypertension and SPC, $X^2(1, N = 4{,}217) = 37.9$, $p < .001$. The Cramer's V (effect size) for hypertension is weak (V: .095, $p < .001$). Based on this result, I failed to reject the null hypothesis, which is no association between hypertension and SPC.

Research Question 2. According to chi square results, there is a significant relationship between obesity and SPC, $X^2(1, N = 4{,}217) = 293.9$, $p < .001$. The Cramer's V (effect size) is weak for obesity (V: .264, $p < .001$). As shown in Table 4, among participants with SPC, 372 participants were obese (79.5%) while 96 participants (20.5%) without obesity had SPC. Based on the p value < .001, the association of obesity and SPC is statistically significant and the null hypothesis is hereby rejected.

Research Question 3. The chi-square analysis about the association of dyslipidemia with SPC is shown in Table 4. There were 90 participants (19.2%) with dyslipidemia who had SPC compared to 378 participants (80.8%) with SPC but without dyslipidemia. There is a significant relationship between no dyslipidemia and SPC, $X^2(1,$

$N = 4,217) = 158.1$, $p < .001$, Cramer's V (effect size) is weak for dyslipidemia (V:.194, $p < .001$); therefore, I failed to reject the null hypothesis, which is no association between dyslipidemia and SPC.

Research Question 4. Research Question 4 about the association of diabetes with SPC is shown in the chi square Table 4. Out of the 468 participants with SPC, 24 participants (5.1%) had diabetes compared to 444 with SPC (94.9%) but without diabetes. There is a significant relationship between no diabetes and SPC, $X^2(1, N = 4,217) = 17.7$, $p < .001$, Cramer's V (effect size) is weak for diabetes (V: .065, $p < .001$); therefore I failed to reject the null hypothesis, which is no association between diabetes and SPC.

Research Question 5. The chi-square test about the association of hypertriglyceridemia with SPC is shown in Table 4. Of the total 1,332 participants with hypertriglyceridemia, 67 participants (14.3%) had SPC and 401 participants (85.7%) had SPC without hypertriglyceridemia. There is a significant relationship between no hypertriglyceridemia and SPC, $X^2(1, N = 4,217) = 72.6$, $p < .001$. Cramer's V (effect size) is weak for hypertriglyceridemia (V: .131, $p< .001$); therefore, the null hypothesis is retained, which is no association between hypertriglyceridemia and SPC.

Research Question 6. The chi-square analysis about the association between the demographics (age, gender, and ethnicity) and SPC is presented in Table 4. Of the three demographics in this research study, only age was found to have a statistically significant relationship with SPC. Of the total participants, 65 to 75-year-olds accounted for 84.8% of participants with SPC compared to 15.2% aged >75 years. This shows that there are

significantly more participants aged 65 to 75 years who had SPC than those >75 years, $X^2(1, N = 4{,}217) = 63.2$, $p < .001$. The Cramer's V (effect size) is weak for age (V: .122, $p < .001$).

Regarding sex, 246 women (50.4%) with SPC were slightly more than men 232 (49.6%), but this relationship was not significant, $X^2(1, N = 4{,}217) = .103$, $p = .748$.

Regarding race/ethnicity (Table 4), Whites were the most populous in the study with SPC, representing (42.3%) followed by 87 Blacks/Africans (18.7%), 55 Hispanics (11.8%), 35 Native Hawaiians (7.5%), 35 Native Americans (7.5%), and 24 others (5.1%). There was no relationship found between race and SPC in this study $X^2(1, N = 4{,}217) = 3.65$, $p = .724$.

According to the results above, the null hypothesis for RQ6 is rejected only for the age variable.

Research Question 7. This is to find out if there is a relationship between MetS and SPC. According to table 4, 60 participants with MetS (12.8%) had SPC out of a total of 468 participants with SPC, compared to the 408 of the participants (87.2%) with no MetS but with SPC, $X^2(1, N=4217) = 42.7$, $p < .001$, therefore I failed to reject the the null hypothesis is retained, which is no association between MetS and SPC. The Cramer's V (effect size) for MetS is weak (V:.101, $p < .001$) for MetS.

Table 4

Bivariate Analysis (Chi-square test) Between Independent and Outcome (SPC) Variables of the Study

	SPC					
Independent variables	Yes *N* (%)	No *N* (%)	Total	χ^2	*p*	*Cramer's V*
Total	468 (11.1)	3749 (88.9)	4217			
Age				63.217	.000	.122
65-75	397 (84.8)	2503 (59.4)	2900			
>75	71 (15.2)	1246 (29.5)	1317			
Gender				.103	.748	
Male	232(49.6)	1888(50.4)	2120			
Female	236(50.4)	1861(49.6)	2097			
Race				3.652	.724	
White	198(42.3)	1561(41.6)	1759			
Black/African American	87(18.6)	760(20.3)	847			
American Indian/Native-Alaskan	35(7.5)	296(7.9)	331			
Asians	34(7.3)	327(8.7)	361			
Hispanic/Latinos	55(11.8)	381(10.2)	436			
Native Hawaiian/Other Pacific Islander	35(7.5)	237(6.3)	272			
Unknown	24(5.1)	187(5.0)	211			
MetS				42.706	.000	.101
Yes	60(12.8)	1002(26.7)	1062			
No	408(87.2)	2747(73.3)	3155			
Obesity				293.954	.000	.264
Yes	372(79.5)	1422(37.9)	1794			
No	96(20.5)	2327(62.1)	2423			
Diabetes				17.756	.000	.065
Yes	24(5.1)	433(11.5)	457			
No	444(94.9)	3316(88.5)	3760			
Hypertension				37.888	.000	.095
Yes	47(10)	837(22.3)	884			
No	421(90)	2912(77.7)	3333			
Dyslipidemia				158.168	.000	.194
Yes	90(19.2)	1874(50.0)	1964			
No	378(80.8)	1875(50.0)	2253		.	
Hypertriglyceridemia				72.658	.000	.131
Yes	67(14.3)	1265(33.7)	1332			
No	401(85.7)	2484(66.3)	2885			

Multivariable Analysis

Additional to bivariate analysis, multiple logistic regression (Binomial Logistic Regression-BLR) was applied in this study to predict the probability to have SPC based on the predictors of age, gender, race and obesity (the only MetS component which was found significant in the bivariate analysis). In order to have valid results from this study, the study variables are expected to meet the required assumptions of BLR. This study variables were checked and met the following assumptions; the dependent variable was dichotomous, there was no multicollinearity, and there were no extreme outliers.

Table 5 displays the Cox & Snell R Square (.086) and Nagelkerke R Square (.171) values, both referred to as the *pseudo* R^2 value and used to calculate and explain the extent of change or variation. The variation in the dependent variable based on this study model ranges from 8.6% to 17.1%, depending on whether the Cox & Snell R^2 or Nagelkerke R^2 methods is referenced, respectively.

Table 5

Binary Logistic Regression Model Summary

Step	-2 Log likelihood	Cox & Snell R Square	Nagelkerke R Square
1	2561.510[a]	.086	.171

The Hosmer and Lemeshow test (Table 6) was conducted to check the fit of model to the data and *p* value equal or greater than .05 is considered as good fit. *P* value of .049 means there is no evidence of lack of fit,.

Table 6

Hosmer and Lemeshow Test

Step	Chi-square	df	Sig.
1	15.542	8	.049

The Table 7 below shows the predictors used in this study to predict the probability of an SPC outcome for a unit change in an independent variable while keeping other independent variables constant. The result shows that the odds of not having SPC is 2.9 times greater for individuals aged >75 years compared to those of 65-75 years (*OR*=2.9, *95%CI*: 2.2-3.8). Also, the odds of not having SPC is 6.5 times greater for not obese individuals compared to obese individuals (*OR*=6.5, *95%CI*: 5.2-8.3). According to the results above null hypothesis for RQ2 and 6 were rejected.

In addition, using the lowest significant *OR* (2.9) as effect size, I conducted post hoc power analysis using regression analysis; the achieved statistical power was found satisfactory 0.99>0.80 (G*Power Calculator).

Table 7

Binary Logistic Regression to Predict non having SPC Having as Predictors Age, Race, Gender and Obesity

							95% C.I. for Odds Ratio	
	B	S.E.	Wald	df	p	Odds* Ratio	Lower	Upper
>75 years (ref. 65-75 y)	1.060	.137	59.478	1	.000	2.886	2.204	3.778
Race (ref. White).			6.213	6	.400			
Black or African Americans	.192	.142	1.814	1	.178	1.211	.916	1.601
American Indian or Alaskan Native	.054	.203	.071	1	.790	1.056	.708	1.573
Asian	.128	.205	.388	1	.533	1.136	.760	1.697
Hispanic/Latino	-.191	.172	1.225	1	.268	.826	.590	1.158
Native Hawaiian or other Pacific /islander	-.230	.208	1.228	1	.268	.794	.529	1.193
Unknown	.096	.240	.159	1	.690	1.100	.687	1.763
Female (ref. male)	-.124	.103	1.439	1	.230	.883	.721	1.082
No obesity (ref. yes)	1.876	.120	242.469	1	.000	6.525	5.153	8.262
Constant	1.124	.101	123.248	1	.000	3.076		

**For odds ratio interpretation, SPC outcome is considered as "non having SPC".*

Summary

The total study population *N* (4217) is characterized by an approximate equal male (50.3%), and female (49.7%) participants. Individuals aged 65-75 years-old (68.8%) were more than the ones aged above 75 years (31.2%). Whites (41.7%) were the predominant race, and 25% of the participants demonstrated MetS, 31.6% had hypertriglyceridemia, 46.6% dyslipidemia, 21% hypertension, and 42.5% of the study population were recorded as obese. In addition, 11.1% of the study population had SPC, and 10.8% were reported to have type 2 diabetes mellitus. According to BLR results, the

odds of not having SPC is 2.9 times greater for individuals aged >75 years compared to those of 65-75 years (*OR*=2.9, *95%CI*: 2.2-3.8). Also, the odds of not having SPC is 6.5 times greater for not obese individuals compared to obese individuals (*OR*=6.5, *95%CI*: 5.2-8.3).

Chapter 5: Discussion, Conclusions, and Recommendations

Introduction

There are limited data on the association of MetS and the SPC among CRC patients of varying ages, genders, and race/ethnic groups in the United States. However, studies have revealed that a person diagnosed with CRC irrespective of the mode of treatment has an increased risk of developing SPC compared to the general population (Donin et al., 2016; Lee et al., 2015). It was reported that 55% of cancer survivors with SPC will die from the SPC (Donin et al., 2016). The role of MetS, age, gender, and ethnicity in increasing the risk of a diagnosis of SPC with CRC has been investigated but needs further clarification because researchers have examined the SPC relationship with other risk factors except MetS (Dasguta et al., 2012; Lee et al., 2016; Raj et al., 2014). Data are indicating that the risk for developing an SPC may be significant for patients already diagnosed with CRC (Dasgupta et al., 2012; Oritz-Mendoza & De la Fuente-vera, 2014).

The purpose of this quantitative study was to examine whether a relationship exists between MetS (including its components: obesity, diabetes, hypertension, dyslipidemia, and hypertriglyceridemia), ethnicity, gender, and age, and the SPC of colorectal cancer like lung, endometrial, stomach, kidney, endometrial, and bladder cancers, among individuals diagnosed with CRC. In Chapter 5, I will start with a brief review of the key findings of the study. I will follow this with a detailed interpretation of the findings as related to existing literature, my theoretical framework, and the study population. I will present the limitations of the study in terms of generalizability and/or

trustworthiness, validity, and reliability. Finally, I will provide recommendations for further research and practice and discuss the implications for social change based on my research conclusions.

Key Findings of the Study

The sample size of the study was 4,217 patients with CRC. According to the results of the study, 25% of the participants demonstrated MetS, 31.6% had hypertriglyceridemia, 46.6% had dyslipidemia, 21% had hypertension, and 42.5% of the study population was recorded as obese. In addition, 11.1% of the study population had SPC, and 10.8% were reported to have Type 2 diabetes mellitus. BLR revealed that the odds of not having SPC is 2.9 times greater for individuals aged >75 years compared to those of 65 to 75 years (*OR* = 2.9, 95% CI: 2.2-3.8). Also, the odds of not having SPC is 6.5 times greater for not obese individuals compared to obese individuals (*OR* = 6.5, 95% CI: 5.2-8.3). There was no statistically significant relationship between gender, race, MetS, hypertension, dyslipidemia, hypertriglyceridemia, diabetes, and SPC.

Interpretation of the Findings

Demographics

Age. The finding of this study was that the odds of not having SPC is 2.9 times greater for individuals aged >75 years compared to those between 65 and 75 years. This can be partly explained by the fact that age <75 years is associated with the increasing risk of nongenetic cancer due the accumulative effect of UV radiation from the sun, smoking, an unhealthy diet, and dysregulation of the immune response over time, resulting in normal cell division to start mutation (Campisi, 2013; Deeks, 2011; NCI,

2015; White et al. 2014). Furthermore, the findings of this study are in accordance with previous research, which revealed that the median age for diagnosis of CRC is 68 years and the median age for cancer diagnosis is 66 (NCI, 2015). Thus, individuals with >75 years may have exceeded the median age of most cancers; hence, the odds of having SPC reduces as the age increases. This study confirms previous findings in literature; for example, Lee et al. (2015) reported that younger CRC patients (< 40 years) had a higher risk of SPC compared to their older counterparts. I aimed to exclude CRCs of genetic origin from the study by using age 65 as an inclusion criterion to enable better examination of the relationship between MetS and SPC; on the other hand, Donin et al. (2016) used age <18 for an exclusion criterion. Further research is needed to investigate the relationship between age and SPC among CRC cancers by including CRC cases of hereditary/genetics etiology as the primary cancers and can cause also SPC (Donin et al., 2016).

Gender. Gender had no statistically significant relationship with the development of SPC in my study. This finding does not agree with the study of Donin et al. (2016), who found that White men were more likely to develop SPC, but among 66 to 80-year-old patients, the risk in women was higher than the men. Ortiz-Mendoza et al. (2016) investigated the relationship between obese women with MetS and SPC and found that MetS in female cancer survivors may be a risk factor for a SPC. On the other hand, Park et al. (2016) found that males have a stronger BMI-cancer association in prediagnosed obese participants compared to females. However, some studies reported that females have a greater risk of developing SPC (Emory Winship Cancer Institute, 2016; Jong,

2015; Raj et al., 2011; Singh et al., 2012). Due to these contradictory results, further research is needed to explore the impact of gender on SPC, especially among CRC patients.

Ethnicity/race. Ethnicity/race was not found to be significant in this study, and this finding was supported by the study by Raj et al. (2011), who concluded that race/ethnicity is not known to be predictive of SPC. It is pertinent to say that race/ethnicity has been inconsistent in the outcome with SPC development in different studies and geographic locations; for example. Jian et al. (2013) found an association between lung adenoma (SPC) and CRC in both sexes in cross-township correlations (within the same country) but not in cross-country comparisons (in which there are different races/ethnicities). This geographic location inconsistency might be associated with the possibility of potential risk factors related to the patient's location such as different dietary behaviors and cultures.

MetS and MetS Components

Obesity. According to the results of this study, the absence of obesity resulted in 6.5 greater odds of not developing SPC. This is because a nonobese person is protected from problems associated with obesity. There is a connection of obesity as risk factors to many disease entities, including cancers (Meijers & De Boer, 2019; Ortiz-Mendoza et al., 2016; Stone, McPherson, & Darlington, 2018). Previous researchers have described the involvement and association of obesity with the pathophysiology of hypertension, diabetes mellitus, dyslipidemia, and hypertriglyceridemia (Park et al., 2016). The finding of obesity as a risk factor for SPC in my study is similar to the studies by Gibson et al.

(2014; *n* = 224; overweight HR, 1.39; 95% CI, 1.01 to 1.92; obese HR, 1.47; 95% CI, 1.02 to 2.12; per 5-unit change in BMI HR, 1.12; 95% CI, 0.98 to 1.29) and Jung et al. (2019), who reported that obese female cancer survivors had a higher risk of overall SPC (aHR, 1.17; 95% CI, 1.04□1.32). There has been an established link in the literature by animal experiments that obesity and cancer can been modified by dietary means (Nogueira et al., 2012a; Nogueira et al., 2012b). Nonobese individuals are excluded from problems potentiated by obesity and are unlikely to develop SPC. A patient who has been counseled to practice lifestyle behavioral modification is encouraged to adopt a nonsedentary lifestyle, perform regular exercise, and adopt a healthy diet to curtail excessive weight gain that can result in the development of other associated risk factors of MetS (Park et al., 2016).

MetS. I did not find a positive association between MetS and SPC, and this result did not agree with the study of Ortiz-Mendoza and De la Fuente-Vera (2014). Ortiz-Mendoza and De la Fuente-Vera found that a high prevalence of obesity among Mexican women population accounted for the MetS observed among cancer survivors. The results of my study on MetS may be attributed to two main factors: First, I did not investigate the possible role of the primary cancer subsite in the colon or rectum that could predict the type and sites of SPC that could also be related to MetS (see Lee et al., 2015; Raj et al. 2011; Stone et al., 2018). Secondly, my study was restricted to only five cancer types SPC of CRC, but Lee et al. (2015) stated that patients having CRC was found to be statistically significant for all cancers. Some of the above-mentioned cancers are not represented in my study, like the uterus, thyroid, breast, ovaries, and prostate cancers,

which are also associated with SPC of CRC (see American Cancer Society, 2020; Lee et al., 2015; Yang et al., 2017). This could explain the weak association obtained for the MetS and its components due to a possible masking effect obtained from the absence of other cancers that were not tested in my study.

Hypertension. Hypertension had no significant association with SPC in my study but Oritz-Mendoza et al (2016) and Emory Winship Cancer Institute, (2016) found that hypertension is a risk factor for SPC and primary cancers, respectively. Seretis, Cividini, Markozannes et al. (2019) found a positive association between hypertension and breast, esophageal adenocarcinoma and squamous cell carcinoma, liver cancers but these cancers were not examined in my study thus partly accounting for the lack of association obtained in my study.

Diabetes. This study found no association between diabetes and SPC. However, the study by Lee et al. (2015) has described diabetes as one of the risk factors for SPC development. Diabetes has been associated with other cancers like postmenopausal breast, pancreatic, liver, and non-Hodgkin's lymphoma (Collins, 2014; Giovannucci et al., 2010) which are excluded in my study. The exclusion of these cancers could account the lack of association obtained in my study.

Hypertriglyceridemia. I did not obtain a statistically significant association between hypertriglyceridemia and SPC. Hypertriglyceridemia has been associated with other cancers like thyroid, prostate, and gynecological cancers (Ulmer et al. 2009) which were not included in my study.

Dyslipidemia. In my study, I did not find a significant association between dyslipidemia and SPC but the study by Lee et al (2015) found a significant association. Dyslipidemia has been associated with cancer such as breast, non-small cell lung cancer, and prostate cancer and these cancers were not included in my analysis.

A more robust study containing all possible cancer associations with MetS components is an important suggestion for future study.

Limitations of the Study

This study was limited to the data available in the dataset. It would have been better to get a wider spread of data from the 50 US states, with larger sample and more types of SPC but the such raw data can be very complex and might take considerable time and resources to extract them. Also, I intended to study the covariates/potential confounders of alcohol, smoking, family history and diet but the received data did not include this information. There might have been selection bias as there was no equal representation of race in the data so to have a more representative sample of the national population with CRC and its possible to have gotten more participants from one region than the other and that could affect the outcome. Also, there was limited availability of study literature to compare my results.

Further, the use of the dependent variable as yes/no could make it difficult to know which of the SPC was being tested. It was impossible to get additional information about subjects in the cohorts, such as other genetic or non-genetic risk factors.

Recommendations

Future studies that examine MetS and SPC in different populations in United States and globally could include potentially important confounders for cancer, such as alcohol, smoking, dietary/nutritional status, chemotherapy/ radiation therapy. In addition, the inclusion of as many SPC cancer types as possible in future investigations on this topic can result in more reliable associations between the predictors and the outcome. The alternative study methodology that I would suggest is the mixed-method study design which can provide additional information on factors that influence the SPCs such as attitudes and beliefs of clinicians and CRC patients regarding screening for SPCs. The findings of the study have the potential implications of enabling early surveillance and screening for SPC among high-risk elderly and obese CRC patients. Furthermore, more studies are needed to further investigate the impact of demographics and MetS components on several types of SPC, thus, to have more reliable results on these potential associations.

Implications for Social Change

This study advanced the understanding of the association between MetS and SPCs (lung, endometrial, stomach, kidney, and bladder cancers) in CRC patients. The importance of early surveillance, detection, and treatment of SPC in CRC patients is significant to achieve better survival rates. My result of a positive association between obesity and age and SPC will be helpful to clinicians by providing treatment algorithms and surveillance for early screening/testing for SPC among CRC patients especially those who are elderly and obese in the populations. It also educates the susceptible elderly and

obese population and their family on SPC. Obesity is a silent pandemic and the adjustment of diet, physical exercise/ weight loss, and healthier behaviors can help to reduce the incidence of SPC in the population.

This study can promote positive social change by enhancing clinicians' and public health policy makers' understanding of the relationship between age, obesity-induced MetS and SPCs in CRC patients. This study can also highlight the need for early introduction of a surveillance program for detection of SPC in CRC survivors by health care and public health professionals and it demonstrates the importance of early intervention in mitigating SPC morbidity and mortality rate.

Conclusion

In this study, the development of SPC has been investigated among CRC patients after diagnosis, or treatment. There is no substantial evidence of the role of MetS in the increasing incidence of SPC among CRC patients. This study filled a gap in the literature on the association of MetS and SPCs of CRC patients. Early detection of cancer remains one of the most valuable interventions to improve health outcomes. A greater understanding of the components of MetS and its association with SPC will enhance positive social change through a reduction in morbidity and mortality among CRC patients that might develop SPC of lung, endometrial, stomach, kidney, and bladder cancers. I found that CRC patients who were aged 65-75 years (*OR*=2.9, *95%CI:* 2.2-3.8) and obese (*OR*=6.5*, 95%CI*: 5.2-8.3) had more odds to develop SPC. These data provide important information for surveillance target groups for risk assessment and therapy and enable clinicians to develop the most effective treatment algorithm for CRC patients.

Although this study does not include all possible covariates, it provides valuable information that can be used to prevent SPC cases in this high-risk population.

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