2017

Type 2 Diabetes Mellitus and Colorectal Cancer Risk and Survival in Oman

Rose Ngozi Mafiana
Walden University

Walden University

College of Health Sciences

This is to certify that the doctoral dissertation by

Rose Ngozi Mafiana

has been found to be complete and satisfactory in all respects,
and that any and all revisions required by
the review committee have been made.

Review Committee
Dr. Hadi Danawi, Committee Chairperson, Public Health Faculty
Dr. Fred Tabung, Committee Member, Public Health Faculty
Dr. Jagdish Khubchandani, University Reviewer, Public Health Faculty

Chief Academic Officer
Eric Riedel, Ph.D.

Walden University
2017

Abstract

Type 2 Diabetes Mellitus and Colorectal Cancer Risk and Survival in Oman

by
Rose Ngozi Mafiana

MSc, University of London, 2009

BPharm, University of Benin, Nigeria, 1986

Dissertation Submitted in Partial Fulfillment

of the Requirements for the Degree of

Doctor of Philosophy

Public Health

Walden University

November 2017

Abstract

Type 2 diabetes mellitus (T2DM) and colorectal cancer (CRC) are 2 chronic diseases with common risk factors related to physical inactivity, obesity, and diet. Literature on T2DM as a risk factor for CRC development and survival in Oman is scarce. Using de-identified archival data provided by Sultan Qaboos University Hospital (SQUH) Oman, a retrospective, case-control, and time-to-event study designs were used to compare odds of developing CRC, and survival rates among adults with and without T2DM. The ecosocial theory provided the theoretical base for this research. Logistic regression was used to examine the odds of developing CRC among 114 cases versus 170 hospital controls. The Cox proportional hazards regression was used to compare survival rates among 228 CRC cases by T2DM status and survival rates by T2DM status across strata of gender, age group, and tumor location and cancer stage. According to the study findings, after having adjusted for potential confounding variables, there was no association between T2DM and odds of developing CRC (*OR* = 1.49, 95% *CI*: 0.29-7.68, $p = 0.64$) or between T2DM and CRC survival rates (*HR* = 1.07, 95% *CI*: 0.65 -1.75, $p = 0.80$). There was also no association between T2DM and CRC survival rates across the strata of potential effect modifiers examined. This research could contribute to positive social change by creating awareness among policy makers that will provide them with information on CRC risk-reduction strategies in the Omani population.

Type 2 Diabetes Mellitus and Colorectal Cancer Risk and Survival in Oman

by

Rose Ngozi Mafiana

MSc, Public Health, University of London, 2009

BPharm, University of Benin, Nigeria, 1986

Dissertation Submitted in Partial Fulfillment

of the Requirements for the Degree of

Doctor of Philosophy

Public Health

Walden University

November 2017

Dedication

I dedicate this dissertation research to my late parents, Wilfred Kanebi and Josephine Gold Osadebe, from whom I learnt that education opens many doors of opportunity and that, with determination and perseverance, I can surmount all odds. To my endless love, my husband and friend, Engineer Ikechukwu Jonathan Mafiana, whose encouragement and support kept me going till the end of this rigorous journey. To my children, Chikadibie, Ngozichukwu, and Isioma; their deep love and concern for my wellbeing during the period of study will not go unrewarded. To God Almighty who is able to do abundantly more than we can ever ask or hope for.

Acknowledgments

I would like to sincerely thank Dr. Hadi Danawi, my chair for guiding me successfully through this dissertation process. His responsiveness and helpful comments gave me immense encouragement. My thanks also go to Dr. Fred Tabung my committee member, for his suggestions and expert contribution to this work, and to Dr Jagdish Khubchandani, the University Research Reviewer.

At Sultan Qaboos University hospital, I am deeply grateful to Professor Mansour Al Moundhri, head of the oncology unit and Dr Ibrahim Al Zakwani, head of pharmacy department, for sharing their expertise with me and ensuring that I successfully complete this research. I also appreciate my friends and professional colleagues at the Pharmacy department who supported me in different ways.

I give special thanks to my husband, Engineer Ikechukwu Mafiana, for always supporting my decision to pursue further education. His love and understanding gave me the strength to finish this work and his financial support made it possible. I thank my children, Chikadibie, Ngozichukwu, and Isioma, for their care despite their own academic concerns. I hope I have set them an example, to always invest in themselves through life-long learning. To my siblings, Aloysius, Patrick, Love, Rita, Christopher and Patricia, I give thanks for their prayers for my success throughout the period.

Finally, I thank God Almighty for showing me mercy and granting me the favor and grace to achieve this feat.

Table of Contents

List of Tables

List of Figures

Chapter 1: Introduction to the Study

Type 2 diabetes mellitus (T2DM) and colorectal cancer (CRC) are two chronic diseases with common risk factors related to diet and lifestyle, such as obesity, smoking, alcohol consumption, high consumption of red and processed meat, a diet low in fruits and vegetables, and physical inactivity (Haq, Ali, Mohammad, & Sarkar, 2012; MacFarlane & Stover, 2007; Yu, Zou, & Dong, 2014). In results from epidemiological studies conducted in Western countries, scholars have suggested that there is a relationship between diabetes and the risk and prognosis of certain cancers, such as breast, prostate, colorectal, and pancreatic cancers (De Bruijn et al., 2013; Ferroni et al., 2015; Luo, Lin, He, & Hendryx, 2014). However, research findings based on Western populations may not be applicable to Arab populations, such as the Omani population. For example, in genetic studies on a sample of Omani CRC patients, Ashktorab et al. (2008) showed that abnormalities in mismatched repair genes differed from similar studies in other populations. Moreover, similar studies on T2DM and CRC in Arab populations are scarce. Therefore, studying the association between T2DM and CRC in the Omani population presents an area of research that could fill this knowledge gap.

The focus of this research was on the association between T2DM and CRC risk and survival in the Omani population. The findings from this research may provide a better understanding of the association between T2DM and CRC risk and survival. First, findings from this research may help increase awareness about the risk of CRC in the Omani population. Secondly, the findings can guide the design of preventive interventions that are tailored towards the Arab or Omani population, thus contributing to

positive social change. Thirdly, preventive measures to address the burden of CRC could lead to a reduction in the direct and indirect costs associated with CRC diagnosis and treatment in Oman

The proceeding sections of this chapter include the background of this research, a statement of the problem, the study design and purpose, research questions, conceptual framework, definition of terms, assumptions, limitations and scope, and the significance of the study.

Background of the Study

The Sultanate of Oman is a country that occupies the South Eastern corner of the Arabian Peninsula and has a total area of 309 500 km^2 (World Population Review, 2016). It is bordered in the northwest by the United Arab Emirates, in the west by Saudi Arabia, and in the southwest by Yemen, and has an estimated population of 4.91 million (World Health Organization [WHO], 2016a). Nearly 50% of the population lives in Muscat, the capital city, which happens to be the largest city in the country (World Population Review, 2016). Oman belongs to the Cooperation Council for the Arab States of the Gulf, a political and economic union of six Arab countries known as the GCC countries. Others are Saudi Arabia, Bahrain, Qatar, United Arab Emirates, and Kuwait. These countries share similar psychosocial characteristics and have been ranked among the top countries with the highest diabetes prevalence in the Middle East and North Africa (MENA) region by the International Diabetes Federation (IDF, 2015).

Diabetes mellitus (DM) is a metabolic disorder of multiple etiologies, related to carbohydrate, fat, and protein metabolism. The hallmark of diabetes is hyperglycemia.

There are two main types of diabetes: Type 1 and T2DM. T2DM is the more common type, representing 90% of all diabetic cases worldwide (IDF, 2015; WHO, 2010). It develops in adulthood and is related to lack of physical activity, unhealthy diets, obesity, and insulin resistance (WHO, 2010). Insulin resistance is a common compensatory mechanism in obese individuals, characterized by hyperglycemia, which ultimately leads to T2DM (De Bruijn et al., 2013). With rising obesity worldwide, the incidence of T2DM is likely to increase (Al Hakmani et al., 2016).

T2DM is a growing public health problem that affects multiple organ systems in the body and reduces health-related quality of life and overall life expectancy. In 2015, T2DM accounted for 14.5% of all-cause mortality among adults 20-70 years of age globally, and more than half of these deaths occurred in persons below the age of 60 years (IDF, 2015). According to the IDF (2015), the high rates of diabetes in Oman may be attributed to the epidemiological transition that has occurred in the country following crude oil discovery in the 1970s; rapid socioeconomic development and good health care planning led to a decline in various communicable diseases, but presented new challenges in the form of lifestyle-related, noncommunicable diseases like diabetes and cancer (Al Shookri, Khor, Chan, Loke, & Al-Maskari, 2011). From 1991 to 2000, the prevalence of T2DM in Oman rose from 8.3% to 11.6 % (Al Shookri et al., 2011). About 12% of the Omani population in 2010 had diabetes, alongside other risk factors, such as obesity, overweight, and insulin resistance (Al Riyami, 2010). According to Al Nohair (2014), this rise in T2DM prevalence is likely due to changes in food consumption, socioeconomic and demographic factors, physical inactivity, and urbanization over the

past 3 decades. In 2010, T2DM was the fourth leading cause of premature death in Oman after ischemic heart disease, mental disorders, and musculoskeletal diseases (Mokdad et al., 2014). This is in addition to the economic burden of diabetes management. According to the IDF, the annual cost per person for managing diabetes in 2015 in Oman was over 1,000 U.S. dollars (IDF, 2015).

CRC is among the most common causes of cancer-related morbidity and mortality worldwide. In 2013, CRC accounted for 1.6 million of the 14.9 million global incident cancer cases (Global Burden of Disease Cancer Collaboration, 2015). Within the same period, CRC was responsible for more than 700,000 of the total 8.2 million cancer-related deaths (Global Burden of Disease Cancer Collaboration, 2015). CRC currently ranks as the third most common cancer in the world and the fourth in cancer-related deaths after lung and breast cancers respectively (Global Burden of Disease Cancer Collaboration, 2015). Although the incidence rates for CRC are higher in more developed countries like Australia, countries in Western Europe, North America, and high-income Asia-Pacific countries (Global Burden of Disease Cancer Collaboration, 2015; Hakulinen, 2007), the Middle Eastern countries, such as Oman, have been witnessing a rising trend over the past decade due to the adoption of Westernized diets and lifestyle (Al Mahrouqi, Parkin, & Sharples, 2011; Brim et al., 2008; Muliira, D'Souza, & Ahmed, 2016). The WHO (2014) indicated that CRC is the most frequent cancer among Omani men, and the third most common in Omani women with incidence rates of 10.2 and 8.5 per 100,000 cases for men and women respectively. CRC accounted for 9.0% of all-cause mortality in adult Omani males and 8.3% in females in the same period (WHO, 2014).

Many scholars have examined the association between diabetes and CRC (De Bruijn et al., 2013; Ferroni et al., 2015; Larsson, Orsini, & Wolk, 2005; Trabulo et al., 2015). Researchers have suggested that impaired glucose metabolism, hyperinsulinemia, insulin resistance, and obesity-related proinflamatory conditions, as well as hyperinsulinemia–related increases in insulin-like Growth Factor-1 and 3 (IGF-1 and IGF-3), play a key role. T2DM typically develops following long-term insulin resistance whereby higher concentrations of endogenous insulin are required for the normal use of circulating glucose. The resulting chronic hyperinsulinemia triggers a chain of metabolic responses involving a reduction in the circulating levels of insulin-like growth factor binding protein-1(IGFBP-1) and an increased tissue availability of IGF -1 and IGF-3 (De Bruijn et al., 2013; Ferroni et al., 2015; Larsson et al., 2005; Trabulo et al., 2015). Hyperinsulinemia in the presence of lower levels of circulating IGFBP-1 has been shown to increase CRC risk in prospective observational studies (Larsson et al., 2005; Trabulo et al., 2015). Chronic proinflamatory conditions and reactive oxygen species (ROS) have also been implicated. ROS invariably promotes tumor growth and proliferation via cell and tissue damage (De Bruijn et al., 2013; Ferroni et al., 2015). Hence, the inflammatory interplay between dysregulated glucose metabolism characteristic of T2DM, the release of cytokines and reactive oxygen species from adipose tissues, and the dysregulation of growth signals involving insulin and IGF-1 present a favorable milieu for colorectal carcinogenesis (K.H. Chen et al., 2014; Giovannucci & Michaud, 2007; Jeon et al., 2013).

Although scholars have examined the association between T2DM and CRC risk and mortality (De Bruijn et al., 2013; Ferroni et al., 2015; Krämer, Schöttker, Raum, & Brenner, 2012; Luo et al., 2014), there is a paucity of data on the Arab population of the Middle East, such as Oman. This gap in the literature, coupled with the burden of both T2DM and CRC in Oman, provided the basis for this research. This research will contribute to positive social change by providing a better understanding of the association between T2DM and CRC risk and survival in the Omani population and inform the design of preventive and health promotion strategies

Problem Statement

T2DM and CRC are two diseases with shared risk factors related to diet and lifestyle, such as obesity, smoking, alcohol consumption, high consumption of red and processed meat, a diet low in fruits and vegetables, and a sedentary lifestyle (Brim et al., 2008; Haq et al., 2012; MacFarlane & Stover, 2007; Yu et al., 2014). About 12% of the Omani population lives with T2DM, alongside other risk factors such as obesity, overweight, and insulin resistance (Al Riyami, 2010). This rise in T2DM and associated risk factors has been attributed to increased inactivity due to the availability and use of technologies such as cars, elevators, and other automated household devices, plus an inclination for Westernized diets of processed and semi processed foods that are rich in saturated fats among many Omanis (Al Shookri et al., 2011; Goh, 2007; Mahfouz, Sadek, Abdel-Latief, Mosallem, & Hassan, 2014; Muliira et al., 2016).

In epidemiological studies in the West, researchers have indicated that there is a link between T2DM and CRC (K.H. Chen et al., 2014; Dehal et al., 2012; Deng, Gui,

Zhao, Wang, & Shen, 2012; Erbach, Mehnert, & Schnell, 2012; Huang et al., 2011; Jeon et al., 2013; Jullumstrø, Kollind, Lydersen, & Edna, 2009; Larsson et al., 2005; Trabulo et al., 2015; Van de Poll-Franse, Haak, Coebergh, Janssen-Heijnen, & Lemmens, 2012; Walker et al., 2013). However, findings based on populations in the Western countries may not be applicable in the Middle East, and more specifically, in the country of Oman. Literature on T2DM as an independent risk factor for CRC incidence and mortality in Oman is scarce. Therefore, I decided to address this knowledge gap with this quantitative research study on the association between T2DM and CRC risk and survival in Oman.

Purpose of the Study

The purpose of this retrospective quantitative research study was to examine the association between T2DM and the risk and survival rates of CRC in Oman while controlling for covariates, such as stage of disease, gender, diet, body mass index (BMI), physical inactivity, alcohol consumption, smoking, age, and family history in men and women in the country of Oman. The findings from this study could contribute to a better understanding of the association between T2DM and CRC risk and survival rates. Moreover, it could provide the basis for the design of preventive interventions to reduce CRC burden in the Omani population.

Research Question(s) and Hypotheses

The following research questions and hypotheses guided this study. Statistical significance was set at 0.05 to be able to accept or reject the null hypotheses.

1. What is the association between T2DM and the risk of developing CRC in Oman?

$H_0$1: There is no association between T2DM and CRC risk in Oman.

H_a1: There is an association between T2DM and CRC risk in Oman.

Participants with T2DM will have a higher CRC risk than those without T2DM

2. What is the association between T2DM and CRC survival in Oman?

$H_0$2: There is no association between T2DM and CRC survival rates in Oman.

H_a2: There is an association between T2DM and CRC survival rates in Oman.

Participants with T2DM will have lower survival rates than those without T2DM.

3. What is the association between T2DM and CRC survival stratified by gender, age group, tumor location, and cancer stage in Oman?

$H_0$3: There are no differences in the association between T2DM and CRC survival rates by gender, age group, tumor location, and cancer stage, in Oman.

H_a3: There are differences in the association between T2DM and CRC survival rates by gender, age group, tumor location, and cancer stage, in Oman.

Theoretical Foundation

The ecosocial theory (Krieger, 2001) provided the theoretical base for this research. The ecosocial theory is used to integrate social and biological knowledge with dynamic and ecological perspectives to explain the distribution of disease. The four constructs of the ecosocial theory are embodiment, pathways of embodiment, dynamic and cumulative interplay between exposure and resistance, and accountability and agency (Krieger, 2001). People embody the adverse social, physical, and biological exposures that cause disease, from their conception to death. Practitioners use the ecosocial theory to analyze the current and changing patterns of population health against the background

of biological, ecological, and social organizations across multiple levels. By so doing, epidemiological associations between changing patterns of health and disease states across time and space can be qualitatively explained (Krieger, 2001).

With regards to the association of T2DM and CRC in the Omani population, T2DM is associated with CRC through shared risk factors of sedentary lifestyle, obesity, and insulin resistance. The constructs of embodiment, and the dynamic and cumulative interplay between exposure and resistance of the ecosocial theory, provided a potential explanation for this relationship; diabetes and related chronic hyperinsulinemia reduce circulating levels of IGFBP-1 (thereby reducing its effect on apoptosis), increase circulating levels of IGF-1 and 3 (these promote cancer cell growth), and enhance the mutagenic effects of insulin (De Bruijn et al., 2013; Ferroni et al., 2015; Trabulo et al., 2015). The embodiment of T2DM is viewed not as a disease of endocrine origin, but a biological process that alters the body's response to cancer: an alteration that occurs via the dynamic and cumulative interplay between endocrine processes and gender-related response to the effect of diet and lifestyle habits (Ferroni et al., 2015). Similarly, the presence of diabetes may alter the body's response to carcinogens at different subsites in the body. In the findings from this study on the association between T2DM and CRC, I highlighted these subsite- and gender-related differences. Agency and accountability at different levels would involve individuals, communities, and governments taking responsibility to counter these biological processes that affect health. This might involve enacting appropriate policies that make it easier for communities and individuals to adopt behaviors that promote health.

Table 1 shows the link between the study variables and the ecosocial theory constructs that were analyzed in this research, and Figure 1 is a visual representation of same.

Table 1

Study Variables as They Relate to Ecosocial Theory Constructs

Variable	Related constructs	Comments
Diabetes	Embodiment (incorporation of human biology with individual and societal lifestyles)	Physiological processes involving endocrine hormones that predispose to T2DM interact with diet and lifestyle and predispose to higher CRC risk and lower survival
Gender, diet quality BMI, physical activity, Age family history	Cumulative and dynamic interplay between exposure, susceptibility and resistance which differs by sex, stage of disease, diet quality, BMI, physical activity level, age and family history	Genetic and physiological factors interact with the lifestyle exposures and endocrine processes that cause diabetes to alter response to CRC

Note. BMI= Body Mass Index

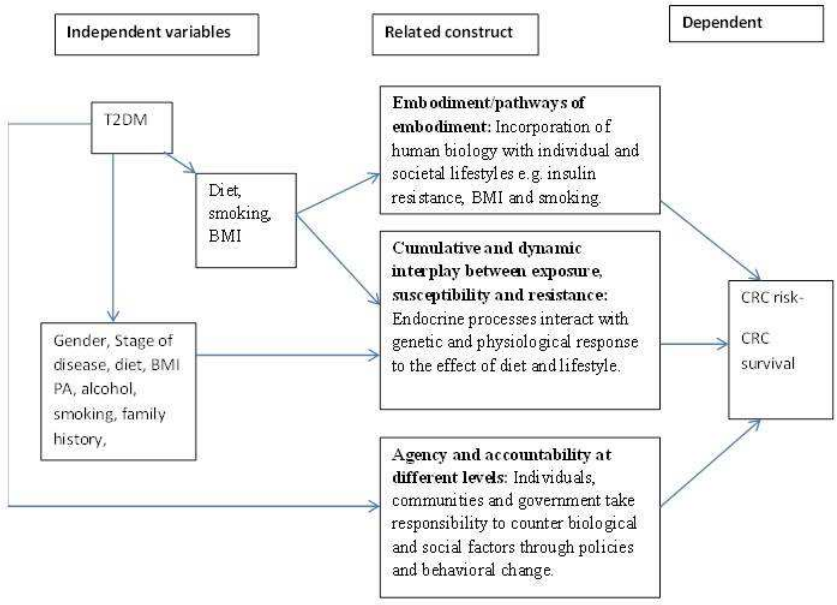


Figure 1. Study variables as they relate to ecosocial theory constructs

Nature of the Study

This research was quantitative in nature and involved a retrospective, case-control study to answer Research Question 1 and a retrospective survival analysis of secondary data for Research Question 2 and 3. Secondary data of CRC patients treated in Sultan Qaboos University Hospital (SQUH), a tertiary institution that treats more than 50% of the cancer cases in Oman, were used to address the research questions. For Research Question 1, a hospital-based, case-control study was used to study the association between T2DM and CRC risk using data from a previous study on gastrointestinal

cancers in Oman. The controls for this previous study were patients admitted into the orthopedic surgery; ear, nose and throat (ENT) and ophthalmology departments of the same hospital; and treated for acute, nonmalignant conditions that ranged from cataract, slipped discs, low back pain, simple fractures, sprains, minor traumas, hernia repair, acute appendicitis, gall bladder stones, and osteoarthritis. For Research Question 2 and 3, a survival analysis of all CRC cases diagnosed from January 2006 (SQUH fully transitioned to the use of electronic health records in January2006) to December 2012 in SQUH was conducted. Identified cases were followed up till December 2016. Those who were still alive at the end of the follow-up period were censored. Multivariable-adjusted analyses based on inclusion of covariates, such as stage of disease, diet, BMI, physical activity, alcohol consumption, smoking status, age, and family history of CRC were conducted. The case-control study provided insight into the association between T2DM and incident CRC, while the time-to-event analysis provided insights into the association between T2DM and CRC survival, in both men and women in Oman

Definitions

Cancer: Cancer is the term used for a collection of more than 100 related diseases characterized by uncontrollable division of cells in any part of the body. When cancer cells develop into masses of densely packed abnormal tissue, they are referred to as solid tumors. Cancers from any part of the body, except for cancers originating from the blood, can form solid tumors. Cancer is named after the organ or part of the body from which it originates. However, it has the ability to invade surrounding tissues, and migrate (metastasize) to other distant parts of the body through the blood or lymphatic system to

form tumors (National Cancer Institute [NCI], 2015). For example, cancer that originates in the colon is referred to as colon cancer. However, cells from this primary cancer can migrate to another organ in the body, such as liver or lung, in which case it is referred to as metastatic colon cancer. Cancers are categorized according to their cells of origin into leukemia, lymphoma, myeloma, and sarcomas, carcinoma, neuroendocrine, and germ-cell cancers (NCI, 2015a).

Cancer registry: A large collection of cancer data related to the diagnosis and treatment of patients in a given geographic area. Registries can be created for individual hospitals, regions, states, and at the national level (American Cancer Society, 2016).

Colorectal cancer (CRC): CRC originates in the colon or the rectum. These cancers can also be named separately as colon or rectal cancer after their site of origin, but are usually grouped together because they have many features in common. The colon and rectum make up the large intestine, also referred to as the digestive system, an organ that is about 5.6 feet (1.80 meters) long with walls consisting of several layers (American Cancer Society, 2016). The colon makes up the first 5 feet (1.5meters) of the digestive system while the rectum consists of the remaining 6inches (0.15meters; American Cancer Society, 2016). CRC starts in the innermost layer (the mucosa) of the wall and can grow through some or all of the other layers (American Cancer Society, 2016). The cancer cells can invade the blood vessels or lymph vessels where they can travel to nearby lymph nodes or to distant parts of the body, such as the liver, brain, or lungs (American Cancer Society, 2016).

Diabetes mellitus: Diabetes mellitus (DM) is a metabolic disorder of multiple etiologies, related to disturbances of carbohydrate, fat, and protein metabolism. It is caused by defects in insulin secretion and /or insulin action (WHO, 2010). The main hall mark of DM is hyperglycemia. Uncontrolled, chronic hyperglycemia causes damage to many of the body's systems, such as the nerves, blood vessels, the kidneys, and the eyes (WHO, 2010). There are two main types of DM: Type 1 and Type 2 DM. Type 1 DM (T1DM) develop in childhood and adolescence with patients requiring lifelong insulin injections (WHO, 2010). Type2 DM (T2DM) is the more common type and represents about 90% of all diabetic cases worldwide (WHO, 2010). It develops in adulthood and is related to obesity, lack of physical activity, and unhealthy diets. Fortunately, T2DM may be reversed by positive lifestyle changes. Other categories of diabetes include gestational diabetes and rarer types caused by genetic syndromes and acquired processes in diseases, such as cystic fibrosis and exposure to certain drugs and viruses (WHO, 2010).

Electronic health records: Electronic health records (EHRs) are databases that contain the results of clinical and administrative encounters between a provider (physician, nurse, telephone triage nurse, and others) and a patient that occur during episodes of patient care. (Ambinder, 2005) The purpose of the EHR is to make all of the information needed for patient care accessible at the point-of-care, for education, and for practice management. Other functions of EHRs are the reduction of medical errors and the reduction of redundant paperwork. Electronic links across care settings also facilitates collaborative and coordinated approaches among caregivers and enhance the tracking and monitoring of the quality of care activities (Ambinder, 2005).

Assumptions

The following assumptions were made for this study: First, for the first part of this study, and to answer Research Question 1, I relied on data from a previous study on gastrointestinal cancers in Oman. It was assumed that the variables relevant to this study were available in this dataset. Secondly, to address Research Question 2 to 3, I relied on the EHRs of patients who were treated and followed up in one of two hospitals that treat cancer patients in Oman. It was assumed that these patients were representative of CRC patients in Oman. This assumption was based on the latest Oman national cancer registry report that indicated that more than 50% of CRC cases diagnosed in 2013 were treated in SQUH (Oman Cancer Registry Report, 2014). Lastly, it was assumed that the data from the electronic health records of patients from the hospital were accurate and complete. These assumptions were critical for obtaining meaningful results.

Scope and Delimitations

The study was delimited to examining the association between T2DM and CRC risk and survival rates in the Omani Population. The study included adult male and female citizens and residents of Oman, 18 years of age or older. The study participants were drawn from secondary data from the EHRs of CRC patients treated in a tertiary hospital that treats more than 50% of the cancer cases in Oman, and a database for a previous study on lifestyle risk factors for gastrointestinal cancers in the same tertiary hospital. Because this hospital handles more than 50% of cancer cases in Oman, the sample was representative of CRC cases in Oman. The study sample was limited to

Omani citizens and residents; hence, the study findings may not be generalizable to non-Arab populations.

Limitations

Potential limitations to this study were as follows: First, the number of cases in the dataset may not be enough to provide the required sample size to conduct subgroup analysis. This could pose a potential threat to the external validity of the result. Secondly, missing values in the dataset could affect sample size and limit the extent to which subgroup analyses can be done. Moreover, this was an observational study; therefore, cause and effect cannot be determined. Selection bias could arise if cases that were not captured in the original dataset did not exactly match the controls. This could threaten internal validity. Finally, the study was limited to cases that attended one of two hospitals that treat cancer cases in Oman; thus, the findings may not be generalized to other non-Arab populations.

Significance of the Study

CRC is a global public health problem that generally has a poor prognosis (Kumar et al., 2015). Of the 900 cancer-related deaths in Oman in 2014, 8.7% were due to CRC (WHO, 2014). Most of what is known about the association of T2DM and CRC risk and mortality has been based on studies from Western countries (K.H. Chen et al., 2014; Dehal et al., 2012; Deng et al., 2012; Erbach et al., 2012; Huang et al., 2011; Jeon et al., 2013; Jullumstrø et al., 2009; Larsson et al., 2005; Trabulo et al., 2015; Van de Poll-Franse et al., 2012; Walker et al., 2013). However, findings based on data from Western countries may not be applicable to populations in the Middle East, such as the Omani

population; therefore, studying the Omani population is important. Moreover, in Oman, CRC tended to occur among persons of younger age than is generally found in the West (Brim et al., 2008; Kumar et al., 2015); yet, the prognostic and risk factors for CRC among the Omani population are not fully understood. This research was intended to fill this knowledge gap by focusing on the association between T2DM (a chronic disease that is also prevalent in the Omani population) and CRC risk and survival rates. The study findings may inform the design of preventive strategies and policies to address the burden of CRC in Oman.

Addressing the burden of CRC could mean longer disease-free periods and overall survival for CRC patients, allowing them longer time to spend with their loved ones. With longer disease-free periods, CRC patients can return to work and once again become productive members of their communities, contributing to positive social change. Positive social change could also be achieved when preventive measures to address the burden of CRC leads to reduction in the direct and indirect costs associated with CRC diagnosis and treatment. CRC treatment consists of surgeries, chemotherapy and radiotherapy, and inpatient and outpatient clinic visits for prolonged periods of time. Direct costs of such care can range from $1,941 to $48,453 per patient depending on the stage of the disease at diagnosis (Wong et al., 2012). The direct medical costs for CRC treatment in the United States in 2011 was $88.7 billion (American Cancer Society, 2015). These figures do not include the indirect costs, such as patient time involved with receiving medical care and productivity losses among patients and caregivers (Yabroff, Borowski, & Lipscomb, 2013).

Summary and Transition

T2DM and CRC are two chronic diseases with significant morbidity and mortality in Oman (Al Mahrouqi et al., 2011; Al Riyami, 2010; Brim et al., 2008; Muliira et al., 2016). An understanding of the association between T2DM and CRC risk and survival may inform appropriate interventions to reduce the burden of CRC. T2DM is a possible independent risk factor for CRC and prognosis. However, the majority of studies have been carried on populations from Western countries (K.H. Chen et al., 2014; De Bruijn et al., 2013; Ferroni et al., 2015; Giovannucci & Michaud, 2007; Jeon et al., 2013; Larsson et al., 2005; Trabulo et al., 2015; Wolpin et al., 2009). Data on the Arab populations of the Middle East, such as Oman, are scarce. The aim of this research outlined in this chapter was to fill this knowledge gap and improve the understanding of this association in the Omani population. This understanding would be guided by a more detailed review of the literature in Chapter 2.

Chapter 2: Literature Review

Cancer is a public health problem worldwide. Despite the progress that has been made in recent years in the prevention and treatment of many cancers, incidence rates continue to rise due to an aging global population and an increase in behavioral risk factors like smoking, obesity, and unhealthy dietary patterns (Lam et al., 2011; Li et al., 2016). Over 8 million deaths worldwide in 2013 were due to cancer, moving it from the third leading cause of death in 1990 to the second, behind cardiovascular disease (Global Burden of Disease Cancer Collaboration, 2015). Among various types of cancers, CRC is the third most common cancer in the world, and the fourth in terms of cancer-related deaths, after lung and breast cancers respectively (Global Burden of Disease Cancer Collaboration, 2015). In Oman, of the 900 cancer-related deaths in 2014, over 78 of them were due to CRC (WHO, 2014).

In many studies on Western populations, scholars have suggested a link between T2DM and CRC potentially mediated by factors related to nutrition, chronic inflammation, and genetic variables (L. Chen et al., 2013). However, despite the epidemiological transition that has taken place in Oman over the past 4 decades (Al Shookri et al., 2011), similar studies on risk factors for chronic diseases like T2DM and CRC are lacking. This is a gap in the literature deserving of research. The purpose of this research was to contribute to the body of existing evidence by studying the association between T2DM and CRC risk and survival rates in the Omani population. The findings from this research may contribute to a better understanding of the prognostic risk factors of CRC. A better understanding of the link between T2DM and CRC would provide an

opportunity for prevention strategies aimed at improving the Omani population health. The social change impact of this may be an increased awareness of the possible risks of CRC among the Omani people. Furthermore, findings may inform policies and preventive strategies to reduce behavioral risk factors that fuel the incidence of CRC, thus contributing to positive social change.

In this chapter, I review the supporting literature and theoretical constructs that formed the basis for this study. This literature review includes a synthesis and summary of recent, peer-reviewed literature on T2DM as not only a disease of endocrine origin, but also a disease that is linked to cultural and societal changes. The impact of T2DM on multiple organs, its role as a significant contributor to morbidity and mortality from chronic diseases such as CRC, and the associated economic implications are reviewed. In addition, the influence of gender, physical inactivity and diet, excessive alcohol, and tobacco use on the association between T2DM and CRC are also reviewed.

Literature Search Strategy

This literature review related to the research questions in this study and was limited to articles published between 2000 and 2016. However, older studies related to the development of the ecosocial theory were also included. Government and authoritative websites (i.e., the WHO, IDF, NCI, the American Cancer Society, the International Association for Cancer Research [IACR], the American Institute for Cancer Research [AICR], the Center for Diseases Prevention and Control [CDC], the World Cancer research Fund [WCRF], the Canadian Cancer Society, the Oman Cancer Registry, and the Oman Ministry of Health websites) were searched for current facts related to the

major themes of this review. The selected literature was limited to research published in peer-reviewed journals and on the previously listed websites. Databases that were searched included Google Scholar, ProQuest central, Thoreau, CINAHL Plus, Academic Search Complete and Medline, PubMed Central, and Dissertations & Theses at Walden University. The reference sections of many of the key articles also provided additional articles. The different themes that were related to the research questions were used to organize the structure for the literature review. The themes included *colorectal cancer, colorectal cancer incidence, colorectal cancer risk, colorectal cancer risk factors, colorectal cancer survival, Type 2 diabetes and cancer, Type 2 diabetes and colorectal cancer, ecological theories, ecosocial theory, diabetes and colorectal cancer survival, diabetes and colorectal cancer occurrence, cancer and diabetes in Oman,* and *colorectal cancer and diabetes in the Arab population*. These themes were used as search terms either individually or in combination to generate the highest number of relevant articles.

The goal of this review was to gain as much insight into these various themes, so as to design a study that would new generate knowledge. This knowledge could be added to what is known about the association between T2DM and CRC, as well as fill a gap in knowledge related to an understanding of the influence of T2DM on CRC risk and mortality in the Omani population.

Theoretical Foundation

The ecosocial theory (Krieger, 1994) provided the theoretical base for this research. The possible association between T2DM and CRC (how this association is affected by diet, physical activity, BMI, and gender) were guided by this theory. The

ecosocial theory (Krieger, 1994) is one of the newer theoretical frameworks of social epidemiology with a focus on the integration of social and biological knowledge with dynamic and ecological perspectives to address the distribution of disease. Building on the framework of social influences of disease (Smith, 1981), and driven by the need to explain who and what drives current and changing patterns of population health, the theory incorporates biological and ecological influences of disease distribution and their relationship with social factors to analyze disease development among different demographic groups. The ecosocial theory includes the consideration of social context of health problems across multiple levels and how these problems contribute to social inequalities in health to contextualize health promotion strategies (Krieger, 1994). Epidemiologists and public health practitioners can use the theory to critically consider their explanations for the persisting and changing patterns of health and how to apply an integrated approach across time and space when interpreting population health.

The four constructs of the ecosocial theory are embodiment, pathways of embodiment, dynamic and cumulative interplay between exposure and resistance to disease, and accountability and agency (Krieger, 2001). These constructs provide a better understanding of what drives disease distribution at multiple levels in a population. Krieger (2001) applied the constructs of ecosocial theory to demonstrate how biological processes interact with social conditions to give rise to biological expressions of social inequality on issues about discrimination, gender inequality, sexism, human rights and justice, as well as social exclusion. Krieger argued that epidemiological analyses of

health outcomes be conceptualized and operationalized in such a way as to capture all the possible expressions of such outcomes.

Embodiment (Krieger, 2005) is the main construct of the ecosocial theory. This construct is based on the premise that human beings are both biological and social entities and carry on their bodies, evidence of the societal and ecological consequences of their existence. Consequently, embodiment is an explanation for patterns and distribution of population health even when such explanations do not match or cannot be deduced from peoples account (Krieger, 2005). For example, BMI, or waist-to hip ratio, are embodied biological characteristics in individuals and populations that can be measured, and depending on the health outcome of interest, can provide an explanation for observed patterns of morbidity and mortality in a population. Embodiment is a process that is important for understanding the political and power dynamics that influence the choices people make and their related unconscious health consequences over a period of time (Krieger, 2005). Embodiment can be used to explain bodily transformations that occur when people choose to consume fast food in preference to healthier local alternatives as a symbol of being "Westernized". Likewise, the increased use of cars and automated technologies that has replaced people's ability to be physically active can result in bodily expressions of obesity. Biological, social, and ecological interactions amongst living organisms occur over time through pathways that may be physical, biological, and social. Hence, embodiment allows practitioners to study all aspects of human existence that impact health: consumption of food, use of language, types and use of recreation, sexual orientation and practices, use of psychoactive substances, use and experience of violence,

and experience of emotion (Krieger, 2005). Another example of the process of embodiment and its pathways is the possible causal relationship between impaired glucose metabolism and cancer risk.

T2DM typically develops following impaired glucose tolerance and long-term insulin resistance whereby higher concentrations of endogenous insulin are required for the normal use of circulating glucose. The resulting chronic hyperinsulinemia triggers a chain of metabolic responses involving a reduction in the circulating levels of IGFBP-1, IGF-1, and IGF-3 (Ferroni et al., 2015). Hyperinsulinemia in the presence of lower levels of circulating IGFBP-1 has been shown to increase CRC risk in prospective observational studies (Larsson et al., 2005; Trabulo et al., 2015). Furthermore, scholars have suggested that dysregulation of growth signals involving insulin and IGF-1 promote carcinogenesis (K.H. Chen et al., 2014; Giovannucci & Michaud, 2007; Jeon et al., 2013; Wolpin et al., 2009). Similarly, researchers have also demonstrated an association between hyperglycemia, insulin resistance, and HER2-expressing breast cancers (Ferroni et al., 2015). Diabetes and related chronic hyperinsulinemia reduce circulating levels of IGFBP-1, thereby reducing its effect on apoptosis; increased circulating levels of IGF-1 and 3 promote cancer cell growth and enhance the mutagenic effects of insulin (Ferroni et al., 2015). From the foregoing, insulin, a well-known regulator of human steroid sex hormones such as estrogen and aromatase, appears to be a common denominator for both breast and colorectal cancers via hormonal, inflammatory, and metabolic pathways that interfere with signal transduction of sex hormones (Ferroni et al., 2015; Vazzana et al., 2012).

The embodiment of T2DM is viewed not as a disease of endocrine origin, but a biological process that alters the body's response to cancer through the dynamic and cumulative interaction between endocrine processes and gender-related response to the effect of diet and lifestyle habits. Similarly, embodiment of T2DM can interact with genetic and physiological predisposition to alter response to cancer treatment or to cause variations in tumor characteristics at different subsites in the body. Agency and accountability at different levels involve individuals, communities, and governments taking responsibility to counter the biological processes that affect health. Appropriate policies can be enacted that make it easier for communities and individuals to adopt behaviors that promote health.

Ecosocial Theory and Related Studies

Using the embodiment construct of the ecosocial theory, Rock (2003) considered current approaches to defining and preventing the impact of T2DM on population health. Rock urged practitioners to consider the rising incidence of T2DM worldwide in light of socioeconomic changes, consumption patterns, and power dynamics that influence how capacity is built and used. Citing the rising incidence of T2DM among the inhabitants of Eeyou Istchee, a remote area in the Northwestern subarctic region of Quebec in Canada, Rock argued that the rise of T2DM in that community corresponded with changes brought about by modernization that followed the construction of a hydroelectric dam in 2000. Similar to Rock's idea, Benyshek, Martin, and Johnston (2001) suggested that economic and social changes contribute to the average rise in blood sugar at any given time within various populations. Citing as an example the prevalence of T2DM among

the native Indians of Nebraska in the United States, Benyshek et al. argued that systems of appropriation, exploitation, and exchange foster a political economy that help shape social organization and cultural norms that could explain the disproportionate rise in T2DM among minority groups. Other researchers have also considered how multiple level factors at the individual, interpersonal, and social and environmental factors influence adherence to antiretroviral therapy (Phillips, 2011), and how multiple level socioecological factors (i.e., gender, individual beliefs and attitudes, and social and environment structures) influence preschool children's engagement in physical activity (Mehtälä, Sääkslahti, Inkinen, & Poskiparta, 2014). Although no previous researchers used the ecosocial theory as a theoretical framework to examine the association between T2DM and CRC was found in the literature, Rock and Benyshek et al. described social factors associated with chronic disease that can be applied to the epidemiological and social changes that have occurred in Oman in the past 4 decades.

Literature Review Related to Key Variables and/or Concepts

Colorectal Cancer

CRC originates in the colon or the rectum. Although both cancers can be named separately as colon or rectal cancer after their site of origin, they are usually grouped together because they have many features in common. CRC is a public health problem. It is the third most common cancer after lung and breast cancers, and the fourth leading cause of cancer-related deaths in the world after lung, liver, and stomach cancers respectively worldwide (Global Burden of Disease Cancer Collaboration, 2015). In 2012, there were an estimated 1.4 million new cases of CRC and almost 694,000 deaths, and it

is predicted that about 2.4 million cases will be diagnosed annually worldwide by 2035 (Torre et al., 2015). Furthermore, about one in three people diagnosed with CRC die of the disease within 5 years after diagnosis (American Cancer Society, 2015). In addition to the human cost of CRC, the tangible and intangible costs of treating CRC are enormous. The direct medical costs for CRC treatment in the United States in 2011 were $88.7 billion (American Cancer Society, 2015). These figures do not include indirect costs, such as patient time involved with receiving medical care and productivity losses among patients and caregivers (Yabroff et al., 2013).

CRC is one of the cancers that are curable if detected early. Most CRCs originate from adenomatous polyps that progress and mutate slowly to cancer within 10 years to 15 years, giving an ample window for early detection and prompt treatment (CDC, 2017; Walsh & Terdiman, 2003). The removal of premalignant adenomas and polyps detected during screening can prevent CRC. On the other hand, the removal of localized cancer found in the early stages during screening may prevent CRC-related death by the institution of early treatment (CDC, 2017). The declining rates of CRC incidence and mortality that has taken place in the United States, Europe, and Australia in the past decade maybe due to improvements in screening and early detection programs, though it has been noted that uptake rates remain low (American Cancer Society, 2015; Ouakrim et al., 2015). According to the American Cancer Society, only 59% of people age 50 or older, for whom screening is recommended, do receive CRC testing as recommended.

Apart from a small percentage of individuals with certain genetic mutations that predisposes them to a higher risk of developing CRC, up to 90% of CRC cases are

nonhereditary and have been linked to modifiable behavioral practices, such as diets high in red or processed meats, physical inactivity, heavy alcohol consumption, and tobacco use. These health behaviors are amenable to public health interventions and have the potential to reduce CRC burden (Spring, Moller, & Coons, 2012). Apart from hereditary and modifiable life style risk factors of CRC mentioned above, other risk factors include gender, family health history, and age (MacFarlane & Stover, 2007). The public health impact of CRC risk is higher in the presence of T2DM (Flood, Strayer, Schairer, & Schatzkin, 2010; Larsson et al., 2005; Yuhara et al., 2011).

Oman

The Sultanate of Oman is situated in the South Eastern corner of the Arabian Peninsula and has a total area of 309,500 km2 (WHO, 2016a) It is bordered in the northwest by the United Arab Emirates, in the west by Saudi Arabia, and in the southwest by Yemen, and it has an estimated population of 4.49million (WHO, 2016a). Prior to 1970, Oman was largely isolated from the rest of the world and its changing economies and societies (Smith, 1981). With a population of just over 1 million prior to 1970, there was only 8 kilometers of paved road and no electricity. Most Omanis lived in rural areas where villagers worked and contributed to their communities in a system of mutual self-reliance (Smith, 1981). Before 1970, there were only two hospitals in Oman; one was opened in 1935 by the American Arabian Mission and run by American Missionaries, the other was established in 1948 and administered by the British Consulate (Al shishtawy, 2010). However, the discovery of crude oil in 1967 and the subsequent wealth that came with oil revenue y transformed the country.

From 1970, and with the use of oil revenue, the Omani government embarked on infrastructural development in all sectors resulting in the transformation of Oman into a modern society (Smith, 1981). Currently, the population of Oman stands at 4,490,000, of which 2,428,300 are Omani nationals while the rest are expatriates working in various occupations in the country (World Population Review, 2016.). There is a network of roads, purified water, electricity to most homes, and a modern health care system (Alshoaibi, 2015). Nevertheless, the epidemiological transition that has taken place in Oman over the past 3 decades has ushered in new challenges. Whereas the government's commitment towards good health care planning and provision has led to a decline in various communicable diseases among the Omanis (Al Shookri et al., 2011), the emergence of noncommunicable diseases, including cancer, present new challenges (Al Shookri et al., 2011).

For example, the availability and increased use of technology such as cars and elevators, and domestic servants has fostered a culture of sedentary lifestyle. Added to this, is a proliferation of fast food restaurants in response to Oman's increasing globalization. As Oman interacts more with the Western world, there has been a shift away from the traditional Omani diets of grains, spices and fruits, towards a preference for westernized diets of processed and semi-processed foods, and calorie-dense sugary drinks. In Oman it is fashionable for whole families to dine at fast foods restaurants as a way of being "Western-like". The consequence of this has been that while communicable diseases have declined, non-communicable diseases such as obesity, cardiovascular diseases, diabetes and cancers are now on the rise in Oman (Al Nohair, 2014).

Although incidence rates for CRC are still higher in more developed countries like Australia, countries in western Europe, North America, and high-income Asia-Pacific countries due to dietary and lifestyle habits of high consumption of red and processed meat, high alcohol consumption and tobacco use (Global Burden of Disease Cancer Collaboration, 2015; Hakulinen, 2007;), Middle Eastern countries such as Oman are witnessing a rising trend (Al Mahrouqi et al., 2011; Brim et al., 2008; Muliira et al., 2016). In addition to the observation that the Omani dietary patterns are being increasingly westernized, there are also distinct variations in Oman cooking practices from that of the West which may predispose to cancer (Azeem et al., 2015). For example, salt- preserved fish is eaten in certain parts of Oman; preserved foods with high sodium content have been linked with CRC (Azeem et al., 2015).

CRC is the most commonly diagnosed cancer among Omani men, and the third most common in Omani women with incidence rates of 10.2 and 8.5 per 100,000 cases for men and women respectively (WHO, 2014). In 2013, CRC accounted for 9.0% of all deaths in adult Omani males and 8.3% in females (WHO, 2014). Furthermore, while there has been marked reduction in incidence and death rates across developed countries due to improved screening services, early detection, and specialized care (American cancer Society, 2016), screening and early detection services for CRC are lacking in Oman. As a result of this, many CRC cases are detected in the late stages where the only option of treatment is palliative. Moreover, observational studies have indicated that CRC occurred among Omanis of younger age than is found in the West (Ashktorab et al.,

2008; Brim et al., 2008). Despite these observations, the prognostic factors for CRC have not been studied in the Omani population. This research study attempted to fill this gap.

Type 2 Diabetes (T2DM)

Diabetes mellitus (DM) is a metabolic disorder of multiple etiologies related to disturbances of carbohydrate, fat, and protein metabolism. It is caused by defects in insulin secretion, and /or insulin action (WHO, 2010). The main hall mark of DM is hyperglycemia. Uncontrolled, chronic hyperglycemia causes serious damage to many of the body's systems, such as the nerves, blood vessels, the kidneys, and the eyes (WHO, 2010). The adverse effects of hyperglycemia on the body systems is responsible for the macro- and microvascular complications of DM, such as cardiovascular diseases, lower limb amputations, diabetic nephropathy and neuropathy, kidney failure, and blindness (IDF, 2015; WHO, 2010). There are two main types of DM: T1DM and T2DM. T1DM usually develops in childhood and adolescence with patients requiring lifelong insulin injections. T2DM is the more common type and represents about 90% of all diabetic cases worldwide. It develops in adulthood and has increased alongside cultural and societal changes (IDF, 2015). It is related to obesity, lack of physical activity, and unhealthy diets (WHO, 2010). T2DM was the focus of this research.

The prevalence of T2DM is increasing worldwide. According to the IDF (2015), the threat of T2DM is one of the biggest global health emergencies of the 21st century. The current estimate of adults with T2DM stands at 415 million. An additional 318 million people have impaired glucose tolerance which puts them at high risk of developing T2DM in the future (IDF, 2015). Up to 12% of global health expenditure is

dedicated to the treatment of T2DM and related complications. The greatest barrier to tackling the scourge of this disease is the lack of awareness of its social and economic impact in many countries (IDF, 2015). The rising prevalence of T2DM worldwide is thought to be due to a combination of factors such as an ageing population, improved detection of undiagnosed T2DM, an increase in the number of people who are overweight or obese, and decreasing population physical activity levels (Smith & Hamer, 2014).

The Cooperation Council for the Arab States of the Gulf comprises of six countries with similar culture (Saudi Arabia, Kuwait, the United Arab Emirates, Qatar, Bahrain, and Oman). According to the IDF (2015), these countries exhibit some of the highest rates of T2DM in the world, attributed to their recent and rapid socioeconomic development and epidemiological transition. The prevalence of T2DM in Oman is also on the rise. From 1991 to 2000, the prevalence of T2DM rose from 8.3% to 11.6 % (Al Shookri et al., 2011). Oman has an anticipated 13.4-14.9% prevalence of diabetes for 2010-2030 (IDF, 2015). About 30% of the Omani population is overweight, 20% are obese and 12% have T2DM (Al Riyami, 2010). These findings, coupled with the observation that CRC occurred in Omanis of younger age than found in Western populations suggests there is a gap in the literature. It also suggests that research such as this study on the association between T2DM with CRC in the Omani population might be useful for healthcare planning and interventions.

T2DM and CRC Risk

Numerous epidemiological studies have reported a positive association between T2DM and CRC (L. Chen et al., 2013; De Bruijn et al., 2013; Deng et al., 2012; Erbach

et al., 2012; He et al., 2010; Jarvandi, Davidson, & Schootman, 2013; Krämer et al., 2012; Larsson et al., 2005; Levi, Pasche, Lucchini, & La Vecchia, 2002; Sandhu, Luben, & Khaw, 2001; Seow, Yuan, Koh, Lee, & Yu, 2006; Trabulo et al., 2015; Yuhara et al., 2011). However, findings have been inconsistent with regards to CRC site- and gender-specific risk. Whereas some studies with large sample sizes, indicated that overall, there was a significant association between T2DM and CRC (Flood et al., 2010; Jarvandi et al., 2013), other studies found an association between T2DM and proximal but not distal colon (Jarvandi et al., 2013). Yet other studies showed that this association was significant for distal colon but not for rectum (Yuhara et al., 2011). These inconsistencies may be attributed in part to differences in baseline characteristics, methodological designs or CRC heterogeneity (L. Chen et al., 2013), or insufficient power due to small sample sizes during subgroup analyses (Jeon et al., 2013).

For example, Sandhu et al. (2001) examined the relationship between T2DM, family history and risk of prevalent CRC in a European population. The authors used a cross sectional sample of 29,343 participants from the East Anglian component of the European Prospective Investigation into cancer (EPIC-Norfolk) study. They found that for both males and females, those who had T2DM had almost three-fold increased risk of CRC compared to those without T2DM. Similar results were reported by Levi et al. (2002), and Seow et al., (2006). Levi et al., (2002) conducted a case control study on a sample of 836 Swiss men and women. These authors found that overall; participants with T2DM had almost a two-fold risk of CRC compared to those without a history of T2DM. When stratified by gender, this risk was slightly higher in women compared to men. In

another study, Seow et al., (2006), examined the association between a history of T2DM and CRC among a sample of 63257 ethnic Chinese population of Singapore. In this prospective study, Seow and colleagues found a 50% higher risk of CRC in diabetics compared to non-diabetics.

With regards to gender- specific differences, some studies have found an increased risk of CRC in women with T2DM but not in men (Chodick et al., 2010; Flood et al., 2010; Levi et al., 2002), while others found increased risk in men but not in women (Campbell et al., 2010; L.Chen et al., 2013). L.Chen et al., (2013) reported an overall higher incidence of CRC in diabetic subjects compared to non-diabetic controls. However, an increased risk of rectal cancer was observed in diabetic men but not in women. Similarly, a subgroup analysis conducted by Seow et al., (2006) above, showed that diabetic men had a slightly higher but, non-significant risk of CRC than diabetic women (RR= 1.5 vs 1.4, p =.64). Krämer et al., (2012) found that T2DM was associated with a moderately increased risk of CRC in both men and women though with a slightly higher risk in women. Their study was a metaanalysis of twenty-nine gender-related studies on the association between T2DM and CRC incidence. This metaanalysis included cohort and case control studies conducted in the Australia, USA, Europe, Japan, Korea, China, Israel and Iran. The slightly higher risk observed in the female gender was attributed to gender-specific differences related to the estrogen pathway and the estrogenic nature of CRC; a finding that was also supported by the study done by Foster, (2013). Krämer and colleagues called for cancer control and prevention strategies that included efforts to address the rise in T2DM.

Despite the numerous individual studies (Campbell et al., 2010; Chodick et al., 2010; He et al., 2010; L. Chen et al., 2013; Levi et al., 2002; Sandhu et al., 2001; Seow et al., 2006), and metaanalysis (Krämer et al., 2012; Larsson et al., 2005; Yuhara et al., 2011) that have reported an association between T2DM and CRC incidence, the strength of this association in terms of site- and gender –specific risk remains inconclusive. The findings from this research could make a contribution towards a better understanding of this association. The findings may aid the formulation of supportive policies aimed at improving CRC prevention strategies in the Omani population.

T2DM and CRC Mortality

The effect of T2DM on CRC prognosis has been inconsistent with studies reporting conflicting results (Huang et al., 2011; Jullumstrø et al., 2009; Larsson et al., 2005; Van de Poll-Franse et al., 2012; Dehal et al., 2012). While some studies have reported no association between T2DM and overall survival in CRC patients (Ahmadi, Mobasheri, Hashemi-Nazari, Baradaran, & Choobini, 2014; Morrison et al., 2011; Noh, Hwang, Choi, & Lee, 2010), other researchers (Huang et al., 2011; K.H. Chen et al., 2014; Luo et al., 2014.) showed that T2DM is associated with higher CRC mortality. Still in other studies, as in the study by Jeon et al. (2013), a positive association was found between T2DM and colon specific survival but, not with rectal cancer. On the other hand, Van de Poll-Franse et al. (2012), reported poor survival in rectal cancer patients with T2DM and a non- significant association between T2DM and colon cancer survival. The inconsistencies in epidemiological studies, coupled with the scarcity of

similar studies on the Arab population of the Middle East such as the Omani population, presented a gap in the literature that this research attempted to fill.

Gross et al. (2006), used data from the Surveillance Epidemiology and End Results (SEER) database to examine the effect of comorbid DM, chronic obstructive pulmonary disease (COPD), and congestive heart failure (CHF) on the survival of older persons diagnosed with stage 1-3 CRC, between 1993 and 1999 in the United States. The authors looked at the effect of each comorbid condition separately, and in combination with others, on the risk of mortality across all stages of CRC. After a median followup period of 4.6 years, the results showed that those with no comorbid condition had a five-year survival rate of 78.3% for stage 1 disease. However, the five-year survival rates decreased to 71% with comorbid DM, 65% for COPD, and 55% for CHF respectively, in patients with stage 1 disease. Further analysis with combinations of comorbid conditions, showed that patients with two or more comorbid conditions had a much lower 5- year survival rate; 49.6% for stage 1 disease. Survival rates further decreased to 42.3% and 27.7% for stages 2 and 3 disease respectively. These results suggest that the presence of multiple morbid conditions in older persons with CRC substantially and negatively impacted prognosis. Gross and colleagues concluded that a greater understanding of the effect of multiple chronic conditions on CRC outcomes in older persons will guide clinical decisions in elderly persons with CRC.

Luo et al. (2014), obtained similar results when they examined the influence of preexisting diabetes on CRC prognosis in another cohort of elderly patients aged 67 years and above. Their sample consisted of CRC cases diagnosed between 2003 and 2009 from

the SEER and Medicare database. These researchers found that patients with T2DM had a 20% higher risk of mortality than those without T2DM for all stages of CRC. This risk was 50% higher in patients who had T2DM with cardiovascular disease (CVD), and COPD complications. When the data were analyzed in terms of site-specific mortality, a significant association was observed only in colon cancer cases that had both T2DM and CVD. Mortality in rectal cancer cases was non-significant (Luo et al., 2014). The authors concluded that pre-existing T2DM increased the risk of all-cause mortality in CRC patients but this risk maybe due to the increased risk from other co-morbid conditions such as cardiovascular complications.

Suggestions that the increased CRC risk in patients with T2DM may be due to co-existing comorbid conditions have been advanced by other authors (Larsson et al., 2005; Jeon et al., 2013; Ahmadi et al., 2014). However, in some other studies (Lam et al., 2011; Yuhara et al., 2011), the association between T2DM and CRC mortality remained positive even after controlling for these potential confounding variables, suggesting that other specific DM mechanisms maybe responsible for this association. According to Onitilo et al. (2012a), T2DM in cancer patients is associated with negative outcomes through complex multifactorial pathways. They argued that none of the many plausible mechanisms that have been advanced to explain this association has yet been substantiated. These researchers suggested that this association be kept in mind during treatment decision making and, in the planning of screening and prevention programs.

One limitation of the study by Gross et al., and Luo et al above, is that the study samples were limited to elderly patients aged 67years and above and may not be

generalized. This study on the association between T2DM and CRC risk and mortality in Oman attempted to overcome this limitation by drawing a sample from the population of all adults, age 18 years and above, diagnosed with CRC in SQUH within the study period. Again, given that advanced age is an independent risk factor for mortality, the findings of the Gross et al. and Luo et al. studies may be biased towards people of younger age. Moreover, comorbid conditions that occur as a result of the natural aging process may contribute to the observed effect on CRC mortality (Sjödahl, Rosell, & Starkhammar, 2013). Hence, these comorbid conditions may have confounded the effect of T2DM on CRC mortality in these two studies. In one study that used a more representative sample than the study of Gross et al. and Luo et al., T2DM was associated with poor survival from colon but not from rectal cancer (Jeon et al., 2013). The authors concluded that the potential mechanisms by which DM affects the different subsites in CRC differs and warrants further studies.

De Bruijn et al., (2013), examined the association between T2DM and cancer incidence, and cancer-specific mortality in patients with breast and colorectal cancer in a large sample of over 1 million individuals with T2DM. This study was a metaanalysis of 20 studies that included one randomized controlled trial, 17 prospective cohort studies, and 2 systematic cohort reviews. T2DM was associated with a 30% increased risk of mortality from CRC even after adjusting for potential confounders. One limitation of this metaanalysis was that it included some studies that did not differentiate between the two types of DM. Also, the mechanism by which the two types of DM are associated with cancer development may differ (Shu et al., 2010). Secondly, the authors did not control

for the use of antidiabetic medications such as metformin that has been demonstrated to have a protective effect on breast and colon cancer (Lee et al., 2012), and insulin which has been implicated in carcinogenesis (Chang, Lin, Wu, Lai, & Chuang, 2012; Dehal et al., 2012; Forssas et al., 2013; K.H. Chen et al., 2014). For example, Dehal et al. (2012), conducted a study to examined the association between T2DM) and survival among patients with CRC, stratified by sex, insulin treatment, and durations of T2DM and insulin use. They used a sample of 2,278 men and women diagnosed with non-metastatic colon or rectal cancer between 1992 and 2007 in the Cancer Prevention Study-II Nutrition Cohort. Compared with CRC patients without T2DM, those with T2DM had a more than 50% risk of all-cause mortality and almost 30% risk of CRC-specific mortality in both men and women. Furthermore, insulin use was independently associated with almost 70% risk of death from all causes in those with T2DM compared with those without. Similar effects of insulin on cancer mortality were observed in the study by K.H.Chen et al., (2014) who reported a more than 50% higher risk of CRC mortality in T2DM patients on insulin. Likewise, Forssas et al. (2013), reported a relative overall excess cancer mortality in diabetic patients, especially in women treated with insulin compared to non-insulin treated participants.

Other pathophysiological mechanisms by which T2DM increases the risk of CRC mortality in diabetic patients have been advanced by numerous studies. These mechanisms include hyperinsulinemia, hyperglycemia (the hallmark of DM) and oxidative stress (Díaz-Algorri et al., 2015; Jeon et al., 2013; Ferroni et al., 2015; Larsson et al., 2005; Onitilo et al., 2012b). Other pathways include insulin resistance and obesity-

related processes such as chronic inflammatory conditions and changes in adipokines (Bardou, Barkun, & Martel, 2013; Jonasson, Cederholm, & Gudbjornsdottir, 2014; Morrison et al., 2011; Noh et al., 2010; Onitilo et al., 2012b). Delayed colon content transit time and hormonal mechanisms involving estrogen, insulin and insulin-like growth factor-1 also play a role (Bardou et al., 2013; Lam et al., 2011; Lauby-Secretan et al., 2016; Shi et al., 2015; Popescu-Vâlceanu et al., 2015).

The adverse effect of colon content transient time in T2DM patients is related to autonomic neuropathy, an often unrecognized side effect of T2DM that causes colonic dysfunction such as constipation and elevated fecal bile acid secretion (Huang et al., 2011; Prawitt, Caron, & Staels, 2011). Constipation causes a delay in bowel content transit time thereby exposing the colonic mucosa to toxins and carcinogens. Moreover, elevated fecal bile acid concentration induces DNA damage and disrupts the normal metabolic functions of bile acid such as the regulation of lipid, glucose and energy metabolism (Ahmadi et al., 2014; Huang et al., 2011; Popescu-Vâlceanu et al., 2015). In addition to the above mentioned mechanisms, lifestyle-related factors common to both diseases, such as unhealthy diet, physical inactivity, obesity, smoking and alcohol consumption may modify the association between T2DM and CRC.

Lifestyle- related factors influencing T2DM and CRC

Recent epidemiological updates from the WHO, IACR, the AICR, WCRF, and the CDC, have established that diet, obesity, physical inactivity and other lifestyle factors such as tobacco and excess alcohol use contribute significantly to CRC and outcomes. The combined impact of these factors on CRC, in the form of a healthy life style index

score, has also been examined by some studies (Aleksandrova et al., 2014; Cavicchia et al., 2013; Kirkegaard et al., 2010; Odegaard, Koh, & Yuan, 2013; Tabung ,Steck, Burch et al., 2015). In these studies, a higher healthy life style index (HLI) score was associated with a lower risk of CRC by as much as 20-60%. However, in some of the studies (Kirkegaard et al., 2010; Odegaard et al., 2013; Cavicchia et al., 2013), this association was only significant for the colon subsite. These same risk factors have been implicated in T2DM and, may in some way, interfere with the association between T2DM and CRC (Ezzati, & Riboli, 2013; He et al., 2010; Onitilo et al., 2012b).

Diet

Major health organizations such as the WCRF, the AICR, the American Cancer Society, the American Diabetic Association, and the Canadian Diabetic Association, have emphasized the important role that diet plays in the risk of CRC and T2DM. Consequently, they have made recommendations on the type, quantity and quality of diet that is essential to reduce the burden of both diseases. According to these organizations, diets rich in whole grains, fruits, vegetables, monounsaturated fats, dietary fibers and nuts are considered healthy and should be consumed in preference to processed and energy-rich foods, red meat and sugar sweetened beverages. These recommendations are based on scientific evidence which showed that diets that consist of fibers, whole grains, fruits, vegetables and monounsaturated fats decrease inflammation and improve insulin sensitivity. Moreover, such diets are associated with weight loss which in turn improves blood sugar control (Onitilo et al., 2012b).

In line with the recommendations of these large health organizations, many epidemiologic studies have also demonstrated a positive association between diet and risk and outcomes of T2DM and CRC. For example, Jarvandi et al., (2013), examined the role of diet quality on the association between T2DM and CRC in a large prospective study of 484,020 individuals, aged 50–71 years. The sample was drawn from the prospective National Institutes of Health-AARP Diet and Health Study. During a followup period of about 9.2 years, 7,598 new cases of CRC were identified. After controlling for non-dietary confounders, the result showed that both history of T2DM and poor diet were associated with increased risk of CRC. Patients with T2DM had a 27% increased risk of CRC compared to nondiabetics. When adjusted for diet quality, this risk was slightly attenuated, but remained significant, indicating that diet and T2DM independently and additively increased the risk of CRC. The Omani diet has moved from the traditional diets grains and dates towards more westernized diet with the advent of crude oil wealth and globalization. However, how this diet shift has affected CRC risk over the years in the Omani population remains unknown. Therefore, this research attempted to fill this knowledge gap.

Overweight and Obesity

Overweight and obesity are the abnormal or excessive accumulation of body fat that results from an imbalance between energy intake in food and drinks, and energy expenditure. In 2014, about 640 million adults were obese (WHO, 2015). According to a WHO report, the estimated age-standardized prevalence of obesity in 2014 was 10.8% among men and 14.9% among women (WHO, 2015). In 2013, an estimated 4.5 million

deaths worldwide were caused by overweight- and obesity- related complications (WHO, 2015). Major cancer research organizations have stated that overweight and obesity increase the risk of many chronic diseases including diabetes and cancer. Recent AICR reports and updates indicate that excess body fat is a risk factor for CRC and ten other different cancers and as much as 20% of many common cancers are caused by excess body fat (AICR, 2016). According to the IACR, the obesity-related cancer burden is about 9% of the cancer burden among women in North America, Europe, and the Middle East (Lauby-Secretan et al., 2016).

In a recent exercise to reassess the preventive effects of weight control on cancer risk, the IACR working group reviewed evidence from more than 1000 observational studies including metaanalyses. They concluded that there was sufficient evidence that BMI which is a marker of obesity was significantly associated with the risk of colon and rectal cancer (Lauby-Secretan et al., 2016). This association followed a positive dose-response pattern and was consistent across gender and geographic regions (Lauby-Secretan et al., 2016). Similar findings were reported by Ma et al., (2013) in their meta-analysis involving a population of more than 10 million from 24 different prospective studies across Asia, Australia, Europe and North America. According to the authors, the causal link between obesity and CRC is mediated through metabolic and endocrine abnormalities, especially through alterations in sex hormone metabolism, insulin and IGF signaling, and oxidative stress arising from release of adipokines, inflammatory cytokines, and reactive oxygen and nitrogen species (Ma et al., 2013). Bardou et al. (2013), also observed a consistent association between obesity and CRC risk and

mortality in men, but less so in women. Their study was a pooled analysis of five metaanalysis involving more than 10,000 subjects (Bardou et al., 2013). Similar to Ma et al., (2013), Bardou and colleagues also pointed to metabolic and endocrine abnormalities as responsible for the association between obesity and CRC. A few studies have however yielded contrary results (Katerina Neumann, Mahmud, Metcalfe, & Hochman, 2015; Morrison et al., 2011). In the study by Morrison et al, no association was found between high BMI, T2DM and CRC outcomes. Similarly, Katerina Neumann and colleagues found no significant association between obesity and the odds of higher grade or stage of CRC whereas, in the study by Jarvandi et al. (2013), obesity was associated with an increased risk of CRC in men, but not in women. Going by this hypothesis, obesity, which is a common comorbidity of T2DM, could confound the association between T2DM and CRC.

Obesity prevalence is on the rise in Oman, more so in females than in males. Al Riyami (2010) reported that 20% of the Omani population is obese. In 2014, the figures rose to 25% (Al Nohair, 2014). More recent WHO estimates indicate that 27.2% adult Omani males and 37.7% females are obese (WHO, 2015). Given that obesity is a risk factor for many chronic diseases including T2DM and cancers, it is no surprise that T2DM also appears to be prevalent in the Omani population. The WHO estimates stand at 17.2% T2DM for males and 15.1%, for females (WHO, 2015). Moreover, T2DM accounted for 10% of total deaths in Oman among both genders within the same period (WHO, 2015). It is important to note that of all the studies about the association between obesity, T2DM and CRC (Bardou et al., 2013; Cong et al., 2014; Karahalios, English, &

Simpson, 2015; Ma et al., 2013; Tilg, & Moschen, 2014), none was conducted in the Omani population. This gap in the literature could be filled by this research to fill.

Physical inactivity

The role of physical inactivity as a risk factor for many cancers has been documented by epidemiological studies. With regards to CRC risk, physical activity was inversely associated with CRC risk in a metaanalysis of cohort and case control studies (Johnson et al., 2013). Other studies have also suggested that physical activity conferred survival benefits in CRC and breast cancer cases (Boyle, Fritschi, Heyworth, & Bull, 2011; Li et al., 2016; Kuiper et al., 2012). This observed protective effect of physical activity on CRC mortality is thought to be related to a number of physiological mechanisms involving the IGF pathway, improved insulin sensitivity, lower BMI, lower sex hormones, reduced adiposity, insulin and c-peptide levels, and inflammation (Sax et al., 2014; L. Chen et al., 2013). Higher levels of physical activity have also been found to reduce risk of T2DM by similar mechanisms (Onitilo et al., 2012b).

Researchers also examined the effects of physical inactivity on the risk of T2DM (Smith, & Hamer, 2014; Grøntved & Hu, 2011). Smith and Hamer (2014) examined the association between television viewing time and risk of incident T2DM in a sample of adults older than 65 years of age in England. Their result showed that participants who were inactive and had high television viewing time at baseline were almost twice more likely to have T2DM at 2-year followup than those who were active with low television viewing time. The result also showed that those who had high television viewing time but were physically active were not at risk. The authors concluded that physical inactivity

was critical to the incidence of T2DM and suggested that interventions that focus on increasing physical activity have the potential to reduce T2DM in the elderly. However, this study sample was limited to adults who are older than 65years and may not be generalized. Grøntved and Hu (2011), conducted a metaanalysis of 8 prospective cohort studies published between 1970 and 2011 to examine the association between television viewing time and T2DM, fatal and nonfatal cardiovascular disease, and all-cause mortality. A total of 175 938 individuals with over 1.1 million person-years of followup were involved in this study. Four of the included studies reported results on the effect of television viewing on T2DM. The results showed that there was a linear increase in the risk of T2DM with the number of hours per day of TV viewing. Although this study was prospective in nature and included large sample sizes and long followup periods, the study population included only studies done in Europe, Australia and North America and, may not be applicable to Arab populations in the Middle East whose bodily response and way of life are distinct from that of the West (Azeem et al., 2015). This study which sought to examine the association between T2DM and CRC in the Omani population could likely fill this gap in the literature.

Alcohol Consumption and Tobacco Use

Published studies on the association between alcohol consumption, tobacco use, and CRC risk and mortality have suggested that tobacco use increases risk of CRC through long term exposure to polycyclic aromatic hydrocarbons and carcinogenic compounds found in cigarette smoke (Slattery et al., 2004; McCleary et al., 2010). On the other hand, the association between alcohol use and CRC related to the formation of free

radicals from the alcohol metabolite, acetaldehyde (Rueda et al., 2012). Moreover, excessive alcohol consumption; and tobacco smoking induces inflammation and DNA instability in the gastrointestinal tract which, in turn, promotes carcinogenesis (Wilson, & George, 2014). Some studies have also shown that both tobacco use and excessive alcohol consumption predispose to the development of chronic inflammatory conditions which eventually progresses to CRC (Giovannucci & Michaud, 2007; Otani et al., 2006; Wilson, & George, 2014).Moreover, a dose-and time- dependent association between tobacco use, and CRC incidence and outcome, was consistent in most of the studies.

In the study by Rueda et al. (2012), those who smoked were 19% more likely to develop CRC than never smokers, an effect that increased in magnitude with increasing number of packs smoked, and the number of years of smoking. As with tobacco use, Rueda et al. also found that the association between alcohol and CRC risk appeared to be dose-dependent, especially in males Moreover, they found that current use of alcohol and/ or tobacco was associated with early onset CRC, prompting them to call for an updated modified screening criteria for CRC, which would include males and females, 40 year of age.

Similar results were reported by Phipps et al. (2013), in randomized phase 3 adjuvant chemotherapy trials among patients with stage III colon cancer. These researchers found that, compared to never smokers, ever smokers were significantly at a higher risk of death. This association was slightly stronger for current than former smokers. They also found that duration and number of cigarettes smoked was associated with poorer outcome. A few studies found that risk differed by gender (Boyle, Fritschi,

Platell, & Heyworth, 2013), and geographical location (Hou et al., 2014). Hou and colleagues evaluated the association between smoking and CRC risk among a large Chinese population and found that in addition to the dose-response association with smoking and alcohol consumption, greater CRC risk was found in rural than in Urban men. In the study by Boyle et al. (2013), female current smokers, but not males, had poorer survival compared to never smokers. On the contrary, Phipps et al. found no significant association between smoking and CRC survival among women. A few other results found no significant association between cigarette smoking and CRC outcomes (McCleary et al., 2010; Nordenvall, Nilsson, Ye, Andersson, & Nyrén, 2013), which according to Phipps et al., might be related to tumor characteristics or, differences in study protocols. Phipps and colleagues stressed the importance of patient and tumor characteristics when evaluating the associations between risk factors and CRC prognosis

Prevalence data on alcohol consumption in the Arab countries of the Middle are scarce due to religious and sociocultural restrictions on alcohol use. The few available prevalence studies were conducted among patients in psychiatric centers or by a review of hospital notes of patients admitted into hospitals for different reasons (Zaidan, Dorvlo, Viernes, Al-Suleimani, & Al-Adawi, 2007; Al Marri & Oei, 2009). One such study (Zaidan et al., 2007), examined the severity of harmful and hazardous drinking in Oman in nonpsychotic Omani nationals that sought treatment in a psychiatric hospital for substance abuse. The authors found that 66% of the 56 patients interviewed consumed alcoholic beverages regularly. More than half of these patients admitted they consumed alcohol on a daily basis. In a study by Al Riyami and Afifi (2004), the crude prevalence

of current smoking among Omanis was 7%. In this study, the highest prevalence of current smokers occurred in the 40-49 age groups. These researchers called for health awareness strategies aimed at adolescents, and government policies to reduce smoking. Till date, no previous study has reported on the effect of alcohol consumption and smoking on the association between T2DM and CRC in the Omani population. This gap in the literature was what this proposed research attempted to fill.

Gender

Epidemiological evidence suggests that men are at a slightly higher risk for T2DM and cancers than females. Generally, men have a higher lifetime probability of being diagnosed with an invasive cancer (45%) compared to 38% in women (Siegel, Naishadham, & Jemal, 2012). Similarly, 11.8% of all men over the age of 20 years have a higher risk of T2DM than 10.8% of women of the same age (CDC, 2011). Study results on the association between T2DM and CRC by gender have been somewhat inconsistent (Campbell et al., 2010; He et al., 2010; Krämer et al., 2012). The study by Campbell et al. (2010), involved a sample of 73,312 men and 81,663 women, of which 227 men, and 108 women had T2DM respectively. The researchers found a 24% higher risk of CRC in men with T2DM compared to those without T2DM. However, in women, there was no difference in risk of CRC in those with T2DM compared to those without. The researchers attributed their finding to sex differences in the use of metformin, and better glucose control in women compared to men. Metformin is more frequently prescribed for women with T2DM, and has been associated with lower risk of CRC (Campbell et al., 2010). Contrary to these findings, He et al., (2010), reported that compared to

nondiabetics, women with T2DM had a significantly greater risk of CRC (28%) than diabetic men (18%). However, in a metaanalysis by Krämer et al., (2012), researchers found that compared to those without diabetes, a significant association between T2DM and CRC was similar for men and women with T2DM. This metaanalysis included 29 cohort and case-control studies conducted in Australia, China, Europe, Iran, Israel, Japan, Korea, and the United States. None of the studies was from the Middle East or Oman for that matter. In this research study, I attempted to fill this literature gap.

Age and family health history

Age and hereditary are nonmodifiable risk factors for many chronic diseases (WHO, 2015). In addition to the natural loss of function of important organs that occurs with aging, the accumulation of modifiable risk factors that occurs throughout the life course predisposes older people to higher risk of chronic diseases including cancers (WHO, 2015). Similarly, the IDF stated that age and a family history of diabetes are among the several risk factors that are associated with T2DM (IDF, 2015). Consequently, accounting for age and family history in the association between T2DM and CRC would aid in the interpretation of findings from this study.

Researchers have recommended that collection of an up to date family history is necessary because it is a strong predictor of an individual's risk of common complex diseases such as diabetes and cancer (Hinton, 2008; Powell et al., 2013). Furthermore, a person's family health history provides opportunity for disease risk assessment, and the implementation of prevention strategies against common but complex diseases in at- risk individuals (Hinton, 2008; Powell et al., 2013). For example, the risk of breast cancer is

about 1.8 times higher in women with a history of breast cancer in a first-degree relative. This risk becomes three times higher if two of her first-degree relatives have cancer (Hinton, 2008; Powell et al., 2013). Similarly, a family history of colon cancer at younger age in a first-degree relative is a criterion for beginning colonoscopy screenings before the age 50 years (Powell et al., 2013), and the referral for genetic testing of family members (Hinton, 2008).

Johnson et al. (2013), conducted a metaanalysis of 12 non-screening risk factors of CRC. Their aim was to develop a risk assessment model that would be useful to clinicians and the public for predicting the risk of developing CRC in different individuals. Among the 12 non-screening risk factors that were analyzed, a family history of CRC in a first degree relative and presence of inflammatory bowel disease, were associated with a higher risk of CRC than other factors such as increased BMI and red meat consumption. The authors found that compared to those without a family history of CRC, individuals with a family history of CRC in a first-degree relative were almost 2 times more likely to develop CRC. Some researchers have reported that CRC tended to occur in Omanis of younger age than found elsewhere (Brim et al., 2008; Kumar et al., 2015). Moreover, marriage between relatives is common in Oman on the basis of the Omani culture. This could be the genetic basis of propagation of CRC in some Omani families yet; there are no studies on the prognostic effect of age and family history of CRC on the association between T2DM and CRC in Oman. This research could make a contribution to the literature in this area.

Summary and Conclusions

The literature review presented in this chapter summarized data on the association between T2DM and CRC risk and survival. Potential confounders, based on existing literature were also reviewed. While findings point to an association between T2DM and CRC, some inconsistencies related to tumor subsite, gender differences, sample size, and study design warrant further studies. Reviewed evidence is in favor of an association between T2DM and CRC risk and mortality. However, inconsistencies were apparent regarding the strength of this association. An apparent gap in this literature review was that none of the studies in the literature were carried out on the Arab populations of the Middle East. Thus, the aim of this research was to address this knowledge gap by assessing the association between T2DM and, CRC risk and survival among the Omani population. The influence of diet, obesity, physical inactivity, alcohol consumption, tobacco use, age, and family history of CRC on this association was examined.

The contributions of this study to the existing knowledge base could lead to positive social changes in the public health and health care in Oman. The social change element in this research would be that the findings could inform the design of preventive strategies and policies to address the burden of CRC in Oman. Addressing the burden of CRC in Oman has implications for population health and economic progress. For example, improved survival for CRC patients means longer disease free periods which would allow them to return to work and become productive members of their communities once again. Positive social change would also be achieved when preventive measures to tackle the burden of CRC leads to reduction in the direct and indirect costs

associated with CRC diagnosis and treatment. CRC treatment consists of surgeries, chemotherapy, radiotherapy, inpatient and outpatient clinic visits for prolonged periods of time. Direct costs of such care can range from $1941 to $48453 per patient per annum depending on the stage of the disease at diagnosis (Wong et al., 2012).

In Chapter 3, the methodology and research design of this study as well as the criteria for selecting the study population, sampling method, recruitment protocol, data collection, and data analysis are presented. Additionally, the ethical considerations and threats to validity as applicable are summarized.

Chapter 3: Research Method

The purpose of this retrospective quantitative study was to examine the association between T2DM and CRC risk and mortality in Oman. Based on the literature review in Chapter 2, the following potential confounders were chosen a priori: age, smoking status, alcohol consumption, BMI, cancer stage, diet, family history of CRC, and physical activity. These are covariates that have been linked with CRC risk and outcomes. The results of study may lead to positive social changes in the public health and health care in Oman. The findings may inform the design of preventive strategies and policies to address the burden of CRC in Oman. Addressing the burden of CRC in Oman has positive implications for the population health and economic progress. In this chapter, the methodology for this quantitative study will be explained in detail, including the following sections: research design and rationale, setting and sample, instrumentation and materials, data collection and analysis, protection of participants' rights, threats to validity, as well as the ethical procedures.

Research Design and Rationale

In this retrospective quantitative research, I used de-identified archival data from the EHRs of CRC cases diagnosed and treated in Sultan Qaboos University Hospital Oman from 2006 to 2016. The goal of the research was to examine the association between T2DM and CRC risk and survival rates in Oman. To answer Research Question 1, a retrospective, case-control study was used to study the association between T2DM and CRC risk. Data for this case-control study were extracted from the database of a previous study in SQUH on lifestyle–related risk factors for gastrointestinal cancers in

Oman. This study included 120 CRC cases (ICD 10: 18.0 [Caecum)], 18.2 [ascending colon], 18.3 [hepatic flexure], 18.4 [transverse colon], 18.5 [splenic flexure], 18.6 [descending colon], 18.7 [sigmoid colon], 18.8 [overlapping lesion of the colon], 18.9 [colon unspecified], 19 [recto-sigmoid junction], 20 [rectum[, and 28 stomach cancer) patients admitted in the oncology wards or who attended the oncology outpatient clinic from February 2016 to November 2016. The controls were 172 patients admitted in the ENT, orthopedic surgery, and ophthalmology departments of the same hospital within the period of the study. The controls were admitted with a wide range of acute nonmalignant conditions that ranged from cataract, slipped discs, low back pain, simple fractures, sprains, minor traumas, hernia repair, acute appendicitis, gall bladder stones, and osteoarthritis. Dietary information was captured with a validated interviewer-administered, semi quantitative Food Frequency Questionnaire that had been tested for reliability and validity (Arafa, Waly, Jriesat, Al Khafajei, & Sallam, 2011). The reproducibility study for this questionnaire yielded intraclass correlations that ranged from 0.56 to 0.88 among food groups (Pietinen et al., 1988). The validity study was conducted on 190 men of similar age and yielded correlations between nutrient intake values that ranged from 0.40 for selenium to 0.80 for alcohol (Pietinen et al., 1988). Participants were asked to report the frequency and portion sizes for each of 33 food items in six food groups commonly eaten in Oman, 2 years prior to CRC diagnosis for cases or prior to their admission for controls. The questionnaire also contained questions on demographic variables, such as gender, age, education and marital status, smoking and alcohol consumption, as well as questions on the frequency of participation in selected

physical activity aimed at achieving the physical activity levels recommended by the WHO for adults, 18-64years and 65 years and over (WHO, 2016b). Upon receiving approval to conduct research from the Walden University Institutional Review Board, the de-identified data of CRC cases and controls from this study were extracted and stored in a secured database in a password-protected personal computer.T2DM cases in this data set were compared with controls with T2DM while controlling for diet, physical activity, BMI, alcohol consumption, smoking status, and family history of CRC to determine the odds of CRC in cases versus controls. Case-control studies are best suited for studying rare diseases such as CRC and have been applied by similar studies in the past (Kuriki, Hirose, & Tajima, 2007; Levi et al., 2002; Pelucchi et al., 2010; Sandhu et al., 2001). Moreover, a hospital–based, case-control study provides an optimal framework for comparing medical histories of both cases and controls (Kuriki et al., 2007; Levi et al., 2002).

For Research Questions 2 and 3, a survival analysis was conducted using secondary data from the hospital records of CRC patients diagnosed and treated in SQUH Oman from 2006 to 2012. Cases were retrospectively followed up till 2016 to determine the effects of T2DM on overall survival (OS). Vital status of cases was ascertained through a review of the medical records of cases. Those who were still alive at the end of the follow-up period were censored. Survival analysis was carried out with the Kaplan Meier method. The differences in survival curves in patients with T2DM compared to those without T2DM was determined with the Log-rank test. A multivariable-adjusted Cox proportional hazards modeling was then performed while controlling for tumor

location, gender, age group, family history of CRC, cancer stage, BMI, smoking, and alcohol.

Methodology

Study Population and Setting Population

The study population for this research were male and female patients with histologically confirmed diagnosis of CRC, according to the international Classification of Diseases ICD-10, namely C18.0, 18.2, 18.3, 18.4, 18.5 18.6, 18.7, 18.8, 18.9, and C19 and C20, treated in SQUH from 2006 to 2016. The histological subtypes represented by the ICD codes above are caecum, ascending colon, hepatic flexure, transverse colon, splenic flexure, colon, sigmoid colon, overlapping lesion of the colon, colon unspecified, recto-sigmoid junction, and-rectum respectively. For the purposes of this study and to answer Research Questions 2 and 3, tumors labeled as histological types C18.0 to C18.9 were designated as colon subsite whereas, tumors labelled as C19 and C20 represented the rectum subsite.

The controls (for Research Question 1) were patients admitted in the ENT, orthopedic surgery, and ophthalmology departments of the same hospital within the period of the study with a range of acute nonmalignant conditions that ranged from cataract, slipped discs, low back pain, simple fractures, sprains, minor traumas, hernia repair, acute appendicitis, gall bladder stones, and osteoarthritis. Permission to acquire and analyze this de-identified data was obtained from the SQUH Institutional Review Board after signing a data use agreement.

Patients who were included in this study were adults aged 18years and above at the time of diagnosis. Only patients with adenocarcinoma of the colon or rectum were included. Patients diagnosed with other rarer types of colorectal malignancy, such as lymphoma, gastrointestinal stromal tumors, gastrointestinal carcinoid tumors, squamous cell, small cell carcinoma, leiomyosarcomas, and melanoma were excluded. Likewise, tumors arising from the appendix (ICD 10: C18.1) or from the anus (ICD 10: C21.0) were not included. The operational definition of CRC for this study was according to the International Classification of Diseases version 10, namely ICD 18.0, 18.2, 18.3, 18.4, 18.6, 18.7, 18.8, 18.9 (colon cancer) and, ICD 19 and 20 (cancer of the rectum). Malignant neoplasm of the appendix (ICD 18.1) are not considered a type of CRC (American Cancer Society, 2016), and they were not included in this study.

The exposure variable was T2DM defined according to the WHO (year) diagnostic criteria as a fasting plasma glucose ≥ 7.0mmol/l (126mg/dl) or 2–h plasma glucose ≥ 11.1mmol/l (200mg/dl). T2DM status was determined through a review of CRC patients' case histories for a diagnosis of T2DM and from the patients' drug use summaries for information on glucose lowering medications as documented in the SQUH EHRs.

Sampling and Sampling Procedures

A nonprobability sampling strategy was applied in this study. It involved a convenience sampling method of all of the CRC cases aged 18 years and above, diagnosed from 2006 to 2012 in the SQUH database. The OpenEpi software version 3.1.9.2 (Dean, Sullivan, & Soe, 2009) was used to calculate the sample size to address

Research Question 1. The sample size for Research Questions 2 and 3 was determined with the PS power software (Cunningham, & McCrum-Gardner, 2007; Dupont & Plummer, 1990).

For Research Question 1, sample size calculation carried out with the OpenEpi software yielded a sample size of 228 (114 in each group) based on 95% confidence interval, 80% power, a 15% diabetes prevalence in controls (IDF, 2015), and a least odds ratio of 2.5. For Research Questions 2 and 3, the PS power software (Dupont & Plummer, 1990) was used to calculate the required sample size. Based on 80% power, an accrual interval of 6-time units, additional follow-up of 4-time units after the accrual interval, and a hazard ratio of 1.5 in CRC subjects with T2DM relative to those without T2DM (De Bruijn et al., 2013), a sample size of 206 was needed to be able to reject the null hypothesis. However, the entire CRC cases available in the dataset within the study period- 2006-2012 were 214, and this served as the sample. The de-identified data were received from SQUH as two separate datasets after signing a data use agreement and upon obtaining the Walden University IRB approvals. The datasets were then stored in a secured database in a password-protected computer.

Operationalization of Study Variables

Incident CRC was the dependent variable for Research Question 1. CRC mortality was the dependent variable for Research Questions 2 and 3. T2DM was the independent variable (IV). The covariates for Research Question 1 were age, smoking status, alcohol consumption, BMI, diet, family history of CRC, and physical activity. Research Question

2 was adjusted for these potential confounding variables and additionally for tumor location, gender, and stage of disease.

CRC was defined according to the ICD version 10, namely malignant neoplasm of the colon ICD 18, malignant neoplasm of the recto-sigmoid junction, ICD19, and malignant neoplasm of the rectum, ICD 20. The histological types for colon cancer subsite included 18.0, 18.2, 18.3, 18.4, 18.5, 18.6, 18.7, 18.8, and 18.9, but excluded malignant neoplasm of the appendix (ICD 18.1).

Tumor location referred to the anatomical site of tumor, and it was categorized broadly as colon (ICD 18.0 18.2, 18.3, 18.4, 18.5, 18.6, 18.7, 18.8, 18.9) and rectum (ICD19 and 20). Age was defined as the chronological age of the patient at the time of diagnosis, and it was captured as a continuous variable. However, prior to the analyses, age was recoded into a categorical variable, age group with three levels: ≤ 40, 41 – 60, and ≥ 61 based on observational studies that CRC tended to occur in Omanis at younger age than found in the Western countries (Brim et al., 2008; Kumar et al., 2015; Muliira et al., 2016). Family history referred to a family history of CRC, and it was dichotomized as yes/no. Physical activity defined as achieving the WHO (2015) standard recommendation of 150 minutes of moderate physical activity or 75 minutes of vigorous physical activity in a week for adults of ages 18-64 years and age 65years and above was dichotomized as active/not active. The not active category comprised participants who reported less than the WHO-recommended standard. The active category was made up of participants in the moderate and vigorous physical activity groups in the original study. Smoking status (ever and never smokers) and alcohol consumption (ever and never drank) were

dichotomized as yes/no. Obesity was denoted by BMI, and it was categorized into three levels: 18.5- 24.99 kg/m^2, 25 - 29.99 kg/m^2, ≥30 kg/m^2 according to the WHO (2015) criteria. The dietary data were available as servings per day or per week across the six food groups (fruits, vegetables, proteins, milk products, grains, and oils) in the USDA food guide 2010. There were also responses to consumption of cake/biscuits/white bread and consumption of energy and sugary drinks. I created a categorical variable, diet quality, with three levels: poor, fair, and good. I then converted participants' responses in the dietary questionnaire into Healthy Eating Index component scores, a set of scores that capture the key recommendations of the 2010 USDA dietary guidelines (Guenther et al., 2013). The HEI 2010 components are scored to derive a single score out of a possible 100 maximum points. Each participant's score could fall within a range of 30-100 points. A diet with a score greater than 80 is considered good, with a score of 51-80 is considered fair, and one with a score of less than 51 is considered poor quality respectively (Guenther et al., 2013). The participants' composite scores were used to group them into one of the three categories of diet quality. The study variables and their level of measurement are as shown in Table 2.

Table 2
Study Variables and Their Level of Measurement

Variable	Type	Level of measurement
T2DM	Independent	Nominal (yes =1, no =0)
Tumor location	Independent	Nominal colon (yes/no), rectum (yes/no)
Year of diagnosis	Independent	scale
Stage of disease	Independent	Ordinal (1- local, 2 = regional spread, 3 = distant spread)
Body Mass Index	Independent	Ordinal 1= 18.5- 24.99 kg/m^2 2= 25 - 29.99 kg/m^2 3= ≥30 kg/m^2
Diet Quality	Independent	Ordinal Poor Fair Good
Physical activity	Independent	Nominal (active/not active)
Alcohol use	Independent	Nominal (ever =1, never = 0)
smoking status	Independent	Nominal (ever =1never = 0)
Age Group	Independent	Ordinal 1= ≤40 2= 41-60 3= ≥61
Family history of CRC	Independent	Nominal (yes =1, n =0)
Incident CRC	Dependent	Nominal (yes/no)
CRC mortality	Dependent	Nominal (yes/no)

Data Analysis Plan

The International Business Machine Corp. (IBM) SPSS Statistics version 21 was used to conduct all analyses. First, the data sets were cleaned through a validation process in SPSS using the *predefined rule* option. This process allowed me to identify missing data, extreme values (outliers), duplicates, and multiple entries (Green & Salkind, 2003). I then created a codebook where I documented the relevant variables for both the descriptive and inferential analyses. The various steps necessary for all my analyses were also detailed in this codebook.

Data analysis started with descriptive analysis to determine the characteristics of the two datasets and the distribution of the relevant variables. The main independent variable T2DM, and all other covariates, were categorical variables; therefore, the chi-square test assumption was first tested to ensure it was not violated. Following the testing of the chi-square test assumption, chi-square test of association was calculated to determine differences among relevant variables between the group with T2DM compared with the no T2DM group both for the case control study and the time-to event analysis. For the purpose of conducting the survival analysis for Research Questions 2 and 3, the Cox proportional hazard assumption was tested for T2DM and all other covariates using the log-log function in the Kaplan Meier plots and the time-covariate Cox proportional regression. Multivariable-adjusted logistic and Cox proportional regression analyses were then carried out to determine the association between T2DM and CRC risk and survival rates. The aim of the research questions for this study was to meet the key objectives of investigating the possible influence of T2DM on the risk of developing CRC and on CRC

survival rates in the Omani population. The following relevant covariates (age, stage of disease, gender, diet, BMI, physical activity, alcohol consumption, smoking status, and family history of CRC) were adjusted for. On completing the descriptive analyses described above, inferential statistics was conducted to answer the research questions.

Research Question 1

What is the association between T2DM and risk of developing CRC in Oman, while controlling for, diet, BMI, physical activity, alcohol consumption, smoking status, age, and family history CRC?

$H_0$1: There is no association between T2DM and risk of CRC in Oman while controlling for, diet, BMI, physical activity, alcohol consumption, smoking status, age, and family history.

H_a1: There is an association between T2DM and risk of CRC in Oman while controlling for, age, diet, BMI, physical activity, alcohol consumption, smoking status, and family history of CRC.

To answer this question, I carried out a multivariable-adjusted logistic regression to determine the odds of developing CRC in cases and controls with T2DM. The variables that were controlled for were diet, physical activity, BMI, alcohol consumption, smoking status and family history of CRC. According to epidemiological studies (Aleksandrova et al., 2014; Cavicchia et al., 2013; Jarvandi et al., 2013; Kirkegaard et al., 2010; Pelucchi et al., 2010; Tabung , Steck, Ma, et al., 2015), these are potential effect modifiers and confounding factors of this association. Odds ratio with corresponding 95% confidence intervals were determined at a statistical significance of 0.05.

Research Question 2

What is the association between T2DM and CRC survival rates in Oman?

$H_0$2: There is no association between T2DM and survival rates in CRC in Oman.

H_a2: There is an association between T2DM and survival rates in CRC in Oman.

To answer this question, I calculated overall survival time in months for each participant by subtracting the date of diagnosis from the date of death, loss to follow up or end of study (which ever was earliest). I generated and compared Kaplan Meier curves for CRC patients with T2DM and those without T2DM using survival time in months as the time indicator and the vital status (1 = death, 0 = censored) as the survival indicator. Then, I conducted log rank test to determine if there were any differences in survival rates between CRC patients with T2DM and those without T2DM.

Finally, I conducted a multivariable–adjusted Cox proportional regression analysis while controlling for tumor location, gender, age, family history of CRC, cancer stage, body mass index, smoking status and alcohol consumption. These are covariates that have been shown in the literature to have prognostic effect on CRC and were chosen *a priori*. The hazard ratio and corresponding 95%confidence interval was generated at statistical significance of less than 0.05.

Research Question 3

What is the association between T2DM and CRC survival rates in Oman stratified by gender, age group, tumor location and cancer stage in Oman while controlling for the following relevant covariates: smoking status, alcohol consumption, BMI, diet, physical activity and family history of CRC?

$H_0$3: There is no association between T2DM and CRC survival rates in Oman stratified by gender, age group, tumor location and cancer stage in Oman while controlling for the smoking status, alcohol consumption, BMI, diet, physical activity and family history of CRC.

H_a3: There is an association between T2DM and CRC survival rates in Oman stratified by gender, age group, tumor location and cancer stage in Oman while controlling for the following relevant covariates: smoking status, alcohol consumption, BMI, diet, physical activity and family history of CRC.

To answer this question, I conducted Kaplan Meier survival analysis stratified by gender, age group, tumor location and cancer stage. The log rank test of equality of differences in survival rates between the groups with and without T2DM was also conducted across strata of these covariates. Then, I conducted multivariable- adjusted Cox regression analysis with interaction terms for T2DM and each of the strata variables to determine if any of them modified the association between T2DM and CRC. Hazard ratios and their corresponding 95%confidence intervals were derived at a statistical significance of less than 0.05.

Threats to Validity

According to (Szklo & Nieto, 2014. pp. 109-150), a valid study should be fit for purpose and the data collected in a reliable and valid manner. Only then can the overall results of the study be said to be unbiased and closer real life situation. However, it is difficult to achieve ideal situations in epidemiological studies. This research was a non-randomized study that used secondary data from SQUH and a nonprobability

convenience sampling method. Potential threats to both internal and external validity include recall bias, selection bias, reporting bias and misclassification of exposure bias.

External Validity

External validity threats bothered on the fact that data from this study was from one of two hospitals that treat cancer patients in Oman and so the results may not be generalized. However, SQUH treats more than 50% of CRC cases in Oman. Moreover, many patients prefer to have their treatment in SQUH, claiming that there are better facilities in SQUH than in the other hospital. Therefore, the samples were to a large extent, representative of the Omani population.

Internal Validity

The data set that addressed Research Question1 included dietary data derived from responses to a food frequency questionnaire. It is possible that the CRC cases may not have accurately recalled their dietary habits. Secondly, misclassification of exposure is common in case –control studies. In this study if participants were unable to accurately recall past exposure to diet and lifestyle habits (recall bias) it could result in misclassification of their exposure status.

Another type of misclassification bias inherent in this secondary data would be if interviewers deviated from study protocols (Szklo & Nieto, 2014. pp.109-150). Research Question1 was addressed with a hospital-based case control study. A particular selection bias that is inherent in hospital-based case control studies is the Berkson's bias (hospital-patient selection bias). Berkson's bias is a systematic bias in the distribution of disease amongst hospitalized patients such that in case-control studies where both cases and

controls are selected from the hospital, the controls tend to be more likely exposed to the exposure under consideration than the general population from which the cases came from (Schwartzbaum, Ahlbom, & Feychting, 2003; Roberts, Spitzer, Delmore, & Sackett, 1978). However, the controls were chosen from among patients admitted to the same hospital for conditions that are unrelated to the case disease therefore, the potential for Berkson's bias would be minimal.

Construct Validity

Construct validity was another inherent threat in this study. This would arise if the instrument that was used to collect the diet and lifestyle information from the participant is not a validated instrument. However, the instrument used has been tested for validity, reproducibility and reliability (Arafa et al., 2011). The reproducibility study for this instrument utilized a sample of 121 men aged 55–69 years and yielded intraclass correlations that ranged from 0.56 to 0.88 among food groups (Pietinen et al., 1988; Rimm et al., 1992). The validity study was conducted on 190 men of similar age and yielded correlations between nutrient intake values that ranged from 0.40 for selenium to 0.80 for alcohol (Pietinen et al., 1988; Rimm et al., 1992).

Statistical conclusion validity threat could have occurred if the appropriate sample size was not calculated for both samples. However, the sample size was calculated and triangulated with two different statistical software, OpenEpi and PS Power software. Finally, unknown confounding factors to both T2DM and CRC that were not accounted for during the analysis could have affected the internal validity of this study.

Ethical Procedures

All possible violation of participants' rights was avoided by taking appropriate measures to minimize any possibility of disclosure of personal information. Thus, on receipt of the de-identified archival data from SQUH, I stored the datasets in a password-protected personal computer dedicated to this doctoral research. An additional copy of the datasets was created and stored in a separate, secure location to prevent loss due to natural disaster. Secondly, this study did not require direct participation of patients or use of live subjects. Thirdly, the datasets were not accessed until the Walden University Institutional Review Board approval was obtained. Additional verification of data during the data cleaning stage of the analysis was obtained with the help of a staff member of the IT unit of SQUH who was specifically assigned to monitor what I was doing.

Summary

This quantitative retrospective case control and time-to-event analysis was carried out with the intention to examine the association between T2DM and CRC risk and mortality in Oman. The purpose of the study is to contribute to the current body of knowledge on this topic with the use of archival data from SQUH. Two methods for power analysis were triangulated to arrive at the appropriate sample size for the study. Upon receiving approval from the Walden University IRB, the required data sets were collected from SQUH and abstracted and stored in a password-protected personal computer. Descriptive and inferential analyses of the data were then conducted.

The inferential analyses focused on examining the possible association betweenT2DM and the risk of developing CRC, and CRC mortality while adjusting for

the following important covariates: age, gender, BMI, physical activity, diet, alcohol consumption and smoking status. The likely threats to validity were selection bias, reporting bias and recall bias. Appropriate ethical procedures including the approval from the Walden University IRB were addressed. Data analysis was carried out with the SPSS version 21 (2012) software. The results of this study are as presented in Chapter 4.

Chapter 4: Results

The purpose of this retrospective, quantitative study is to examine the association between T2DM and the risk and survival rates of CRC in Oman while controlling for covariates, such as stage of disease, gender, diet, BMI, physical activity, alcohol consumption, smoking, age, and family history of CRC. The research questions and hypotheses are as follows:

1. What is the association between T2DM and the risk of developing CRC in Oman?

$H_0$1: There is no association between T2DM and CRC risk in Oman.

H_a1: There is an association between T2DM and CRC risk in Oman.

2. What is the association between T2DM and CRC survival in Oman?

$H_0$2: There is no association between T2DM and CRC survival rates in Oman.

H_a2: There is an association between T2DM and CRC survival rates in Oman.

3. What is the association between T2DM and CRC survival stratified by gender, age group, tumor location, and cancer stage in Oman?

$H_0$3: There are no differences in the association between T2DM and CRC survival rates by gender, age group, tumor location, and cancer stage, in Oman.

H_a3: There are differences in the association between T2DM and CRC survival rates by gender, age group, tumor location, and cancer stage, in Oman.

This chapter will include a discussion about data collection and an explanation of any discrepancies in data from the data analysis plan discussed in Chapter 3. Descriptive statistics of the sample will be presented in narrative and tabular form. The findings from

the analysis will also be provided in this chapter. This will include detailed descriptive statistics, evaluation of statistical assumptions, and answers to the research questions. The overall findings will then be summarized before proceeding to Chapter 5.

The data used in this study were provided by the SQUH. They were extracted from the EHRs of CRC patients treated in SQUH. The de-identified data for all CRC patients treated between 2006 and 2016 in the hospital were given to me in a flash drive by the director of the hospital information system after signing a data use agreement. Upon receiving approval to begin research from the Walden University IRB, I opened the storage device containing the data sets. On examination, the flash drive contained two files in Excel format. The first file was labelled CRC_Lifestyle and contained variables used for a previous hospital-based, case-control study. This was the dataset that was used to address Research Question 1. The second file was labelled CRC_All and contained all CRC cases treated in SQUH from 2006 to 2016. This was the dataset that was used to answer Research Questions 2 and 3.

Data Cleaning

Dataset for Research Question 1

This dataset was expected to contain information on 120 CRC and 28 gastric cancer patients and 172 controls. On opening the CRC_Lifestyle data set, I discovered that there were 125 CRC cases, 28 gastric cancer cases, and 170 controls. First, the gastric cancer cases were deleted, and the reduced dataset was saved as CRC sample for Research Question 1. On further inspection of the reduced dataset, I found that out of the 125 CRC cases, three were primary pancreatic cancer cases, seven were cancer of the

duodenum, and one case was cancer of the appendix. These 11 cases were deleted because cancers of the appendix; duodenum and pancreas were not in the predefined inclusion criteria. This left me with a final sample of 114 CRC cases and 170 controls for Research Question 1. The predefined sample size necessary to reject the null hypothesis was of 228 (114 in each group). The data were exported from the Excel format to SPSS 21.

A frequency check on the variables was performed to look for missing values and outliers. All relevant variables to address Research Question 1 were included in the dataset. However, BMI information was missing for eight controls. In order not to compromise statistical power by deleting the entries with missing BMI values (this would lead to a reduction in sample size), the sex-specific mean BMI was imputed for the missing values. Hence, the final sample for Research Question1 remained as 114 CRC cases and 170 controls. In further inspection of the BMI of participants, I found that only nine cases and two controls were in the underweight category; therefore, BMI was collapsed into a categorical variable with three levels: underweight/normal, overweight, and obese categories.

Age was originally categorized into seven age groups. However, due to few cases in some of the categories, age group was further collapsed into three categories: ≤40, 41-60, and ≥61. Physical activity responses were available as not active (did not engage in any physical activity), moderately active (engaged in activities like walking), and vigorously active (engaged in activities like running, aerobics, and cycling), representing participants who did not engage in any physical activity, those who devoted up to 150

minutes of moderate physical activity per week, and those who put in 75 minutes of vigorous physical activity per week according to the WHO (2016b) standard recommendation for adults. I categorized physical activity into two categories as active and not active categories. The not active category included participants who reported no/less than the WHO-recommended standard physical activity for adults. The active category included participants in the moderate and vigorous physical activity groups in the original dataset.

Dietary responses were available as servings per day or per week across the six food groups (fruits, vegetables, proteins, milk products, grains, and oils) in the USDA food guide 2010. There were also responses to consumption of cake/biscuits/white bread and consumption of energy and sugary drinks. I constructed another variable (dietary score) using the Healthy Eating Index (HEI 2010). The HEI-2010 components are a set of scores that capture the key recommendations of the 2010 USDA dietary guidelines (Guenther et al., 2013). The HEI 2010 components are scored to derive a single score out of a possible 100 points. A diet with a score greater than 80 is considered good, one with a score of 51-80 is considered fair, and one with a score of less than 51 is considered poor (Guenther et al., 2013). I summed up scores for each participant across the six main food groups according to the HEI standards. Those who consumed servings within the USDA-recommended serving per day received 10 full points whereas those who consumed more or less than the recommended serving were assigned 5 points (half the maximum points). In addition to the scores for the main food groups, a score of 0 or 20 was assigned for participants who documented that they consumed (0 points) or did not consume (20

points) cakes, biscuits, white bread, and those who consumed (0 points) or did not consume (20 points) energy and soft drinks, according to the HEI 2010 scoring standards. With these scoring standards, participants' total dietary score could fall within the range of 30 to 100 points. I then summed up scores for each participant and, depending on the HEI scores, participants were assigned to one of three categories of the diet quality: poor, fair, and good. The HEI-2010 has been used as a tool for assessing changes in diet quality over time, examining the relationship between diet cost and diet quality, and in research, to better understand relationships between nutrients/or dietary patterns and health-related outcomes (Guenther et al., 2013). Family history of colorectal cancer was categorized as yes/no. Likewise, smoking and alcohol intake were categorized as yes/no.

Dataset for Research Questions 2 and 3

This dataset contained all CRC cases treated in SQUH from 2006 to 2016. The variables in this data set included demographic variables, diagnosis (colon/rectum), date of diagnosis, comorbidities (hypertension, congestive heart failure diabetes), height in meters, weight in kilograms, stage and grade of disease at diagnosis, and type of treatment. The data were inspected, and all relevant variables to address Research Questions 2 and 3 were present in the dataset. However, some of the cases were diagnosed as far back as 2002. These cases (n= 32) were deleted in line with the predefined inclusion criteria. This left me with a sample of 228 cases to conduct the analysis. The calculated sample size based on 80% power, an accrual interval of 6-time units, additional follow-up of 4-time units after the accrual interval, and a hazard ratio of 1.5 in CRC subjects with T2DM relative to those without T2DM (De Bruijn et al., 2013),

was 206. Therefore, this available sample size of 228 was sufficient to address Research Questions 2 and 3.

I was granted access to the patients' EHR under the supervision of a staff member of the hospital information system. This enabled me to gather information related to smoking, alcohol consumption, and vital status for these 228 patients over the entire study period. Information about diet and exercise was available for only 42 patients. Therefore, a separate descriptive analysis was conducted with this subset of patients to see if their characteristics differed from the rest of the sample.

Height in meters and weight in kilograms were available for each patient. BMI was then calculated for each patient by dividing weight in kilograms by the square of height in meters. BMI as a continuous variable was normally distributed. Similar to Research Question1, BMI was converted into a categorical variable, BMIcat, with three categories: underweight/normal, overweight, and obese categories. Age was available as a continuous variable and was then converted into age group, a categorical variable with two categories: ≤ 60 years and ≥ 61 years. Cancer stage was categorized as local (for localized disease), regional spread (disease had spread to lymph nodes), and distant spread (disease has metastasized to distant organs); T2DM was categorized as T2DM and no T2DM; and family history of CRC was categorized as yes/no. Similarly, smoking, alcohol consumption, diet, and physical activity were as categorized in the sample for Research Question 1.

Data Analysis

The Chi-Square Assumption

In the two samples for Research Question 1 and Research Questions 2 and 3, the age and BMI variables were converted into categorical variables (as described above) before conducting the analyses. All other variables necessary for answering the research questions were categorical. The chi-square test was therefore used to assess the distribution of these participant characteristics among cases and controls for Research Question 1, and among cases with T2DM or without T2DM for Research Questions 2 and 3. The assumptions of the chi-square test require that the sample size be large enough such that none of the cells in the contingency table has expected counts of less than 5 (Field, 2013). The expected frequencies in each cell were greater than 5, and the sample sizes were sufficiently large, indicating that the conditions for the chi-square assumption were met.

Proportionality of Hazards Assumption

For the purposes of conducting the survival analysis, Cox proportional hazard modelling was applied to answer Research Questions 2 and 3. I tested the proportionality of hazards assumption, a major assumption for the Cox proportional hazards model. This assumption requires that the effect of a given set of covariates be the same over time or that the shape of the survival function is the same for all cases or groups over time (Tabachnick, Fidell, & Osterlind, 2001, pp. 510-570). If this assumption is violated, then the result of the analysis cannot be said to be valid. To graphically assess this assumption, I generated Kaplan Meier log-log curves separately for each predictor variable. For this

assumption to hold, the log-log plot should show separate lines for the variable that is being compared. As an example, the log-log curve for patients with and those without T2DM is presented in Figure 2. Similar log-log function curves were also generated for other covariates (Appendix A). I also conducted a time-dependent covariate Cox regression to determine if the effect of T2DM and other independent variables on CRC survival was time dependent. The result of this analysis is shown in Table 3. The *p*-values in Table 3 indicate that the effect of the variables on CRC survival was not time dependent.

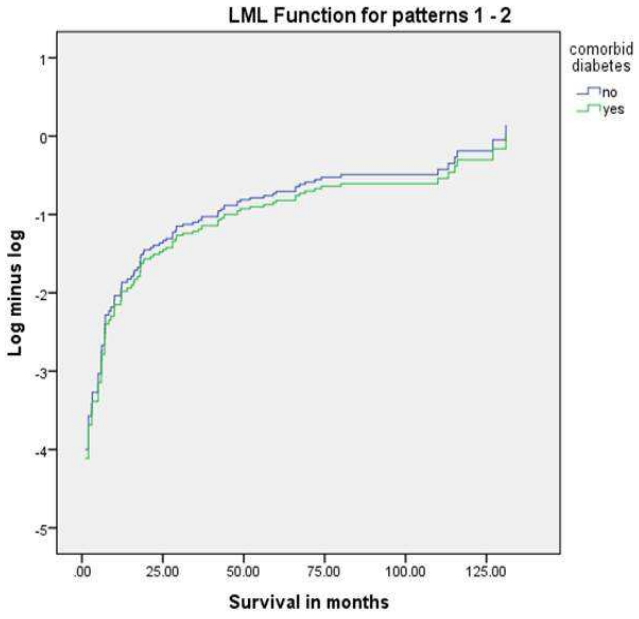


Figure 2. Log-log function for T2DM

Table 3

*Test of Proportionality Hazard for Time*Covariates*

Variable	*B*	*SE*	Wald	*P*	Exp*B*	95% *CI* for Exp (*B*)	
						LL	UL
T_COV_	0.00	0.01	0.00	.10	1.00	0.99	1.01
T2DM	0.11	0.34	0.11	0.74	1.12	0.58	2.18
T_COV_	-0.01	0.01	0.70	0.40	0.99	0.98	1.01
Gender	0.44	0.32	1.93	0.17	1.55	0.84	2.89
T_COV_	0.00	0.00	2.77	0.09	1.00	0.99	1.01
Location	-0.17	0.11	2.43	0.12	0.84	0.68	1.05
T_COV_	-0.01	0.00	2.70	0.10	0.99	0.97	1.00
Age group	0.54	0.33	2.76	0.10	1.72	0.91	3.24
T_COV_	-0.00	0.01	0.35	0.55	1.00	0.99	1.01
Cancer	0.98	0.25	15.00	0.00	2.66	1.62	4.36
Stage							
T_COV_	-0.002	0.009	0.03	0.84	0.1	0.98	1.02
FH	-0.2	0.42	0.02	0.64	0.82	0.36	1.88
T_COV_	-0.00	0.01	0.36	0.55	1.00	0.99	1.01
BMI	-0.13	0.20	0.40	0.53	0.88	0.59	1.31
T_COV_	-0.00	0.12	0.23	0.63	0.99	0.96	1.02
Alcohol	0.16	0.56	0.08	0.78	1.17	0.39	3.51
T_COV	0.01	0.01	0.18	0.67	1.01	0.98	1.03
Smoking	0.27	0.50	0.30	0.58	0.76	0.29	2.01
T_COV_	0.00	0.01	0.00	.10	1.00	0.99	1.01

Study Results

Descriptive Statistics

Research Question 1:. Descriptive statistics stratified by cases and controls was carried out with the final sample (*n*= 284) for Research Question 1. Chi-square tests were used to compare differences in categorical and binary variables between cases and controls. Table 4 contains descriptive statistics and summary characteristics of cases and controls in this sample. According to the descriptive analysis, there were differences in the gender distribution of the cases and controls. Whereas there were more males among cases (58.8%) than in controls (44.7%), females were more among controls (55.3%) than in cases (41.2%). This table also shows that about half (49.4%) of controls were overweight, and there were more obese cases than controls (28.1% vs 26.5%). In addition, the table also reveals that 48.2% of the cases consumed good quality diet according to the USDA food guide and HEI 2010 standards and 15.8% of cases had a family history of CRC. There were no statistically significant differences between cases and controls with respect to age, smoking, alcohol consumption, and physical activity.

Table 4

Characteristics of the Final CRC Sample for RQ1 by Case-Control Status

	CRC case (*N* = 114)	**control (*N* = 170)**	
Variable	*N* (%)	*N* (%)	*P* value
Age group			
≤40	15 (13.2)	36 (21.2)	0.08
41-60	48 (42.1	78 (45.9)	
>60	51 (44.7)	56(32.9)	
Gender			
Male	67 (58.8)	76 (44.7)	
Female	47 (41.2)	94 (55.3)	0.02[a]
Smoking			
No	86 (75.4)	131(77.1)	
Yes	28 (24.6)	39 (22.9)	0.43
Alcohol			
No	98 (86.0)	148 (87.1)	
Yes	16 (14.0)	22 (12.9)	0.46
Physical activity			
Not Active	59 (51.8)	96 (56.5)	
Active	55 (48.2)	74 (43.5)	0.24

Table continues

	CRC case (N = 114)	**control (N = 170)**	
Variable	N (%)	N (%)	*P* value
Body Mass Index (Kg/m^2)			
Underweight/Normal (< 25kg/m^2)	48 (42.1)	41 (24.1)	
Overweight (25 - 29.99 kg/m^2)	34 (29.8)	84 (49.4)	0.01[b]
Obese (≥30 kg/m^2)	32 (28.1)	45 (26.5)	
Diet			
Poor	8 (7.0)	18 (9.2)	
Fair	51 (44.7)	95 (55.9)	0.04[c]
Good	55 (48.2)	57 (33.5)	
Family History of CRC			
No	96 (84.2)	159 (93.5)	
Yes	18 (15.8)	11 (6.5)	0.01[d]
T2DM			
No	77 (67.5	107 (67.9)	0.25
Yes	37 (32.5)	63 (37.1)	

Note. a: x2 =5.49, df (1), b: x2 = 13.41 df (2), c: x2 = 6.35, df (2), d: x2 = 6.463, df (1)

Research Questions 2 and 3: The sample contained a total of 228 CRC patients of which 72 (31.6%) had T2DM compared to 156 (69.4%) without T2DM. Table 5 shows the descriptive characteristics of the patients by T2DM status. There were almost equal proportion of males (56.9% versus 59.6%) and females (43.1% versus 40.4%) in the 2 groups. In terms of tumor location, almost twice as many colon cancer patients had T2DM (65.3%) compared to the rectal cancer patients (34.7%). More of the patients with T2DM cases were in the younger age group of ≤ 60 years. However, there were more cases with regional and distant metastasis in the nonT2DM group (33.3% and 44.9%) compared to the T2DM group (36.1% and 37.5%). The table also shows that there were statistically significant differences in BMI by T2DM status. The T2DM group was more obese than the noT2DM group (37.5% compared to 22.4%) whereas there were more underweight/normal weight cases in the noT2DM group. The T2DM group consumed more alcohol (13.9%) compared to the noT2DM group (7.7%). Likewise, there were more smokers in the T2DM group (16.7%) compared to the noT2DM group (14.1%). By the end of the follow up period, the proportion of events was similar in the T2DM and noT2DM groups (37.5% versus 35.9%). The proportion of censored cases was also similar in the two groups (62.5% versus 64.1%).

Table 5

*Characteristics of the sample for RQs 2 and 3 by *T2DM status*

	T2DM (N =72)		noT2DM N =156)		
Variable	N	%	N	%	*P* value
Gender					
Male	41	56.9	93	59.6	0.41
Female	31	43.1	63	40.4	
Tumor Location					
Colon	47	65.3	85	54.5	0.08
Rectum	25	34.7	71	45.5	
Age Group					0.08
≤ 60	38	53.8	99	63.5	
≥ 61	34	47.2	57	36.5	
Year of Diagnosis					
2006	14	19.4	36	23.1	
2007	6	8.3	13	8.3	
2008	6	8.3	23	14.7	
2009	8	11.1	17	10.9	0.32

Table continues

	T2DM (N =72)		noT2DM N =156)		
Variable	N	%	N	%	*P* value
2010	14	19.4	13	8.3	
2011	9	12.5	20	12.8	
CRC stage					
Localized	19	26.4	34	21.8	
Regional	26	36.1	52	33.3	0.55
Distant	27	37.5	70	44.9	
Family History of CRC					
Yes	15	20.8	28	17.9	0.36
No	57	79.2	128	82.1	
Body Mass Index (Kg/m^2)					
Underweight /Normal (<25 kg/m^2)	18	25	62	39.7	
Overweight (25 - 29.99 Kg/m^2)	27	37.5	59	37.8	0.03

Table continues

Variable	T2DM (N =72) N	%	noT2DM N =156) N	%	*P* value
Obese (≥30 kg/m^2)	27	37.5	35	22.4	
Alcohol consumption					
Yes	10	13.9	12	7.7	0.11
No	62	86.1	144	92.3	
Smoking					
Yes	12	16.7	22	14.1	0.37
No	60	83.3	134	85.9	
Status					
Dead	27	37.5	56	35.9	0.46
Censored	45	62.5	100	64.1	

Note. T2DM = fasting plasma glucose ≥ 7.0mmol/l (126mg/dl) or 2–h plasma glucose ≥ 11.1mmol/l (200mg/dl). Localized = early disease stage, Regional = disease spread to lymph nodes, Distant = disease spread to distant organs

Characteristics of the diet and physical activity subsample

Diet and physical activity data were available for only 42 patients in the sample that addressed research questions 2 and 3. These two variables were therefore not included in the multivariate adjusted models. Table 6 shows the descriptive statistics for

this subsample. A comparison of the patient characteristics in this subsample with those in the whole sample in table 5 reveal very little differences between the two groups except that almost all the patients in the diet-physical activity subsample (90.5%) were censored. The 9.5% that experienced the event had no T2DM. Moreover, more than half (54.2%) of the diet-physical activity subsample were diagnosed in 2012 compared to those in the sample without the diet and physical activity. This can be attributed to the fact that the diet and exercise data were collected through personal interviews of patients who came to the hospital. Patients were interviewed during their hospital visit between February and November 2016. Given the natural cause of CRC, it is possible that patients diagnosed earlier were too sick to be available for personal interviews. It is also possible that earlier diagnosed patients were not alive to be part of those being interviewed about their dietary and physical activity habits. It was worthwhile to conduct a separate analysis of this subsample due to the small sample size. Therefore, I decided to discuss the implications of the absence of diet and physical activity variables in the multivariate-adjusted Cox regression models in chapter 5.

Table 6

Characteristics of the diet and physical activity subsample (n= 42)

Variable	N	%
Gender		
Male	28	66.7
Female	14	33.3
Tumor Location		
Colon	32	76.2
Rectum	10	23.8
Age Group		
≤40	5	11.9
41-60	17	40.5
≥61	20	37.6
Year of Diagnosis		
2006	2	4.8
2007	2	4.8
2008	5	11.9
2009	1	2.4
2010	5	11.9

Table continues

Variable	N	%
2011	5	11.9
2012	22	54.2
Stage of Disease		
Localized	11	26.2
Regional Spread	15	35.7
Distant Metastasis	16	38.1
Family History of CRC		
Yes	9	21.4
No	33	78.6
*T2DM		
Yes	13	31.0
No	29	69.0
BMI		
Underweight /Normal (<25 kg/m^2)	11	26.2
Overweight (25 - 29.99 kg/m^2)	15	35.7
Obese (≥30 kg/m^2)	16	38.1

Table continues

Variable	N	%
Diet		
Poor	20	47.6
Fair	22	52.4
Good		
Active	17	40.5
Not active	25	59.5
Drinking		
Yes	4	9.5
No	38	90.5
Smoking		
Yes	8	19.
No	34	81.0
Status		
Dead	4	9.5
Censored	38	90.5

Note. T2DM = fasting plasma glucose ≥ 7.0mmol/l (126mg/dl) or 2–h plasma glucose ≥ 11.1mmol/l (200mg/dl).

Answering the Research Questions

The following inferential analyses were conducted for each of the three research questions and associated hypotheses:

Research Question 1

What is the association between type 2 diabetes mellitus (T2DM) and the risk of developing colorectal cancer (CRC) in Oman? The related null and alternative hypotheses for this question were:

$H_0$1: There is no association between T2DM and CRC risk in Oman.

*H*a1: There is an association between T2DM and CRC risk in Oman.

To answer this research question, multivariate logistic regression was carried out to determine the association between T2DM and the dependent variable CRC while controlling for cancer stage, gender, diet, body mass index, physical activity, alcohol consumption, smoking and family history of CRC. These were variables selected *a priori* based on my literature review. The models were systematically built by first fitting T2DM alone (Model 1). This was followed by fitting a minimally adjusted model (model 2) with T2DM and age as the independent variables. Model 3 contained model 2 and the interaction term for T2DM and age. Finally, a fully adjusted model that included model 3 plus other potential confounding variables mentioned above, was built. The result of this analysis is as reported in Table 7.

The result shows that the final model was not statistically significant (*OR* = 1.49, 95% *CI*: 0.29-7.68, $p = 0.64$), indicating that, having adjusted for potential confounding

variables, there is no statistically significant association between T2DM and CRC risk. Therefore, the null hypothesis cannot be rejected.

Table 7

Logistic regression models for the association between T2DM and risk of CRC

	OR	95% *CI*	*P*
Model 1	0.83	0.50-1.37	0.46
Model 2	0.73	0.43-1.22	0.23
Model3	1.25	0.27-5.83	0.78
Model 4	1.49	0.29 -7.68	0.64

Note. T2DM = fasting plasma glucose ≥ 7.0mmol/l (126mg/dl) or 2–h plasma glucose ≥ 11.1mmol/l (200mg/dl), noT2DM is the referent group

Research Question 2

What is the association between T2DM and CRC survival rates in Oman? The related null and alternative hypotheses for this question were:

$H_0$2: There is no association between T2DM and survival rates in CRC in Oman.

H_a2: There is an association between T2DM and survival rates in CRC in Oman.

To answer this question, overall survival time in months for each participant was determined by subtracting the date of diagnosis from the date of death, loss to follow up or end of study (which ever was earliest). CRC patients who died were coded as 1 and the censored cases were coded as 0. Survival curves were generated using survival time in months as the time indicator and the vital status (1 = death, 0 = censored) as the survival indicator. The Kaplan Meier curves for CRC patients with T2DM and those without

T2DM were generated and compared (Figure 3). The log rank test was conducted to determine if there were any differences in survival rates between CRC patients with T2DM and those without T2DM. Table 8 shows that the median survival for CRC patients with T2DM was 113.2 months compared to 115.2 months for those without T2DM. The log-rank test, $\chi 2$ (1) = .24, p = 0.63 was not statistically significant (Table 9). This indicates that there is no difference in survival rates between the groups studied at all time points in the study period.

Finally, a multivariate Cox proportional regression analysis was carried out while controlling for tumor location, gender, age, family history of CRC, cancer stage, body mass index, smoking and alcohol consumption. These are covariates that have been shown in the literature to have prognostic effect on CRC and were chosen *a priori*. The multivariate Cox regression models were built by first fitting T2DM, age and cancer stage (model 1). Model 2 included model 1 plus all other covariates. The hazard ratio of T2DM, adjusted for these potential confounding covariates is shown in Table 10. Results from the multivariable-adjusted model (model 2) were not statistically significant (*HR* = 0.99, 95% *CI*: 0.62 -1.60, p = 0.99), indicating that, having adjusted for potential confounding variables, there is no statistically significant association between T2DM and CRC survival rates. Therefore, the null hypothesis cannot be rejected.

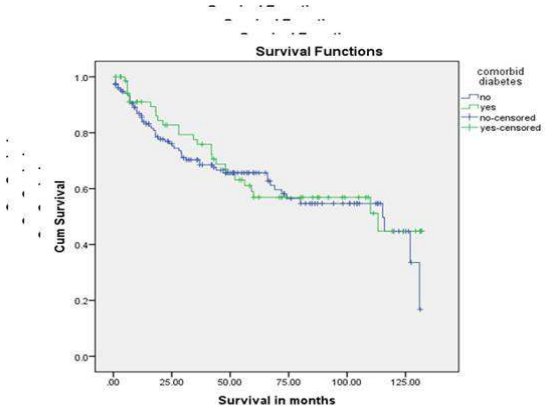


Figure 3. Kaplan Meier survival curves of cases with T2DM compared to those without T2DM

Table 8

Mean and median survival times by T2DM status

	Mean			Median		
T2DM Status	No of months	*SE*	95% *CI*	No of months	*SE*	95% *CI*
No	83.56	4.84	[74.07, 93.05]	115.20	23.10	[68.17, 62.23]
Yes	86.34	6.60	[73.42, 99.27]	113.20	40.72	[33.40, 193.12]
Overall	84.65	3.93	[76.94, 92.35]	115.20	16.45	[82.97, 147.43]

Estimation is limited to the largest survival time if it is censored

Table 9

Log rank test of equality of survival for CRC cases with and without T2DM.

	Chi-Square	df	*P* value.
Log Rank (Mantel-Cox)	0.24	1	0.63

Test of equality of survival distributions for the different levels of T2DM

Table 10

Multivariable-adjusted Cox Regression Models for association between T2DM and CRC survival

	HR	95%CI	*P value*
Model 1	0.98	0.62-1.56	0.94
Model 2	0.99	0.62-1.60	0.99

Note. noT2DM = referent

Research Question 3

What is the association between T2DM and CRC survival stratified by gender, age group, tumor location and cancer stage in Oman?

$H_0$3: There are no differences in the association between T2DM and CRC survival rates by gender, age group, tumor location and cancer stage, in Oman

H_a3: There are differences in the association between T2DM and CRC survival rates by gender, age group, tumor location and cancer stage, in Oman.

To test this hypothesis, I conducted Kaplan Meier survival analysis stratified by gender, age group, tumor location and cancer stage. The log rank test of equality of differences in survival rates between the groups with and without T2DM was also conducted across strata of these covariates. Then, I conducted multivariable- adjusted

Cox regression analysis with interaction terms for T2DM and each of the strata variables to determine if any of them modified the association between T2DM and CRC. The first model included gender, tumor location, cancer stage, age, and gender*T2DM. Followed by gender, tumor location, cancer stage, age, and tumor location*T2DM, then, gender, tumor location, cancer stage, age, cancer stage*T2DM and finally, gender, tumor location, cancer stage, age, and age*T2DM. Finally, I conducted a multivariable-adjusted Cox regression analysis stratified by these four covariates. To build the models, I fitted T2DM plus the respective stratum covariate (model 1). Model 2 included model 1 and all other potential effect modifiers (body mass index, drinking status, smoking status, family history of CRC).

The Kaplan Meier plots for gender are shown in figure 4 and figure 5. Similar plots were generated for age group, tumor location and cancer stage. The result of the stratified log rank tests for the variables is as shown in Table 11. The *p* values for all the covariates were not statistically significant, meaning that there are no statistically significant differences among the strata with regards to the association between T2DM and CRC. The Wald *P* values for these interaction terms were not statistically significant (Table 12). The hazard ratios and corresponding 95% confidence intervals for different strata of the covariates from the multivariate Cox proportional models are shown in Tables 13 to 16. These results demonstrated that across strata of gender, age group, tumor location and cancer stage, controlling for confounding variables, there are no statistical significance difference in survival rates between CRC cases with T2DM and those without T2DM. Therefore, I fail to reject the null hypothesis.

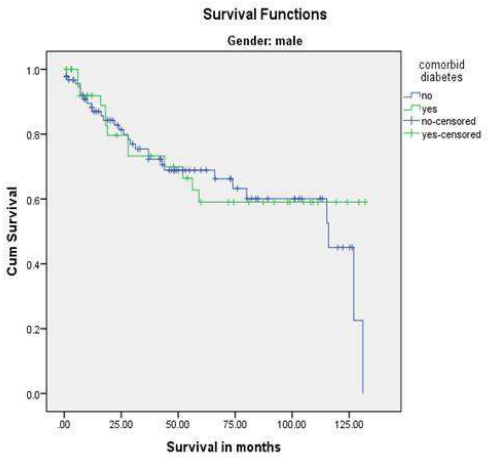


Figure 4. Kaplan Meier survival functions for males.

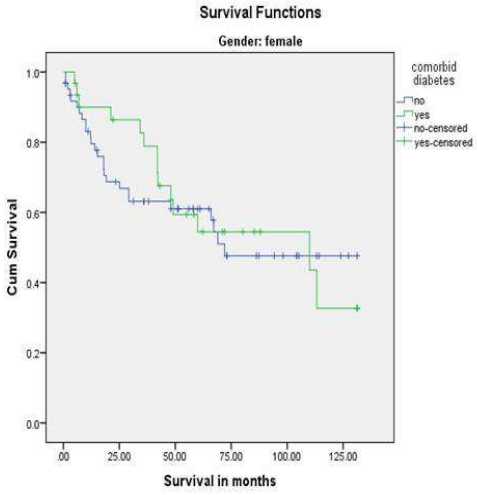


Figure 5. Kaplan Meier survival functions for females

Table 11

Log Rank test of equality for differences in survival in strata of potential confounders

Variable	Chi-Square	df	*p*-value
Gender			
Male	0.18	1	0.67
Female	0.09	1	0.77

Table continues

Variable	Chi-Square	df	*p*-value
Age Group			
≤ 60	0.01	1	0.94
≥ 61	0.58	1	0.45
Cancer Stage			
Localized	0.06	1	0.81
Regional	0.00	1	0.97
Distant	0.03	1	0.86
Tumor Location			
Colon	2,59	1	0.11
Rectum	2.69	1	0.10

Test of equality of survival distributions for the different levels of predictor variables

Table 12

Multivariable-adjusted models with interaction terms

Model	Variable	Wald	*P*
Model 1	T2DM*gender	0.00	0.96
Model 2	T2DM*tumor location	1.13	0.29
Model 3	T2DM*cancer stage	0.20	0.91
Model 4	T2DM*age group	0.21	0.65

Note. Variables included in each model: gender, tumor location, cancer stage and age group

Table 13

Multivariable-adjusted association between T2DM and CRC by gender

	Male			Female		
	HR	95% *CI*	*P*	*HR*	95% *CI*	*P*
Model 1	0.87	0.45-1.67	0.60	0.91	0.47-1.70	0.77
Model 2	1.06	0.53-2.13	0.60	0.96	0.49-1.87	0.91

Note Referent = noT2DM

Table 14

Multivariable-adjusted association between T2DM and CRC by age group

	≤60years			≥ 61 years		
	HR	95% *CI*	*P*	*HR*	95% *CI*	*P*
Model 1	0.75	0.36-1.57	0.45	0.98	0.54-1.77	0.90
Model 2	1.08	0.47-2.48	0.86	1.13	0.61-2.08	0.71

Note. Referent = noT2DM

Table 15

Multivariable-adjusted association between T2DM and CRC by tumor location

	Colon			Rectum		
	HR	95% *CI*	*P*	*HR*	95% *CI*	*P*
Model 1	0.62	0.34-1.12	0.11	1.85	0.87-3.91	0.11
Model 2	0.83	0.44-1.57	0.60	1.50	0.68-3.31	0.31

Note. Referent = noT2DM

Table 16

Multivariable-adjusted association between T2DM and CRC by cancer stage 14

	Local			Regi on			Distant		
	HR	95% *CI*	*P*	*HR*	95%*CI*	*P*	*HR*	95% *CI*	*P*
Model 1	1.20	0.27-5.42	0.81	0.98	0.42-2.30	0.99	1.05	0.58-.90	0.8
Model 2	3.73	0.24-6.30	0.34	1.02	0.40-2.59	0.97	1.02	0.55-.90	0.5

Note. Referent = noT2DM

Summary

The purpose of this retrospective quantitative research was to examine the association between T2DM and the risk of developing CRC as well as the association between T2DM and survival rates of CRC in Oman while controlling for the potential confounding variables diet, BMI, physical activity, alcohol consumption, smoking status, age, and family history. Stage of disease and tumor location was additionally adjusted for in models for survival analysis. Analysis of the two data sets provided by the Sultan Qaboos University Hospital (SQUH) enabled testing the hypotheses, and answering the research questions. The following null hypotheses were tested.

$H_0$1: There is no association between T2DM and CRC risk in Oman

$H_0$2: There is no association between T2DM and survival rates in CRC in Oman.

$H_0$3: There are no differences in the association between T2DM and CRC survival rates in categories defined by gender, age group, tumor location and cancer stage in Oman.

Based on the findings from the analyses, none of the three null hypotheses could be rejected.

To answer Research Question 1, multivariable-adjusted logistic regression was carried out to test the association between T2DM (the independent variable) and odds of developing CRC (the dependent variable). The results of the multivariable- adjusted analysis indicated there was no statistically significant association between T2DM and odds of developing CRC (OR = 1.49, 95% CI: 0.29-7.68, p = 0.64); therefore, the null hypothesis was not rejected.

For Research Question 2, Kaplan Meier curves for CRC patients with T2DM and those without T2DM were generated and compared. The median survival for CRC patients with T2DM was 113.2 months compared to 115.2 months for those without T2DM. The log-rank test, $\chi 2$ (1) = .239, p = 0.625 was not statistically significant. The multivariable-adjusted Cox regression analysis was not statistically significant (*HR* = 1.07, 95%*CI*: 0.65-1.75, p = 0.80) therefore; the null hypothesis of no association between T2DM and CRC survival rates in Oman was not rejected.

For Research Question 3, a stratified Kaplan Meier survival analysis was conducted across strata of gender, age group, tumor location and cancer stage respectively. The result of the log rank test of equality of differences in survival rates by T2DM status showed no statistically significant differences across all strata of the variables. The hazard ratios and corresponding 95% confidence intervals for the different strata of the covariates from the multivariate Cox proportional hazards models were not statistically significant (male, *HR* = 1.09, 95% *CI*: 0.52-2.20, p = 0.83, female: *HR* = 1.00, 95% *CI*: 0.51-1.98, p = 0.99; age group: ≤ 40, *HR* = 0.83, 95% *CI*: 0.16-4.39, p = 0.88, 41-60, *HR* = 1.36, 95% *CI*: 0.67-2.75, p = 0.39, ≥ 61, *HR* = 1.03, 95% *CI*: 0.44-2.40, p = 0.96, tumor location: colon, *HR* = 0.93, 95% *CI*: 0. 48-1.79, p = 0.82, rectum, *HR* = 1.29, 95% *CI*: 0.57-2.93, p = 0.54, cancer stage: local, HR = 2.25, 95% *CI*: 0.11-48.50, p = 0.60, regional, *HR* = 1.09, 95% *CI*: 0.42-2.80, p = 0.86, distant, *HR* = 1.07, 95% *CI*: 0.57-2.05, p = 0.80). Therefore, the null hypothesis of no differences in the association between T2DM and CRC survival, in strata of gender, age group, tumor location and cancer stage could not be rejected.

In Chapter 5 there will be an in-depth interpretation of the findings from this study with the view to place them within the larger body of literature presented in Chapter 2. A review of the study's limitations, recommendations for further research, and the implication for social change will also be discussed.

Chapter 5: Discussion, Conclusions, and Recommendations

Introduction

In this retrospective, quantitative study, I examined the association between T2DM and the risk and survival rates of CRC in Oman while controlling for stage of disease, gender, diet, BMI, physical activity, alcohol consumption, smoking, age, and family history of CRC. The ecosocial theory guided this study. The hypotheses and research questions were addressed using the data provided by the SQUH. In this chapter, I will summarize the key findings of this research study, provide an interpretation of the findings in relation to the existing literature, and highlight some of the study limitations. This will be followed by a series of recommendations for further research and action, a discussion about the social change implications of the research findings, and conclusions.

Summary of Findings

I employed logistic regression analysis to answer Research Question 1 and Cox proportional hazard regression analysis to answer Research Questions 2 and 3. In Research Question 1, it was hypothesized that T2DM is associated with higher odds of developing CRC. In Research Question 2, I hypothesized that there is an association between T2DM and CRC survival rates, while for Research Question 3, it was hypothesized that the association between T2DM and CRC survival is different in categories defined by gender, age group, tumor location, and cancer stage.

The independent variable in this study, T2DM, had no statistical significance and was not associated with an increase in the odds of developing CRC (*OR* = 1.49, 95% *CI*: 0.29-7.68, $p = 0.64$), neither was it associated with poorer CRC survival rates (*HR* = 1.07,

95% *CI*: 0.65 -1.75, *p* = 0.80). In the analyses stratified by gender, age group, tumor location, and cancer stage, T2DM was also not statistically significantly associated with CRC survival (gender: male, *HR* = 1.09, 95% *CI*: 0.52-2.20, *p* = 0.83, female: *HR* = 1.00, 95% *CI*: 0.51-1.98, *p* = 0.99; age group: ≤ 40, *HR* = 0.83, 95% *CI*: 0.16-4.39, *p* = 0.88, 41-60, *HR* = 1.36, 95% *CI*: 0.67-2.75, *p* = 0.39, ≥ 61, *HR* = 1.03, 95% *CI*: 0.44-2.40, *p* = 0.96, tumor location: colon, *HR* = 0.93, 95% *CI*: 0. 48-1.79, *p* = 0.82, rectum, *HR* = 1.29, 95% *CI*: 0.57-2.93, *p* = 0.54, cancer stage: local, *HR* = 2.25, 95% *CI*: 0.11-48.50, *p* = 0.60, regional, *HR* = 1.09, 95% *CI*: 0.42-2.80, *p* = 0.86, distant, *HR* = 1.07, 95% *CI*: 0.57-2.05, *p* = 0.80).

Interpretation of Findings

T2DM and Risk of Developing CRC

In Research Question 1, I asked if there was an association between T2DM and the risk of developing CRC. I found that having adjusted for potential confounding variables, there was no statistically significant association between T2DM and higher odds of CRC. Therefore, the null hypothesis could not be rejected. This finding contradicts the results of similar previous studies on the association between T2DM and the odds of developing CRC (L. Chen et al., 2013; Levi et al., 2002; Seow et al., 2006). L. Chen et al. reported overall higher odds of CRC in T2DM cases compared to controls. Levi et al. conducted a retrospective case control study on a sample of 836 Swiss men and women and found that, compared to those without a history of T2DM, participants with T2DM had almost two-fold odds of developing CRC. On the other hand, Seow et al. used a prospective study design to examine the association between a history of T2DM

and CRC among a sample of the ethnic Chinese population of Singapore and found a 50% higher risk of developing CRC in diabetics compared to nondiabetics.

The study results on the association between T2DM and CRC, irrespective of study design, were generally inconsistent (Campbell et al., 2010; Chodick et al., 2010; Jarvandi et al., 2013; Yuhara et al., 2011). Campbell et al., (2010) found increased odds of developing CRC was found in men but not in women; whereas, Chodick et al. found an increased risk in women with T2DM but not in men. On the other hand, Jarvandi et al. (2013) found an association between T2DM and odds of developing cancer for proximal but not distal colon while Yuhara et al. (2011) reported a significant association for distal colon but not for rectal subsite. Therefore, this retrospective quantitative study, the first to examine the association between T2DM and CRC among an Arab population, adds to the literature on the association between T2DM and the risk of developing CRC and warrants further studies.

T2DM and Survival Rates of CRC

In Research Question 2, I asked if there was any association between T2DM and CRC survival rates in Oman. I found that the association was not statistically significant; therefore, the null hypothesis was not rejected. This finding is in conformity with the studies of Noh et al. (2010), Morrison et al. (2011), and Ahmadi et al. (2014). Ahmadi et al. found no significant difference in median survival time between CRC patients with T2DM compared to those without T2DM. Similarly, Noh et al. did not find any relation between the presence of T2DM and CRC survival or recurrence. The authors called for more studies to elucidate whether the presence of T2DM truly contributed to poorer

survival in CRC cases. Ahmadi et al. suggested future scholars can examine if survival of CRC patients was dependent on other factors such as stage of disease at diagnosis and not necessarily on T2DM. However, in this present study, I found no association between T2DM and CRC survival rates by categories of stage of disease.

Contrary to the findings in this research, some authors (Dehal et al., 2012; Huang et al., 2011; Van de Poll-Franse et al., 2012) found that T2DM was associated with poorer CRC survival rates. However, Huang et al. (2011) did not differentiate between types of DM even though the mechanism by which both types of diabetes cause cancers may differ (Shu et al., 2010). Further studies on participants with T2DM were warranted. Although I focused on CRC cases with T2DM, I found no association between T2DM and CRC survival rates. Similar to my study, Van de Poll-Franse et al. (2012) did not have information about the diabetes duration, insulin use, as well as metformin use. Insulin use has been shown to negatively impact CRC survival (Chang et al., 2012). Further studies about the association between T2DM and CRC can overcome these limitations. Onitilo et al. (2012b) acknowledged that the association between T2DM is an ongoing debate, and they argued that glycemic influences on CRC survival rates observed in some studies may be an indirect reflection of the complexities of managing CRC patients with T2DM, such as offering less aggressive treatments to CRC patients with T2DM. This nonstatistically significant association between T2DM and CRC survival in the current study adds to the body of existing literature and warrants further studies.

T2DM/CRC Survival Rates by Gender, Age, Tumor Location, and Cancer Stage

In Research Question 3, I asked if the association between T2DM and CRC survival was different in categories defined by gender, age group, tumor location, and cancer stage.

In the multivariable-adjusted Cox proportional hazards regression result, I found that across strata of gender, age group, tumor location, and cancer stage, there were no statistically significant differences in survival rates between CRC cases with T2DM and those without T2DM. Therefore, the null hypothesis was not rejected. Similar results were obtained by Dehal et al. (2012), who found that though in general, cancer patients who had T2DM had a significantly increased risk of dying from a cancer compared with those who did not have T2DM; there were no significant differences by sex. Rudolph et al. (2014) found that there was no survival advantage in the association between T2DM and CRC survival by sex.

With regards to age group, the natural aging process, plus comorbid conditions that tend to occur more with advancing age, may modify any observed association between T2DM and CRC survival differently. Moreover, advanced age is an independent risk factor for mortality (Morrison et al., 2011). Age did not confound the association between T2DM and CRC survival in this research study. Nevertheless, being the first research of its kind in an Omani population, this finding should be interpreted with caution until replicated in future studies.

Tumor location did not influence the association between T2DM and CRC. This finding did not align with previous studies (Jeon et al., 2013; Van de Poll-Franse et al.,

2012),). In the study by Jeon et al. (2013), a positive association was found between T2DM and colon specific survival but, a non-significant association was found with rectal cancer survival. Contrary to this finding, the study by Van de Poll-Franse et al., (2012), reported poor survival in rectal cancer patients with T2DM and a non- significant association between T2DM and colon cancer survival. Jeon et al. (2013) opined that the observed differences in survival by tumor subsite may be related to the potential mechanisms by which T2DM affects the different subsites in CRC patients. These mechanisms are related to distinct differences in anatomy, embryology, physiology and genetics between the colon and rectal subsites (Jeon et al., 2013). My research utilized archival data which had no information on these variables mentioned by Jeon et al., (2013). Their suggestion could therefore not be verified.

The finding about cancer stage did not align with the results of the study by Gross et al. (2006), which reported a five-year survival rate of 78.3% in stage 1 CRC disease with no T2DM compared to 71% survival rate in patients with similar CRC stage with comorbid T2DM. According to Gross et al. (2006), the combinations of chronic conditions in an individual affect CRC survival to different degrees and may contribute to poor survival. The authors advocated for more empirical investigation to elucidate how cancer stage affect the association betweenT2DM and CRC survival. Comorbid chronic conditions were not considered as potential confounders in this study, therefore, it was not possible to elucidate how such chronic conditions could have influenced the association between T2DM and CRC in this population. Nevertheless, this research study, being the first in an Arab population, has provided baseline information that

further studies can build upon to better understand the association between T2DM and CRC in this population..

Limitations of the Study

The limitations of this study include selection bias, information bias and recall bias. External validity was also a limitation. Selection bias occurs when the group studied varies significantly from the general population. A particular selection bias that is inherent in hospital-based case control studies is the Berkson's bias (hospital-patient selection bias). Berkson's bias is a systematic bias in the distribution of disease amongst hospitalized patients such that in case-control studies where both cases and controls are selected from the hospital, the controls tend to be more likely exposed to the exposure under consideration than the general population from which the cases came from (Schwartzbaum et al., 2003; Roberts et al., 1978). When Berkson's bias occurs, the odds ratio tends to be underestimated.

The dataset that addressed research question1 was a hospital based case-control study. According to Schwartzbaum et al., (2003), Berkson's bias can be reduced in hospital-based case control studies by choosing hospital controls from among patients admitted to the hospital for conditions that are unrelated to the case disease. Furthermore, cases should be admitted in the hospital for reasons unrelated to the exposure. In this study, controls were chosen from among patients admitted into the ENT, orthopedic surgery and ophthalmology departments for a wide range of acute nonmalignant conditions. Moreover, the cases were in the hospital for reasons unrelated toT2DM, the exposure disease. The cases were interviewed during their oncology outpatient visit or

while they were admitted in the oncology wards for their cancer management. Therefore, the potential for Berkson's bias in this study is minimized.

This study used data from one of two hospitals that treat cancers in Oman. Although SQUH treats about 65% of cancer cases in Oman, it is possible that those 35% not captured in this study differed significantly from the participants. Therefore, the findings from this research may not be representative of the general population in Oman. However, a review of the demographic characteristics of the study sample in Table 4 showed that the male/ female ratio is 1.42, similar to the male/female ratio in the general Omani population (World Population Review, 2016.).

The relatively small sample size used in this study compared to studies done in other populations may have affected the findings. Morrison et al., (2011), stated that the relationship between T2DM and CRC is most clearly seen in bigger samples with higher prevalence (above 20%) of T2DM. The prevalence of T2DM in the Omani population is 15% (IDF, 2015). Nevertheless, the minimum sample sizes necessary to reject the null hypotheses in this study were obtained by two different types of sample size calculators namely, the OpenEpi software version 3.1.9.2 (Dean et al., 2009) and the PS power software (Dupont & Plummer, 1990). This study was also limited to the population of Oman and may not be generalized to other non-Arab populations.

In the sample that was used to answer Research Question 2 and 3, information on diet and physical activity status was only available for 42 cases. A subgroup analysis could not be conducted with this sample of 42 cases due to the small sample size. Therefore, it was not possible to examine how diet and physical activity could have

affected the results. The latest WCRF report on diet, nutrition, physical activity and CRC states that there is strong evidence that physical activity, consuming diets of whole grains fiber and dairy products reduce the risk of developing CRC whereas consumption of red and processed meat and excess body fat increases the risk (WCRF, 2017). The WCRF recommends that to reduce risk of developing CRC, individuals should take steps to eat healthy diet, maintain healthy body weight and minimize alcohol intake Similar recommendations are stipulated in the AICR guideline for CRC prevention (AICR, 2016) The absence of diet and physical activity information in this study was a major limitation therefore, caution should be applied in the interpretation the results.

Information exposure misclassification and recall bias may also have occurred in this study. Information bias arising from misclassification of exposure status of participants, wrong definition of study variables, as well as faulty data collection technique are some of the internal validity threats in case-control studies (Szklo, & Nieto, 2014, Pp. 117-130). For example, this study used data collected on an interviewer-administered food frequency questionnaire to answer Research Question 1. Participants were asked questions about their T2DM status in addition to questions about their diet before the diagnosis of their cancer. It is possible participants did not correctly recall their T2DM status. However, this limitation was overcome by verifying self-reported T2DM status from a review of patients' case histories and drug summaries. Secondly, the participants may not have correctly recalled their diet habits which may have resulted in misclassification of cases with regards to their diet. Moreover, information bias would also occur if participants were not honest enough in their responses to questions on

alcohol consumption and smoking. The question about alcohol consumption is particularly sensitive given that Oman is a Muslim country where alcohol consumption is prohibited. The presence of information bias in this study may have biased the results towards the null. Finally, this study was an observational study therefore, cause and effect could not be determined (Creswell, 2009), plus, other unknown confounders could have also affected the findings.

Recommendations for Action

In this quantitative retrospective study, T2DM was not associated with higher odds of developing CRC, neither was it associated with poorer CRC survival rates. Nevertheless, the high prevalence of T2DM and other established CRC risk factors such as obesity in the Omani population (Al Riyami, 2010; Al Nohair, 2014; WHO, 2015), calls for proactive action among stakeholders. On the part of the researchers, more studies should be conducted with a more representative sample. The responsibility of the Omani government would be to support country-wide health education programs about weight reduction and, screening and early detection targeted at groups at risk of both T2DM and CRC. Health care professionals can also take action to educate people on how to minimize their risk of developing CRC by being physically active, consuming diets rich in fiber, whole grains and dairy products and, to cut down on consumption of red and processed meat and, alcoholic beverages as recommended by the WCRF and the AICR. Public health education should also include information on how to recognize CRC symptoms and seek help early in order to improve CRC survival outcomes.

Recommendations for Further Study

The sample for this research was drawn from the population of CRC patients that attended one of two hospitals that treat CRC cases in Oman. A similar study could be conducted with sample from both hospitals. Such study would be more representative than this current study. A study with a bigger sample size could help to better understand the association between T2DM and CRC in Oman. Moreover, this study was retrospective in nature. Although it provided data on the variables of interest in this study at low cost, a nationwide prospective study with collaboration between the two centers that treat all malignancies in Oman can be undertaken to better elucidate the true association between T2DM and CRC in the Omani population.

The archival data that was used to address Research Question 2 and 3 did not contain data on diet and physical activity status of the participants. Given the recommendations from international health organizations such as the WCRF and the AICR about the importance of diet, physical activity and the need to maintain a healthy bodyweight in reducing the risk of CRC, a more robust study that includes information on diet and physical activity as well as all potential risk factors and effect modifiers of the association between T2DM and CRC is warranted.

In this study, BMI was calculated from participants' medical records as weight in kilograms divided by the square of height in meters (kg/m^2). However, studies have shown that BMI studies based on self-reported measurements and retrospective chart reviews tend to be imprecise (Gurunathan, & Myles, 2016). Future studies in which BMI is prospectively derived by trained personnel are more likely to yield accurate values and

should be considered. Better still, future studies should consider using waist circumference which is a more accurate measure of visceral fat as an indicator of overweight and obesity (Gurunathan, & Myles, 2016). Lastly, the classification of the exposure variable T2DM was based on self-reported response in the interviewer-administered questionnaire, as well as chart reviews. Future studies whereby diabetes status is determined by laboratory values of blood sugar levels will more likely yield accurate results, and should be conducted.

Implications for Social Change

The social change implication of this study is about informing preventive strategies for reducing the burden of CRC in Oman. This study filled a gap in the literature in that it is the first of such study in an Arab population. Although the study did not find any association between T2DM and CRC risk and survival, the findings could generate interest for more of such studies in this population. Results from such studies could build on the findings from this current research to better inform preventive strategies to lower the burden of CRC in Oman. The literature review that informed this research pointed to possible links between T2DM and other covariates, and CRC. Therefore, this study may create awareness about the possible contribution of T2DM and the other covariates explored in this study to the overall burden of CRC in Oman. This awareness may stir policy makers into taking action around CRC risk-reduction strategies tailored towards the Omani population. Such risk reduction programs may include public awareness programs that encourage individuals and communities to maintain healthy body weight and to participate in CRC screening and early detection programs. This

could lead to a positive social change impact across the country. Moreover, positive social change will occur when such programs create a greater self- awareness of the risk factors for CRC among individual members of the Oman population.

Conclusions

This quantitative, retrospective study used secondary data from SQUH Oman and found no association between T2DM and the odds of developing CRC in an Omani population. The study also found that T2DM was not associated with CRC survival rates in this population. CRC remains a public health problem in Oman with significant human and healthcare costs. It is the second most common cancer in Omani males and the third most common in females. The findings from this research could generate interest for further studies into the risk and prognostic factors for CRC in the Omani population. Further studies with a more representative CRC sample is recommended to build on the findings from this research.

References

Ahmadi, A., Mobasheri, M., Hashemi-Nazari, S. S., Baradaran, A., & Choobini, Z. M. (2014). Prevalence of hypertension and type 2 diabetes mellitus in patients with colorectal cancer and their median survival time: A cohort study. *Journal of research in medical sciences: the official journal of Isfahan University of Medical Sciences*, *19*(9), 850. Retrieved from http://jrms.mui.ac.ir/index.php/jrms

Aleksandrova, K., Pischon, T., Jenab, M., Bueno-de-Mesquita, H. B., Fedirko, V., Norat, T., ... Dartois, L. (2014). Combined impact of healthy lifestyle factors on colorectal cancer: A large European cohort study. *BMC Medicine*, *12*(1), 1. doi:10.1186/s12916-014-0168-4

Al Hakmani, F. M., Al-Fadhil, F. A., Al-Balushi, L. H., Al-Harthy, N. A., Al-Bahri, Z. A., Al-Rawahi, N. A., ... Padmakumar, H. (2016). The effect of obesity on pregnancy and its outcome in the population of Oman, Seeb Province. *Oman Medical Journal*, *31*(1), 12. doi: 10.5001/omj.2016.03

Al Mahrouqi, H., Parkin, L., & Sharples, K. (2011). Incidence of stomach cancer in Oman and the other gulf cooperation council countries. *Oman Medical Journal*, *26*(4), 258. doi: 10.5001/omj.2011.62

Al Marri, T. S., & Oei, T. P. (2009). Alcohol and substance use in the Arabian Gulf region: A review. *International Journal of Psychology*, *44*(3), 222-233.

AL Nohair, S. (2014). Obesity in gulf countries. *International Journal of Health Sciences*, *8*(1), 79. doi: 10.1080/00207590801888752

Al Riyami, A. (2010). Type 2 diabetes in Oman: Can we learn from the Lancet

editorial. *Oman Medical Journal*, *25*(3), 153. doi: 10.5001/omj.2010.48

Al Riyami, A. A., & Afifi, M. (2004). Smoking in Oman: Prevalence and characteristics of smokers. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/16335652

Al shishtawy, M. M. (2010). Four decades of progress: Evolution of the health system in Oman. *Sultan Qaboos University Medical Journal, 10*(1), 12. Retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3074664/

Alshoaibi, H. (2015). Evolution of the Omani higher education system and economic challenges 1970-2014. *Evolution*. Retrieved from http://opensiuc.lib.siu.edu/gs_rp/617/

Al Shookri, A., Khor, G. L., Chan, Y. M., Loke, S. C., & Al-Maskari, M. (2011). Type 2 diabetes in the sultanate of Oman. *Malaysian Journal of Nutrition*, *17*(1), 129-141.Retrieved from http://www.nutriweb.org.my/publications/mjn0023_1/default.php

Ambinder, E. P. (2005). Electronic Health Records. *Journal of Oncology Practice*, *1*(2), 57–63. doi: 10.1200/jop.2005.1.2.57

American Cancer Society. (2016). Colorectal cancer overview. Retrieved from http://www.cancer.org/cancer/colonandrectumcancer/detailedguide/colorectal-cancer-what-is-colorectal-cancer

American Cancer Society. (2015). Economic impact of cancer. Retrieved from http://www.cancer.org/cancer/cancerbasics/economic-impact-of-cancer

American Institute for Cancer Research. (2016). Obesity and cancer: What you need to know. Retrieved from http://www.aicr.org/enews/2016/11-november/obesity-and-

cancer-what-you-need-to-know

Arafa, M. A., Waly, M. I., Jriesat, S., Al Khafajei, A., & Sallam, S. (2011). Dietary and lifestyle characteristics of colorectal cancer in Jordan: a case-control study. *Asian Pac J Cancer Prev*, *12*(8), 1931-1936. Retrieved from http://journal.waocp.org/

Ashktorab, H., Brim, H., Al-Riyami, M., Date, A., Al-Mawaly, K., Kashoub, M., ... & Ganguly, S. S. (2008). Sporadic colon cancer: mismatch repair immunohistochemistry and microsatellite instability in Omani subjects. *Digestive diseases and sciences*, *53*(10), 2723-2731. doi: 10.1007/s10620-007-0189-3

Azeem, S., Gillani, S. W., Siddiqui, A., Jandrajupalli, S. B., Poh, V., & Sulaiman, S. A. S. (2015). Diet and colorectal cancer risk in Asia: A systematic review. *Asian Pac. J. Cancer Prev*, *16*, 5389-5396. doi:http://dx.doi.org/10.7314/APJCP.2015.16.13.5389

Bardou, M., Barkun, A. N., & Martel, M. (2013). Obesity and colorectal cancer. *Gut*, *62*(6), 933-947. doi: 10.1136/gutjnl-2013-304701.

Benyshek, D. C., Martin, J. F., & Johnston, C. S. (2001). A reconsideration of the origins of the type 2 diabetes epidemic among Native Americans and the implications for intervention policy. *Medical Anthropology*, *20*(1), 25-64. doi: 10.1080/01459740.2001.9966186

Boyle, T., Fritschi, L., Heyworth, J., & Bull, F. (2011). Long-term sedentary work and the risk of subsite-specific colorectal cancer. *American journal of epidemiology*, *173*(10), 1183-1191. doi: 10.1093/aje/kwq513

Boyle, T., Fritschi, L., Platell, C., & Heyworth, J. (2013). Lifestyle factors associated

with survival after colorectal cancer diagnosis. *British journal of cancer*, *109*(3), 814-822. doi: 10.1038/bjc.2013.310

Brim, H., Mokarram, P., Naghibalhossaini, F., Saberi-Firoozi, M., Al-Mandhari, M., Al-Mawaly, K., ... & Ashktorab, H. (2008). Impact of BRAF, MLH1 on the incidence of microsatellite instability high colorectal cancer in populations based study. *Molecular Cancer,* 7(1), 68. doi: 10.1186/1476-4598-7-68.

Campbell, P. T., Deka, A., Jacobs, E. J., Newton, C. C., Hildebrand, J. S., McCullough, M. L., ... & Gapstur, S. M. (2010). Prospective study reveals associations between colorectal cancer and type 2 diabetes mellitus or insulin use in men. *Gastroenterology*, *139*(4), 1138-1146. doi: 10.1053/j.gastro.2010.06.072

Cavicchia, P. P., Adams, S. A., Steck, S. E., Hussey, J. R., Liu, J., Daguisé, V. G., & Hebert, J. R. (2013). Racial disparities in colorectal cancer incidence by type 2 diabetes mellitus status. *Cancer Causes & Control*, *24*(2), 277-285. doi: 10.1007/s10552-012-0095-7

Center for Diseases Control and Prevention. (2011). National diabetes fact, 2011. Retrieved from https://www.cdc.gov/diabetes/pubs/pdf/methods11.pdf.

Center for Diseases Control and Prevention. (2017). Basic information about colorectal cancer. Retrieved from https://www.cdc.gov/cancer/colorectal/basic_info/index.htm

Chang, C. H., Lin, J. W., Wu, L. C., Lai, M. S., & Chuang, L. M. (2012). Oral insulin secretagogues, insulin, and cancer risk in type 2 diabetes mellitus. *The Journal of Clinical Endocrinology & Metabolism*, *97*(7), E1170-E1175. doi:

10.1210/jc.2012-1162

Chen, K. H., Shao, Y. Y., Lin, Z. Z., Yeh, Y. C., Shau, W. Y., Kuo, R. N., ... Lai, M. S. (2014). Type 2 diabetes mellitus is associated with increased mortality in Chinese patients receiving curative surgery for colon cancer. *The oncologist*, *19*(9), 951-958. doi: 10.1634/theoncologist.2013-0423

Chen, L., Li, L., Wang, Y., Li, P., Luo, L., Yang, B., ... Chen, M. (2013). Circulating C-peptide level is a predictive factor for colorectal neoplasia: evidence from the meta-analysis of prospective studies. *Cancer Causes & Control*, *24*(10), 1837-1847. doi: 10.1007/s10552-013-0261-6

Chodick, G., Heymann, A. D., Rosenmann, L., Green, M. S., Flash, S., Porath, A., ... & Shalev, V. (2010). Diabetes and risk of incident cancer: a large population-based cohort study in Israel. *Cancer Causes & Control*, *21*(6), 879-887. doi: 10.1007/s10552-010-9515-8

Cong, Y. J., Gan, Y., Sun, H. L., Deng, J., Cao, S. Y., Xu, X., & Lu, Z. X. (2014). Association of sedentary behaviour with colon and rectal cancer: a meta-analysis of observational studies. *British journal of cancer*, *110*(3), 817-826. doi: 10.1038/bjc.2013.709

Creswell, J. W. (2009). Research design: Qualitative, quantitative, and mixed methods approaches (3rd ed.). Thousand Oaks, Calif.: Sage Publications.

Cunningham, J. B., & McCrum-Gardner, E. (2007). Power, effect and sample size using GPower: practical issues for researchers and members of research ethics committees. *Evidence-Based Midwifery*, *5*(4), 132-137. Retrieved from

https://www.rcm.org.uk/access-evidence-based-midwifery-journal

Dean, A. G., Sullivan, K. M., Soe, M. M. (2009) OpenEpi: Open Source Epidemiologic Statistics for Public Health, Version 3.01. Retrieved from www.OpenEpi.com.

De Bruijn, K. M. J., Arends, L. R., Hansen, B. E., Leeflang, S., Ruiter, R., & van Eijck, C. H. J. (2013). Systematic review and meta-analysis of the association between diabetes mellitus and incidence and mortality in breast and colorectal cancer. *British Journal of Surgery*, *100*(11), 1421-1429. doi: 10.1002/bjs.9229

Dehal, A. N., Newton, C. C., Jacobs, E. J., Patel, A. V., Gapstur, S. M., & Campbell, P. T. (2012). Impact of diabetes mellitus and insulin use on survival after colorectal cancer diagnosis: the Cancer Prevention Study-II Nutrition Cohort. *Journal of Clinical Oncology, 30(1), 53-59.* doi: 10.1200/JCO.2011.38.0303

Deng, L., Gui, Z., Zhao, L., Wang, J., & Shen, L. (2012). Diabetes mellitus and the incidence of colorectal cancer: an updated systematic review and meta-analysis. *Digestive diseases and sciences*, *57*(6), 1576-1585. doi: 10.1007/s10620-012-2055-1

Díaz-Algorri, Y., Lozada, M. E., López, S. M., Bertrán-Rodríguez, C. E., González-Hernández, C. M., González, D., ...González-Pons, M. (2015). Type 2 diabetes mellitus and colorectal neoplasia risk in Hispanics: a case–control study. *Journal of diabetes and its complications*, *29*(4), 502-507. doi: 10.1016/j.jdiacomp.2015.01.010

Dupont, W. D., & Plummer, W. D. (1990). Power and sample size calculations: a review and computer program. *Controlled clinical trials*, *11*(2), 116-128.

https://doi.org/10.1016/0197-2456(90)90005-M

Erbach, M., Mehnert, H., & Schnell, O. (2012). Diabetes and the risk for colorectal cancer. *Journal of diabetes and its complications*, *26*(1), 50-55. doi: 10.1016/j.jdiacomp.2011.11.003

Ezzati, M., & Riboli, E. (2013). Behavioral and dietary risk factors for non-communicable diseases. *New England Journal of Medicine*, *369*(10), 954-964. doi: 10.1056/NEJMra1203528

Ferroni, P., Riondino, S., Buonomo, O., Palmirotta, R., Guadagni, F., & Roselli, M. (2015). Type 2 Diabetes and Breast Cancer: The Interplay between Impaired Glucose Metabolism and Oxidant Stress. *Oxidative medicine and cellular longevity*, *2015*. doi: 10.1155/2015/183928

Field, A. (2013). *Discovering statistics using IBM SPSS statistics*. London, England: Sage.

Flood, A., Strayer, L., Schairer, C., & Schatzkin, A. (2010). Diabetes and risk of incident colorectal cancer in a prospective cohort of women. *Cancer Causes & Control*, *21*(8), 1277-1284. doi: 10.1007/s10552-010-9555-0

Forssas, E., Sund, R., Manderbacka, K., Arffman, M., Ilanne-Parikka, P., & Keskimäki, I. (2013). Increased cancer mortality in diabetic people treated with insulin: A register-based follow-up study. *BMC Health Services Research, 13*, 267. doi: 10.1186/1472-6963-13-267 https://doi.org/10.1186/1472-6963-13-267

Foster, P. A. (2013). Oestrogen and colorectal cancer: mechanisms and controversies. *International journal of colorectal disease*, *28*(6), 737-749. doi:

10.1007/s00384-012-1628-y

Global Burden of Disease Cancer Collaboration. (2015). The Global Burden of Cancer 2013. JAMA Oncology, 1(4), 505–527. http://doi.org/10.1001/jamaoncol.2015.0735

Goh, K. L. (2007). Changing trends in gastrointestinal disease in the Asia–Pacific region. *Journal of digestive diseases, 8(4), 179-185.* doi: 10.1111/j.1751-2980.2007.00304.x

Giovannucci, E., & Michaud, D. (2007). The role of obesity and related metabolic disturbances in cancers of the colon, prostate, and pancreas. *Gastroenterology*, *132*(6), 2208-2225. doi: 10.1053/j.gastro.2007.03.050

Green, S. B., & Salkind, N. J. (2003). *Using SPSS for Windows and Macintosh: Analyzing and Understanding Data* (Ed.). Upper Saddle River, NJ: Prentice Hall.

Grøntved, A., & Hu, F. B. (2011). Television viewing and risk of type 2 diabetes, cardiovascular disease, and all-cause mortality: a meta-analysis. *Jama*, *305*(23), 2448-2455. doi: 10.1001/jama.2011.812

Gross, C. P., Guo, Z., McAvay, G. J., Allore, H. G., Young, M., & Tinetti, M. E. (2006). Multimorbidity and survival in older persons with colorectal cancer. *Journal of the American Geriatrics Society, 54(12),* 1898-1904. doi: 10.1111/j.1532-5415.2006.00973.x

Guenther, P. M., Casavale, K. O., Kirkpatrick, S. I., Reedy, J., Hiza, H. A. B., Kuczynski, K. J., … Krebs-Smith, S. M. (2013). Update of the Healthy Eating Index: HEI-

2010. *Journal of the Academy of Nutrition and Dietetics*, *113*(4), 10.1016/j.jand.2012.12.016. http://doi.org/10.1016/j.jand.2012.12.016

Gurunathan, U., & Myles, P. S. (2016). Limitations of body mass index as an obesity measure of perioperative risk. *British Journal of Anaesthesia, 116(3), 319–321.* https://doi.org/10.1093/bja/aev541

Hakulinen, T. (2007). Gastrointestinal tract cancers-global burden and trends .*Acta Oncologica*, *46*(3), 400-401. http://dx.doi.org/10.1080/02841860701251304

Haq, S., Ali, S., Mohammad, R., & Sarkar, F. H. (2012). The complexities of epidemiology and prevention of gastrointestinal cancers. *International journal of molecular sciences, 13(10),* 12556-12572. doi: 10.3390/ijms131012556

He, J., Stram, D. O., Kolonel, L. N., Henderson, B. E., Le Marchand, L., & Haiman, C. A. (2010). The association of diabetes with colorectal cancer risk: the Multiethnic Cohort. *British journal of cancer*, *103*(1), 120-126. doi: 10.1038/sj.bjc.6605721

Hinton, R. B. (2008). The family history: reemergence of an established tool. *Critical care nursing clinics of North America*, *20*(2), 149-158. doi: 10.1016/j.ccell.2008.01.004

Hou, L., Jiang, J., Liu, B., Nasca, P. C., Wu, Y., Zou, X., ... Pang, H. (2014). Association between smoking and deaths due to colorectal malignant carcinoma: a national population-based case–control study in China. *British journal of cancer*, *110*(5), 1351-1358. doi: 10.1038/bjc.2014.9

Huang, Y. C., Lin, J. K., Chen, W. S., Lin, T. C., Yang, S. H., Jiang, J. K., ...Yang, Y. W. (2011). Diabetes mellitus negatively impacts survival of patients with colon

cancer, particularly in stage II disease. *Journal of cancer research and clinical oncology*, *137*(2), 211-220. doi: 10.1007/s00432-010-0879-7

International Diabetes Federation (2015). *IDF Diabetes Atlas, 7th ed.* Brussels, Belgium. Retrieved from http://www.diabetesatlas.org.

Jarvandi, S., Davidson, N. O., & Schootman, M. (2013). Increased risk of colorectal cancer in type 2 diabetes is independent of diet quality. *Plos one*, *8*(9), e74616. doi: 10.1007/s00432-010-0879-7

Jeon, J. Y., Jeong, D. H., Park, M. G., Lee, J. W., Chu, S. H., Park, J. H., ... Kim, N. K. (2013). Impact of diabetes on oncologic outcome of colorectal cancer patients: colon vs. rectal cancer. *PloS one*, *8*(2), e55196. doi: 10.1371/journal.pone.0055196

Johnson, C. M., Wei, C., Ensor, J. E., Smolenski, D. J., Amos, C. I., Levin, B., & Berry, D. A. (2013). Meta-analyses of Colorectal Cancer Risk Factors. *Cancer Causes & Control : CCC*, *24*(6), 1207–1222. doi: 10.1007/s10552-013-0201-5

Jonasson, J. M., Cederholm, J., & Gudbjornsdottir, S. (2014). Excess body weight and cancer risk in patients with type 2 diabetes who were registered in Swedish national diabetes register–register-based cohort study in Sweden. *PloS one*, *9*(9), e105868. doi: 10.1371/journal.pone.0105868

Jullumstrø, E., Kollind, M., Lydersen, S., & Edna, T. H. (2009). Diabetes mellitus and outcomes of colorectal cancer. *Acta Oncologica*, *48*(3), 361-367. doi: 10.1080/02841860802637765

Karahalios, A., English, D. R., & Simpson, J. A. (2015). Weight change and risk of

colorectal cancer: A systematic review and meta-analysis. *American journal of epidemiology*, *181*(11), 832-845. doi: 10.1093/aje/kwu357

Katerina Neumann, M. D., Mahmud, S. M., Metcalfe, J., & Hochman, D. J. (2015). Is obesity associated with advanced stage or grade of colon cancer? *Canadian Journal of Surgery*, *58*(2), 140-142. doi: 10.1503/cjs.004414

Kirkegaard, H., Johnsen, N. F., Christensen, J., Frederiksen, K., Overvad, K., & Tjønneland, A. (2010). Association of adherence to lifestyle recommendations and risk of colorectal cancer: a prospective Danish cohort study. *Bmj*, *341*, c5504. doi: 10.1136/bmj.c5504

Krämer, H. U., Schöttker, B., Raum, E., & Brenner, H. (2012). Type 2 diabetes mellitus and colorectal cancer: meta-analysis on sex-specific differences. *European Journal of Cancer*, *48*(9), 1269-1282. doi: 10.1016/j.ejca.2011.07.010

Krieger, N. (1994). Epidemiology and the web of causation: has anyone seen the spider? *Social science & medicine*, *39*(7), 887-903.Retrieved from https://www.journals.elsevier.com/social-science-and-medicine

Krieger, N. (2001). Theories for social epidemiology in the 21st century: an ecosocial perspective. *International journal of epidemiology*, *30*(4), 668-677. https://doi.org/10.1093/ije/30.4.668

Krieger, N. (2005). Embodiment: a conceptual glossary for epidemiology. *Journal of Epidemiology and Community Health*, *59*(5), 350-355. doi: 10.1136/jech.2004.024562

Kuiper, J. G., Phipps, A. I., Neuhouser, M. L., Chlebowski, R. T., Thomson, C. A., Irwin,

M. L., ...Kampman, E. (2012). Recreational physical activity, body mass index, and survival in women with colorectal cancer. *Cancer Causes & Control*, *23*(12), 1939-1948. doi: 10.1007/s10552-012-0071-2

Kumar, S., Burney, I. A., Zahid, K. F., Souza, P. C. D., Belushi, M. A., Meki, T. D. M. W. A., ... Mansour, S. A. L. (2015). Colorectal Cancer Patient Characteristics, Treatment and Survival in Oman–a Single Center Study. *Asian Pac J Cancer Prev*, *16*, 4853-4858. doi: 10.7314/APJCP.2015.16.12.4853

Kuriki, K., Hirose, K., & Tajima, K. (2007). Diabetes and cancer risk for all and specific sites among Japanese men and women. *European journal of cancer prevention*, *16*(1), 83-89. doi: 10.1097/01.cej.0000228404.37858.40

Lam, E. K., Batty, G. D., Huxley, R. R., Martiniuk, A. L., Barzi, F., Lam, T. H., ... Tamakoshi, A. (2011). Associations of diabetes mellitus with site-specific cancer mortality in the Asia-Pacific region. *Annals of oncology*, *22*(3), 730-738. doi: 10.1093/annonc/mdq405

Larsson, S. C., Orsini, N., & Wolk, A. (2005). Diabetes mellitus and risk of colorectal cancer: a meta-analysis. *Journal of the National Cancer Institute*, *97*(22), 1679-1687. doi: 10.1093/jnci/dji375

Lauby-Secretan, B., Scoccianti, C., Loomis, D., Grosse, Y., Bianchini, F., & Straif, K. (2016). Body fatness and cancer -- viewpoint of the IARC working group.*The New England Journal of Medicine, 375*(8), 794-798. doi: 10.1056/NEJMsr1606602

Lee, J. H., Kim, T. I., Jeon, S. M., Hong, S. P., Cheon, J. H., & Kim, W. H. (2012). The

effects of metformin on the survival of colorectal cancer patients with diabetes mellitus. *International Journal of Cancer*, *131*(3), 752-759. doi: 10.1002/ijc.26421

Levi, F., Pasche, C., Lucchini, F., & La Vecchia, C. (2002). Diabetes mellitus, family history, and colorectal cancer. *Journal of epidemiology and community health*, *56*(6), 479-480. doi: 10.1136/jech.56.6.479

Li, T., Wei, S., Shi, Y., Pang, S., Qin, Q., Yin, J., ... Liu, L. (2016). The dose–response effect of physical activity on cancer mortality: findings from 71 prospective cohort studies. *British journal of sports medicine*, 50(6), 339-45. doi: 10.1136/bjsports-2015-094927

Luo, J., Lin, H. C., He, K., & Hendryx, M. (2014). Diabetes and prognosis in older persons with colorectal cancer. *British journal of cancer, 110(7),* 1847-54. doi: 10.1038/bjc.2014.68

Ma, Y., Yang, Y., Wang, F., Zhang, P., Shi, C., Zou, Y., & Qin, H. (2013). Obesity and risk of colorectal cancer: a systematic review of prospective studies. *PloS one*, *8*(1), e53916. doi: 10.1371/journal.pone.0053916

MacFarlane, A. J., & Stover, P. J. (2007). Convergence of genetic, nutritional and inflammatory factors in gastrointestinal cancers. *Nutrition reviews, 65(s3), S157-S166.*Retrieved from https://academic.oup.com/nutritionreviews

Mahfouz, E. M., Sadek, R. R., Abdel-Latief, W. M., Mosallem, F. A., & Hassan, E. E. (2014). The role of dietary and lifestyle factors in the development of colorectal cancer: case control study in Minia, Egypt. *Central European journal of public*

health, *22*(4), 215-22.doi: 10.21101/cejph.a3919

McCleary, N. J., Niedzwiecki, D., Hollis, D., Saltz, L. B., Schaefer, P., Whittom, R., ... Meyerhardt, J. A. (2010). Impact of smoking on patients with stage III colon cancer. *Cancer*, *116*(4), 957-966. doi: 10.1002/cncr.24866

Mehtälä, M. A. K., Sääkslahti, A. K., Inkinen, M. E., & Poskiparta, M. E. H. (2014). A socio-ecological approach to physical activity interventions in childcare: a systematic review. *International Journal of Behavioral Nutrition and Physical Activity*, *11*, 22. doi: 10.1186/1479-5868-11-22

Mokdad, A. H., Jaber, S., Aziz, M. I. A., AlBuhairan, F., AlGhaithi, A., AlHamad, N. M.,... Hossein, M. (2014). The state of health in the Arab world, 1990–2010: an analysis of the burden of diseases, injuries, and risk factors. *The Lancet,* 383(9914), 309-320. doi: 10.1016/S0140-6736(13)62189-3

Morrison, D. S., Batty, G. D., Kivimaki, M., Smith, G. D., Marmot, M., & Shipley, M. (2011). Risk factors for colonic and rectal cancer mortality: evidence from 40 years' follow-up in the Whitehall I study. *Journal of epidemiology and community health*, 65:1053-1058. doi: 10.1136/jech.2010.127555

Muliira, J. K., D'Souza, M. S., & Ahmed, S. M. (2016). Contrasts in practices and perceived barriers to colorectal cancer screening by nurses and physicians working in primary care settings in Oman. Journal of Cancer Education, 31(1), 15-25. doi: 10.1007/s13187-015-0806-3.

National Cancer Institute. (2015). Defining cancer. Retrieved from http://www.cancer.gov/cancertopics/cancerlibrary/what-is-cancer

Noh, G. Y., Hwang, D. Y., Choi, Y. H., & Lee, Y. Y. (2010). Effect of diabetes mellitus on outcomes of colorectal cancer. *Journal of the Korean Society of Coloproctology*, *26*(6), 424-428. doi: 10.3393/jksc.2010.26.6.424

Nordenvall, C., Nilsson, P. J., Ye, W., Andersson, T. M. L., & Nyrén, O. (2013). Tobacco use and cancer survival: a cohort study of 40,230 Swedish male construction workers with incident cancer. *International journal of cancer*, *132*(1), 155-161. doi: 10.1002/ijc.27587

Odegaard, A. O., Koh, W. P., & Yuan, J. M. (2013). Combined lifestyle factors and risk of incident colorectal cancer in a Chinese population. *Cancer prevention research*, *6*(4), 360-367. doi: 10.1158/1940-6207.CAPR-12-0384

Oman Cancer Registry Report (2014). Cancer incidence in Oman. Retrieved from https://www.moh.gov.om/

Onitilo, A. A., Engel, J. M., Glurich, I., Stankowski, R. V., Williams, G. M., & Doi, S. A. (2012a). Diabetes and cancer I: risk, survival, and implications for screening. *Cancer Causes & Control*, *23*(6), 967-981. doi: 10.1007/s10552-012-9972-3

Onitilo, A. A., Engel, J. M., Glurich, I., Stankowski, R. V., Williams, G. M., & Doi, S. A. (2012b). Diabetes and cancer II: role of diabetes medications and influence of shared risk factors. *Cancer Causes & Control*, *23*(7), 991-1008. doi: 10.1007/s10552-012-9971-4

Otani, T., Iwasaki, M., Sasazuki, S., Inoue, M., Tsugane, S., & Japan Public Health Center–Based Prospective Study Group. (2006). Plasma C-reactive protein and

risk of colorectal cancer in a nested case-control study: Japan Public Health Center–based prospective study. *Cancer Epidemiology Biomarkers & Prevention*, *15*(4), 690-695. doi: 10.1158/1055-9965.EPI-05-0708

Ouakrim, D. A., Pizot, C., Boniol, M., Malvezzi, M., Boniol, M., Negri, E., ... Autier, P. (2015). Trends in colorectal cancer mortality in Europe: retrospective analysis of the WHO mortality database. Bmj, 351, h4970. doi: https://doi.org/10.1136/bmj.h4970

Pelucchi, C., Negri, E., Talamini, R., Levi, F., Giacosa, A., Crispo, A., ... La Vecchia, C. (2010). Metabolic syndrome is associated with colorectal cancer in men. *European journal of cancer*, *46*(10), 1866-1872. doi: 10.1016/j.ejca.2010.03.010

Phillips, J. C. (2011). Antiretroviral therapy adherence: Testing a social context model among Black men who use illicit drugs. *Journal of the Association of Nurses in AIDS Care*, *22*(2), 100-127. doi: 10.1016/j.jana.2010.07.008

Phipps, A. I., Shi, Q., Newcomb, P. A., Nelson, G. D., Sargent, D. J., Alberts, S. R., & Limburg, P. J. (2013). Associations between cigarette smoking status and colon cancer prognosis among participants in North Central Cancer Treatment Group Phase III Trial N0147. *Journal of Clinical Oncology*, *31*(16), 2016-2023. doi: 10.1200/JCO.2012.46.2457

Pietinen, P., Hartman, A. M., Haapa, E., Räsänen, L., Haapakoski, J., Palmgren, J., ... Huttunen, J. K. (1988). Reproducibility and validity of dietary assessment instruments I. A self-administered food use questionnaire with a portion size

picture booklet. *American Journal of Epidemiology*, *128*(3), 655-666. Retrieved from http://aje.oxfordjournals.org/

Popescu-Vâlceanu, H. C., Bratu, M., Stoicea, M., Ilie, V. M., Nan, R., Drăguţ, R. M., ... Radulian, G. (2015). COLORECTAL CANCER AND DIABETES, A REAL LINK? *Internal Medicine/Medicina Interna*, *12*(5), 31-35.Retrieved from http://www.medicina-interna.ro

Powell, K. P., Christianson, C. A., Hahn, S. E., Dave, G., Evans, L. R., Blanton, S. H., ... Hinrich, V. C. (2013). Collection of family health history for assessment of chronic disease risk in primary care. *NCMJ*, *74*(4), 279-86.

Prawitt, J., Caron, S., & Staels, B. (2011). Bile acid metabolism and the pathogenesis of type 2 diabetes. *Current diabetes reports*, *11*(3), 160-166. doi: 10.1007/s11892-011-0187-x

Rimm, E. B., Giovannucci, E. L., Stampfer, M. J., Colditz, G. A., Litin, L. B., & Willett, W. C. (1992). Reproducibility and validity of an expanded self-administered Semi-quantitative food frequency questionnaire among male health professionals. American journal of epidemiology, 135(10), 1114-1126. Retrieved from https://academic.oup.com/aje

Roberts, R. S., Spitzer, W. O., Delmore, T., & Sackett, D. L. (1978). An empirical demonstration of Berkson's bias. *Journal of chronic diseases, 31(2),* 119-128. Retrieved from http://www.sciencedirect.com/science/journal/00219681

Rock, M. (2003). Sweet blood and social suffering: Rethinking cause-effect relationships

in diabetes, distress, and duress. *Medical anthropology*, *22*(2), 131-174. doi: 10.1080/01459740306764

Rudolph, A., Shi, H., Försti, A., Hoffmeister, M., Sainz, J., Jansen, L., ... Chang-Claude, J. (2014). Repeat polymorphisms in ESR2 and AR and colorectal cancer risk and prognosis: results from a German population-based case-control study. BMC cancer, 14(1), 817. doi: 10.1186/1471-2407-14-817

Rueda, M., Robertson, Y., Acott, A., Rueda, S., Keikhoff, A., Guerrero, W., & Mancino, A. T. (2012). Association of tobacco and alcohol use with earlier development of colorectal pathology: should screening guidelines be modified to include these risk factors? *The American Journal of Surgery*, *204*(6), 963-968. doi: 10.1016/j.amjsurg.2012.07.026

Sandhu, M. S., Luben, R., & Khaw, K. T. (2001). Self-reported non-insulin dependent diabetes, family history, and risk of prevalent colorectal cancer: population based, cross sectional study. *Journal of epidemiology and community health*, *55*(11), 804-805. doi: 10.1136/jech.55.11.804

Sax, A. T., Jenkins, D. G., Devin, J. L., Hughes, G. I., Bolam, K. A., & Skinner, T. L. (2014). The insulin-like growth factor axis: A biological mechanism linking physical activity to colorectal cancer survival. *Cancer epidemiology*, *38*(4), 455-459. doi: 10.1016/j.canep.2014.05.011

Schwartzbaum, J., Ahlbom, A., & Feychting, M. (2003). Commentary: Berkson's Bias reviewed. *European journal of epidemiology, 18(12),* 1109-1112. Retrieved from http://link.springer.com/journal/10654

Seow, A., Yuan, J. M., Koh, W. P., Lee, H. P., & Yu, M. C. (2006). Diabetes mellitus and risk of colorectal cancer in the Singapore Chinese Health Study. *Journal of the National Cancer Institute*, *98*(2), 135-138. doi.org/10.1093/jnci/djj015

Shi, J., Xiong, L., Li, J., Cao, H., Jiang, W., Liu, B., ... Cai, K. (2015). A Linear Dose-Response Relationship between Fasting Plasma Glucose and Colorectal Cancer Risk: Systematic Review and Meta-analysis. *Scientific reports*, *5*, 17591. doi: 10.1038/srep17591

Shu, X., Ji, J., Li, X., Sundquist, J., Sundquist, K., & Hemminki, K. (2010). Cancer risk among patients hospitalized for Type 1 diabetes mellitus: a population-based cohort study in Sweden. *Diabetic Medicine*, *27*(7), 791-797. doi: 10.1111/j.1464-5491.2010.03011.x

Siegel, R., Naishadham, D., & Jemal, A. (2012). Cancer statistics, 2012.*CA: a cancer journal for clinicians*, *62*(1), 10-29. doi: 10.3322/caac.20138

Sjödahl, R., Rosell, J., & Starkhammar, H. (2013). Causes of death after surgery for colon cancer-impact of other diseases, urgent admittance, and gender. *Scandinavian journal of gastroenterology*, *48*(10), 1160-1165. doi: 10.3109/00365521.2013.828771

Slattery, M. L., Samowtiz, W., Ma, K., Murtaugh, M., Sweeney, C., Levin, T. R., & Neuhausen, S. (2004). CYP1A1, cigarette smoking, and colon and rectal cancer. *American Journal of Epidemiology*, *160*(9), 842-852. doi: 10.1093/aje/kwh298

Smith, B. E. (1981). Black lung: the social production of disease. *International Journal of*

Health Services, *11*(3), 343-359. doi: 10.2190/LMPT-4G1J-15VQ-KWEK

Smith, L., & Hamer, M. (2014). Television viewing time and risk of incident diabetes mellitus: the English Longitudinal Study of Ageing. *Diabetic Medicine*, *31*(12), 1572-1576. doi: 10.1111/dme.12544

Spring, B., Moller, A. C., & Coons, M. J. (2012). Multiple health behaviours: overview and implications. *Journal of Public Health*, *34*(suppl 1), i3-i10. doi: 10.1093/pubmed/fdr111

Szklo, M., & Nieto, F. J. (2014). *Epidemiology: Beyond the Basics. (3rd ed.).* Jones & Bartlett Learning. Burlington, MA.

Tabachnick, B. G., Fidell, L. S., & Osterlind, S. J. (2001). Using multivariate statistics. Boston: Allyn and Bacon

Tabung, F. K., Steck, S. E., Burch, J. B., Chen, C. F., Zhang, H., Hurley, T. G., ...Lloyd, S. C. (2015). A healthy lifestyle index is associated with reduced risk of colorectal adenomatous polyps among non-users of non-steroidal anti-inflammatory drugs. *The journal of primary prevention*, *36*(1), 21-31. doi: 10.1007/s10935-014-0372-1

Tabung, F. K., Steck, S. E., Ma, Y., Liese, A. D., Zhang, J., Caan, B., …Wactawski-Wende, J. (2015). The association between dietary inflammatory index and risk of colorectal cancer among postmenopausal women: results from the Women's Health Initiative. *Cancer Causes & Control*, *26*(3), 399-408. doi: 10.1007/s10552-014-0515-y

Tilg, H., & Moschen, A. R. (2014). Mechanisms behind the link between obesity and

gastrointestinal cancers. *Best Practice & Research Clinical Gastroenterology*, *28*(4), 599-610. doi: 10.1016/j.bpg.2014.07.006

Torre, L. A., Bray, F., Siegel, R. L., Ferlay, J., Lortet-Tieulent, J., & Jemal, A. (2015). Global cancer statistics, 2012. *CA: a cancer journal for clinicians*, *65*(2), 87-108. doi: 10.3322/caac.21262

Trabulo, D., Ribeiro, S., Martins, C., Teixeira, C., Cardoso, C., Mangualde, J., ...Oliveira, A. P. (2015). Metabolic syndrome and colorectal neoplasms: An ominous association. *World Journal of Gastroenterology: WJG*, *21*(17), 5320. doi: 10.3748/wjg.v21.i17.5320

Van de Poll-Franse, L. V., Haak, H. R., Coebergh, J. W. W., Janssen-Heijnen, M. L. G., & Lemmens, V. E. P. P. (2012). Disease-specific mortality among stage I–III colorectal cancer patients with diabetes: a large population-based analysis. *Diabetologia, 55(8),* 2163-2172. doi: 10.1007/s00125-012-2555-8

Vazzana, N., Riondino, S., Toto, V., Guadagni, F., Roselli, M., Davi, G., & Ferroni, P. (2012). Obesity-driven inflammation and colorectal cancer. *Current medicinal chemistry*. *19*(34), 5837-5853. doi: 10.2174/092986712804143349

Walker, J. J., Brewster, D. H., Colhoun, H. M., Fischbacher, C. M., Lindsay, R. S., Wild, S. H., & Scottish Diabetes Research Network (SDRN) Epidemiology Group. (2013). Cause-specific mortality in Scottish patients with colorectal cancer with and without type 2 diabetes (2000–2007). *Diabetologia*, *56*(7), 1531-1541. doi 10.1007/s00125-013-2917-x

Walsh, J. M., & Terdiman, J. P. (2003). Colorectal cancer screening: scientific

review. *Jama*, *289*(10), 1288-1296. doi:10.1001/jama.289.10.1288

Wilson, G. S., & George, J. (2014). Physical and chemical insults induce inflammation and gastrointestinal cancers. *Cancer letters*, *345*(2), 190-195. doi: 10.1016/j.canlet.2013.07.011

Wolpin, B. M., Meyerhardt, J. A., Chan, A. T., Ng, K., Chan, J. A., Wu, K., ... Fuchs, C. S. (2009). Insulin, the insulin-like growth factor axis, and mortality in patients with non-metastatic colorectal cancer. *Journal of Clinical Oncology*, *27*(2), 176-185. doi: 10.1200/JCO.2008.17.9945

Wong, C. K., Lam, C. L., Poon, J. T., McGhee, S. M., Law, W. L., Kwong, D. L., ... Chan, P. (2012). Direct medical costs of care for Chinese patients with colorectal neoplasia: a health care service provider perspective. *Journal of evaluation in clinical practice, 18(6),* 1203-1210. doi: 10.1111/j.1365-2753.2011.01776.x

World Cancer Research Fund. (2017). Continuous Update Project; Colorectal cancer. Retrieved from http://www.wcrf.org/int/research-we-fund/continuous-update-project-findings-reports/colorectal-bowel-cancer

World Health Organization. (2010). NCDs: Burden: mortality, morbidity and risk factors. "Global status report on NCDs 2010". Retrieved from http://www.who.int/nmh/publications/ncd_report_chapter1.pdf

World Health Organization. (2014). Cancer country profiles. Retrieved from http://www.who.int/cancer/country-profiles/en/

World Health Organization. (2015). Obesity and Overweight. Fact Sheet No. 311. Retrieved from http://www.who.int/mediacentre/factsheets/fs311/en/

World Health Organization. (2016a). Country profiles. Retrieved from http://www.who.int/countries/omn/en/

World Health Organization. (2016b). Physical Activity Fact Sheet. Retrieved from http://www.who.int/mediacentre/factsheets/fs385/en/

World Population Review. (2016). Oman population, 2016. Retrieved from http://worldpopulationreview.com/countries/oman-population/

Yabroff, K. R., Borowski, L., & Lipscomb, J. (2013). Economic Studies in Colorectal Cancer: Challenges in Measuring and Comparing Costs. *Journal of the National Cancer Institute. Monographs, 2013*(46), 62–78. doi: 10.1093/jncimonographs/lgt001

Yu, X. F., Zou, J., & Dong, J. (2014). Fish consumption and risk of gastrointestinal cancers: A meta-analysis of cohort studies. *World journal of gastroenterology: WJG, 20(41),* 1539 doi: 10.3748/wjg.v20.i41.15398.

Yuhara, H., Steinmaus, C., Cohen, S. E., Corley, D. A., Tei, Y., & Buffler, P. A. (2011). Is diabetes mellitus an independent risk factor for colon cancer and rectal cancer quest. *The American journal of gastroenterology*, *106*(11), 1911-1921. doi: 10.1038/ajg.2011.301

Zaidan, Z. A., Dorvlo, A. S., Viernes, N., Al-Suleimani, A., & Al-Adawi, S. (2007). Hazardous and harmful alcohol consumption among non-psychotic psychiatric clinic attendees in Oman. *International Journal of Mental Health and Addiction, 5(1)*, 3-15. doi: 10.1007/s11469-006-9046-4

Appendix A: Log-Log function for Covariates

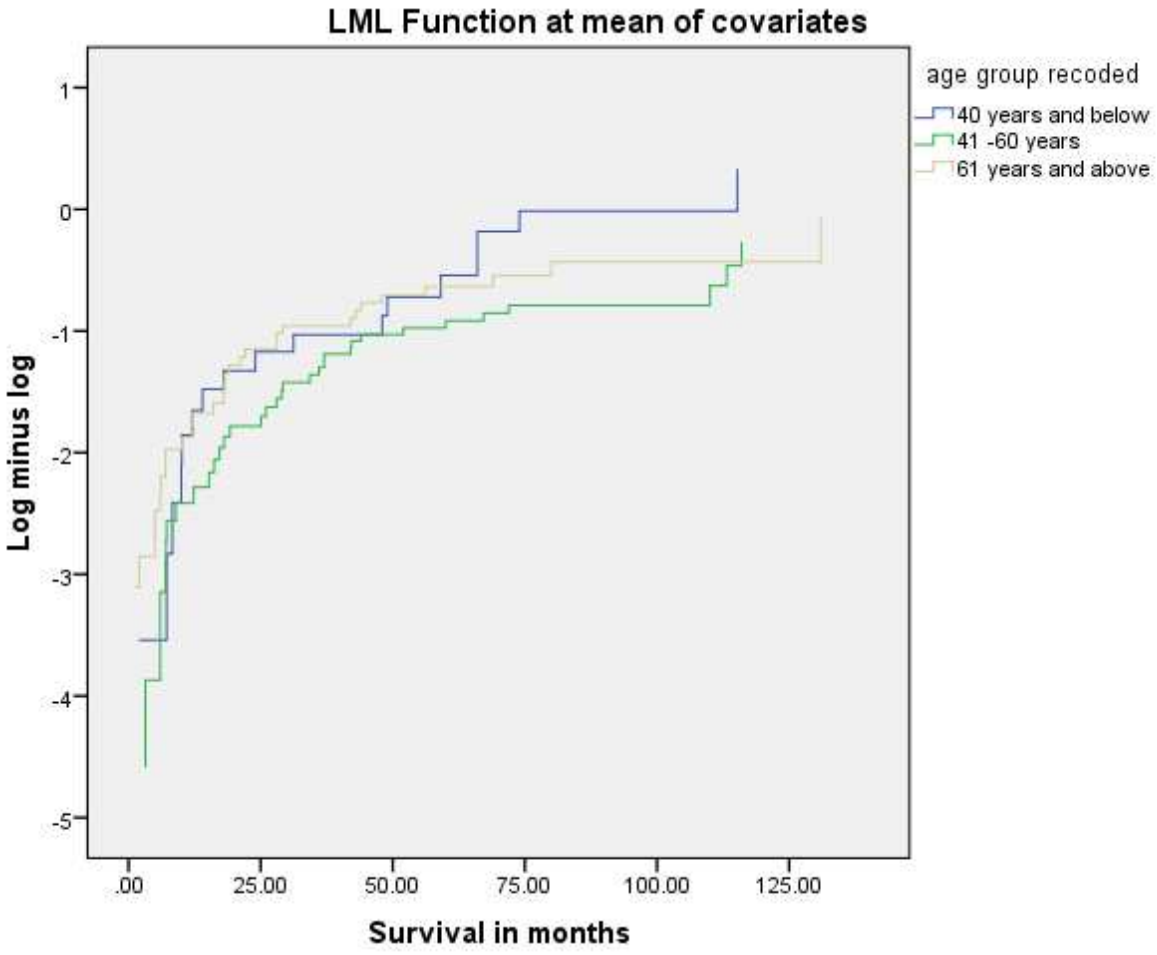


Figure A1 Kaplan Meier Log-Log function for age group

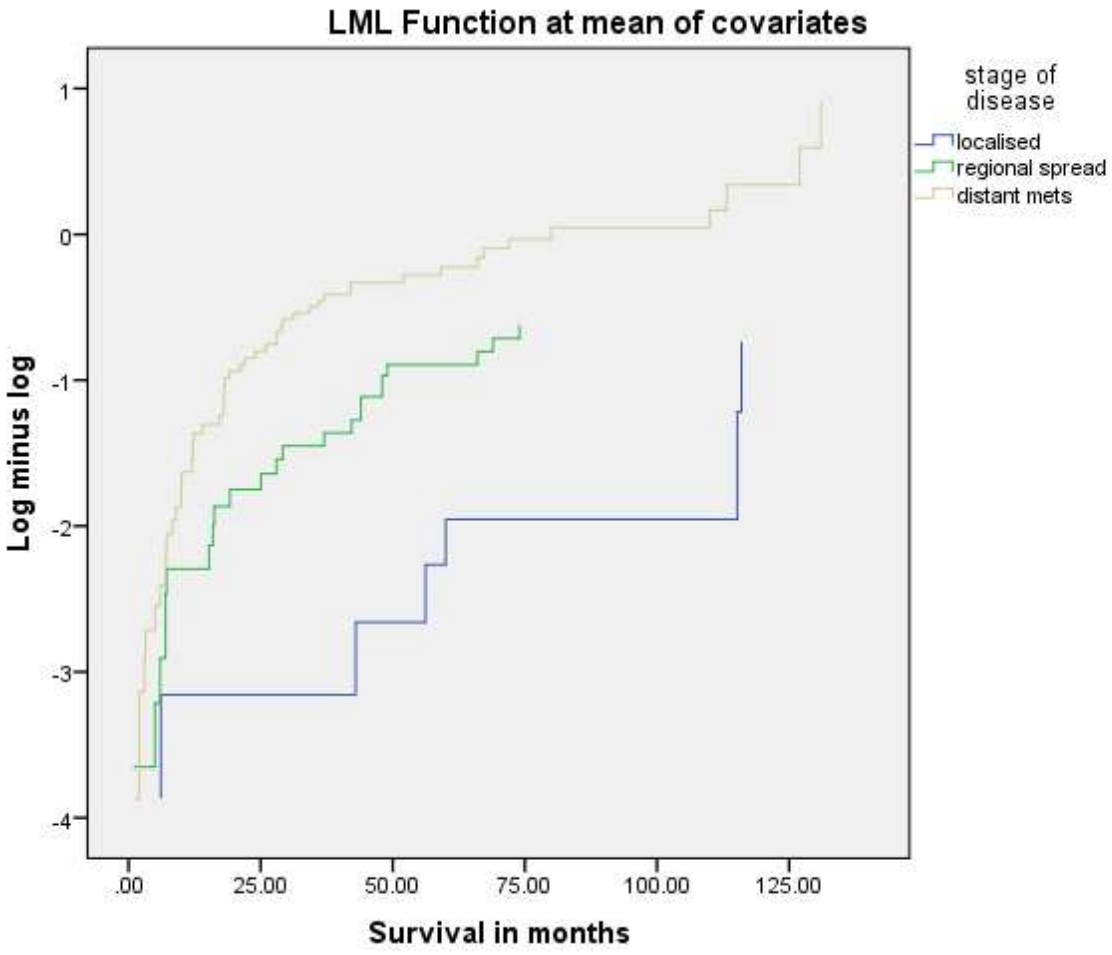


Figure A2 Kaplan Meier Log-Log function for stage of disease

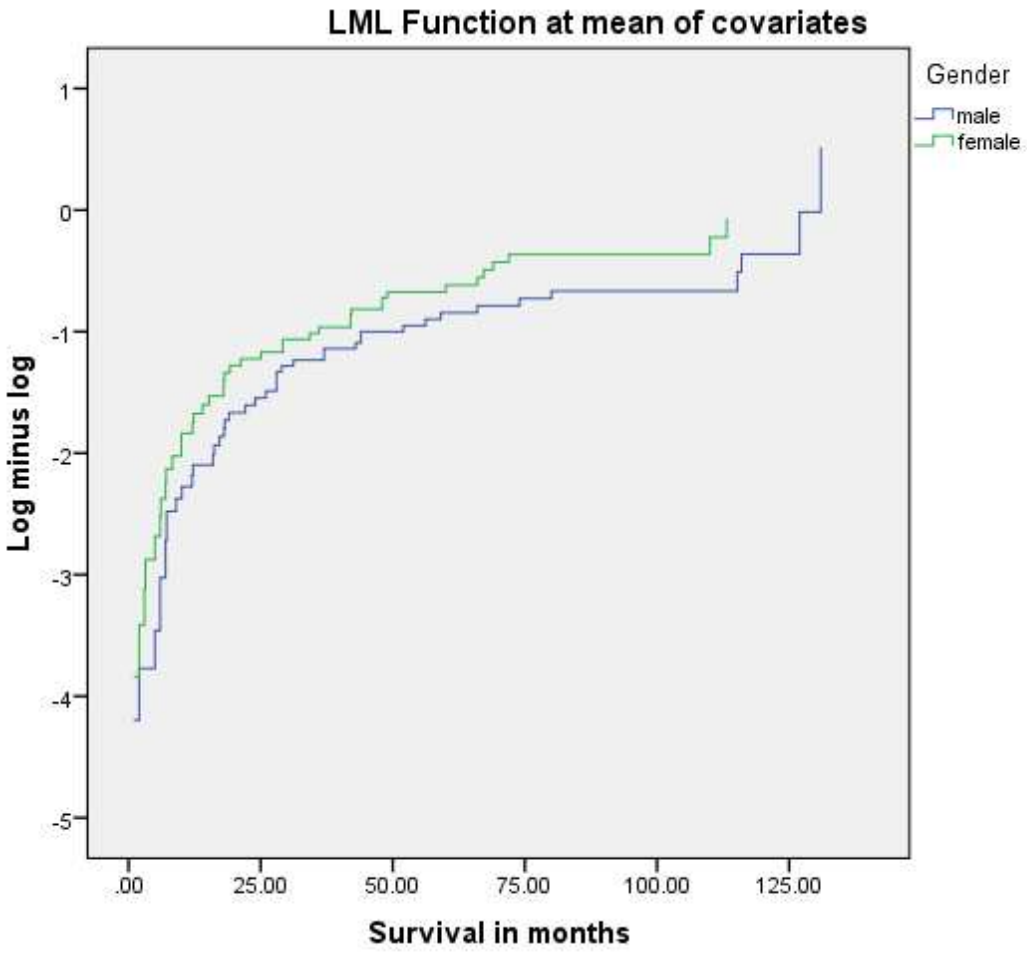


Figure A3 Kaplan Meier Log-Log function for gender

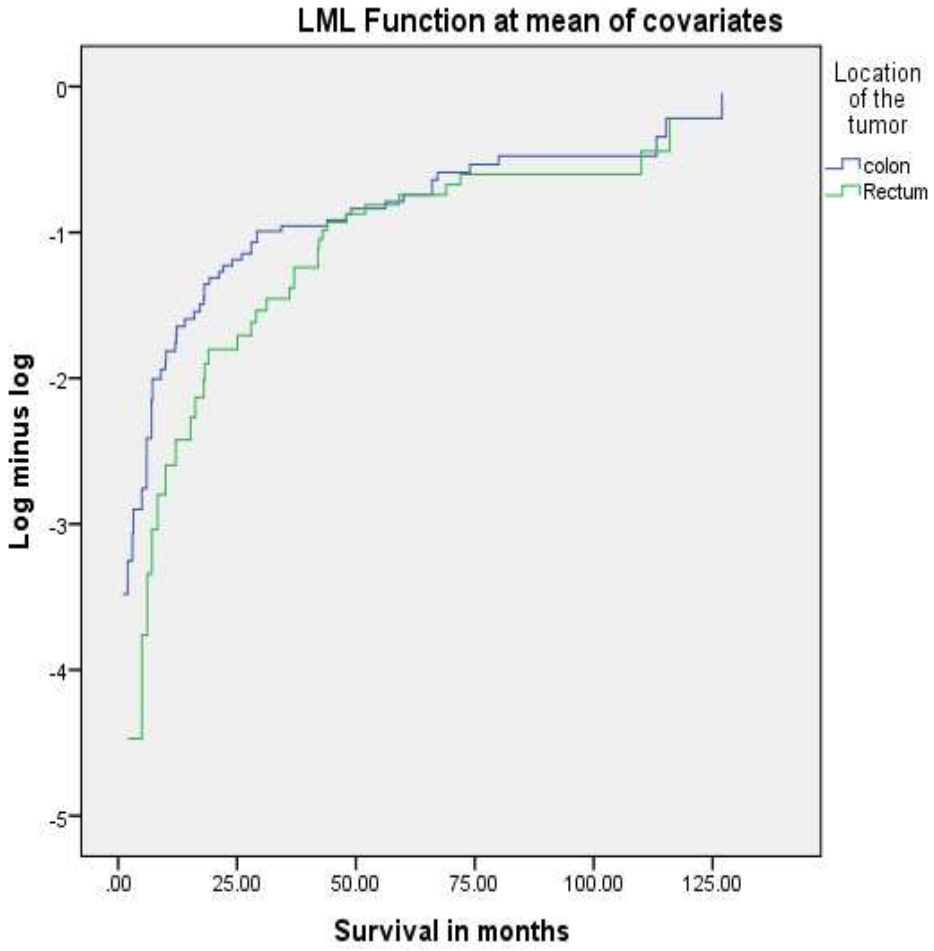


Figure A4 Kaplan Meier Log-Log function for tumor location

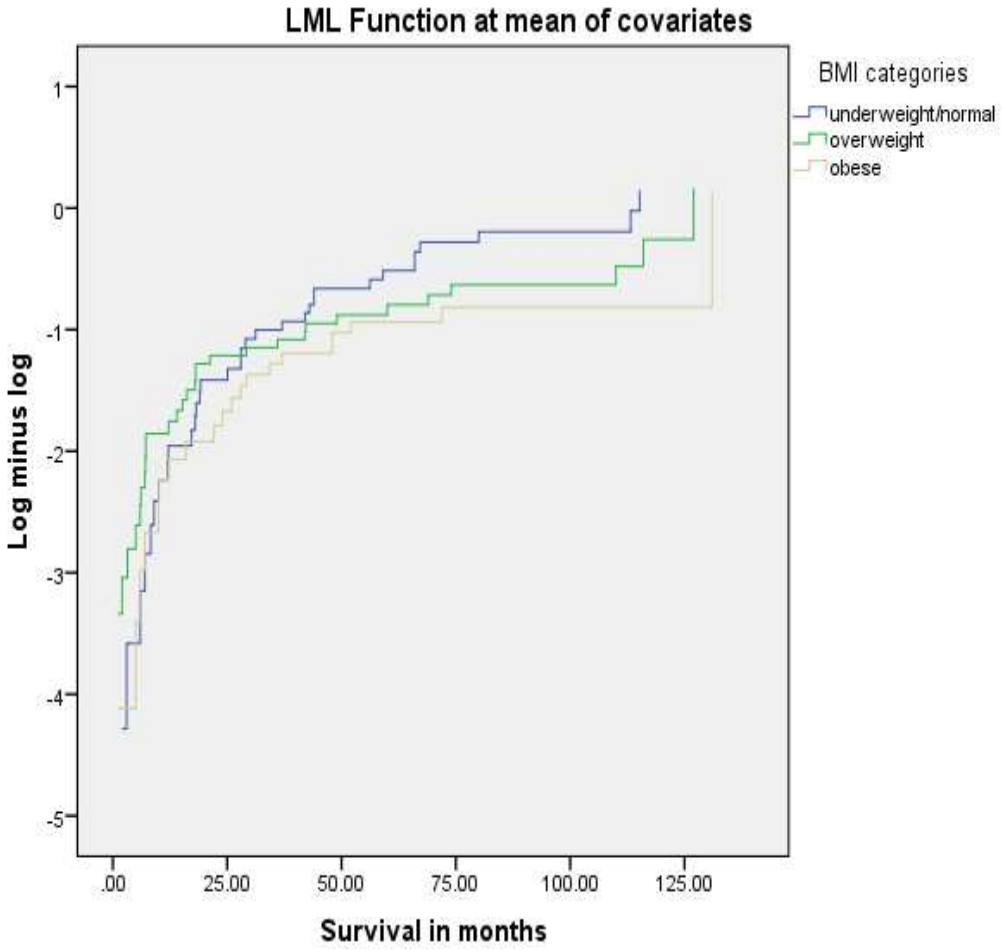


Figure A5 Kaplan Meier Log-Log function for BMI

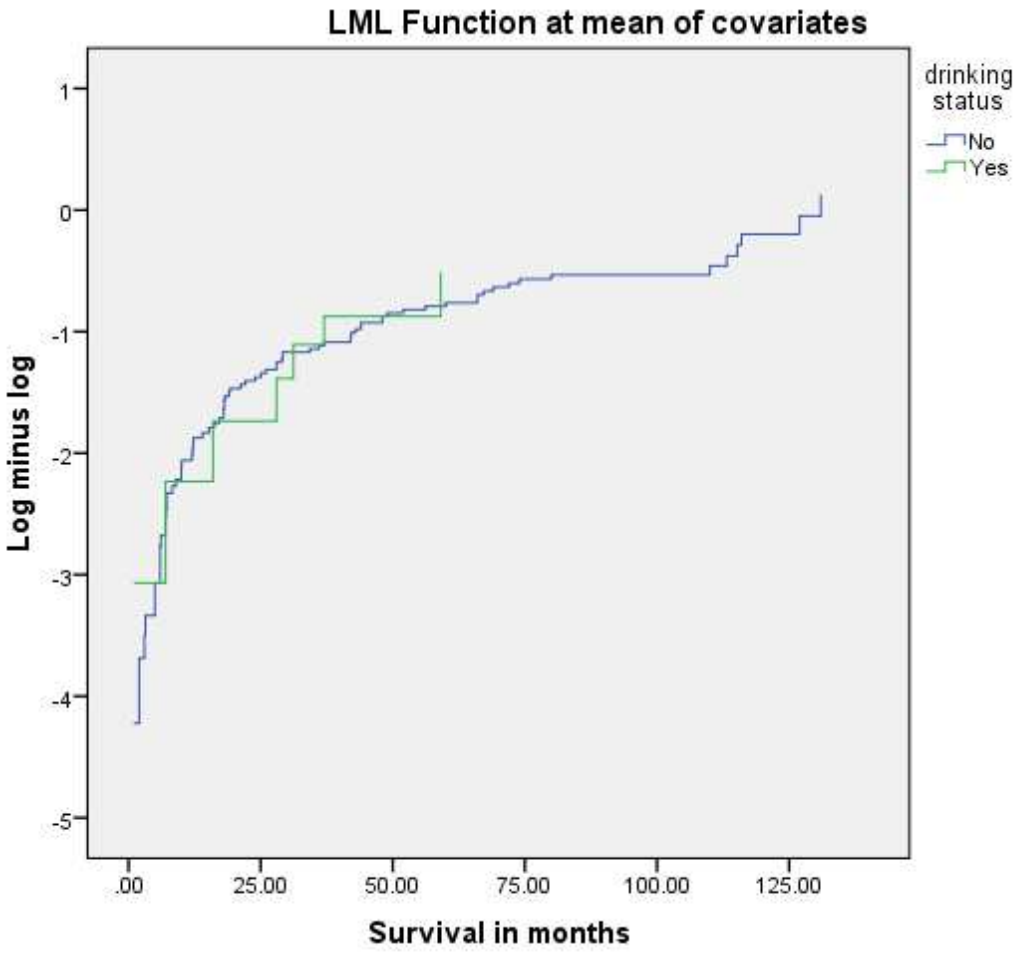


Figure A6 Kaplan Meier Log-Log function for alcohol consumption

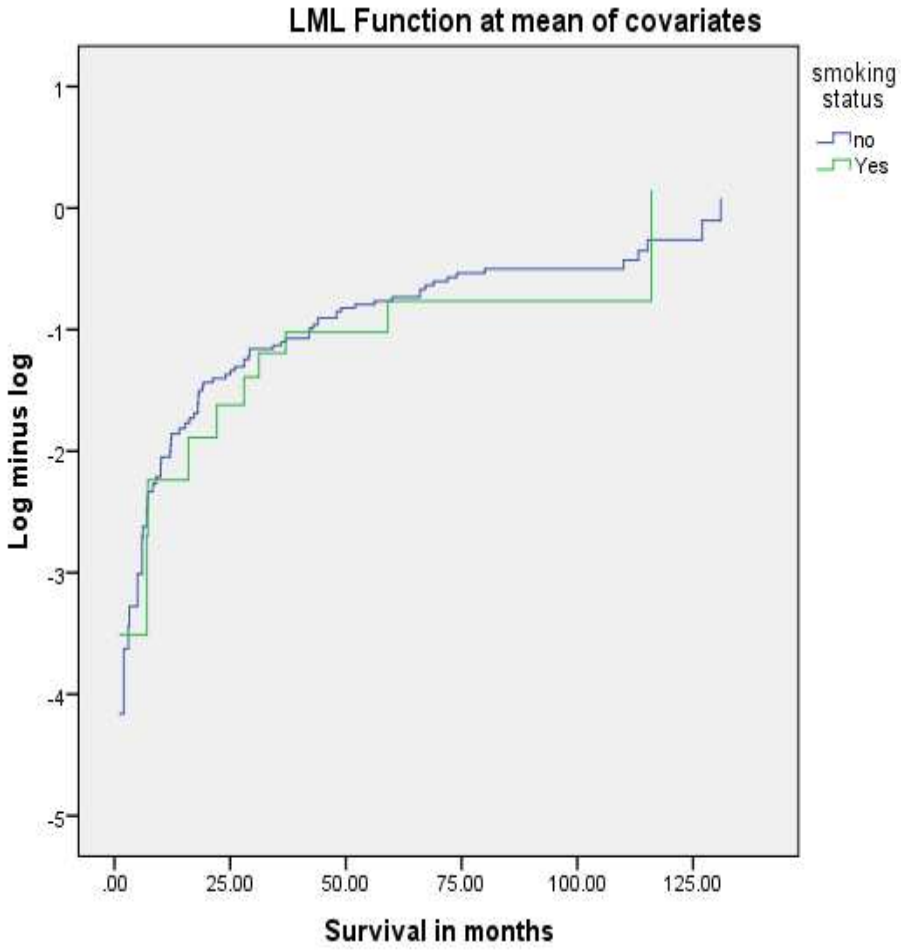
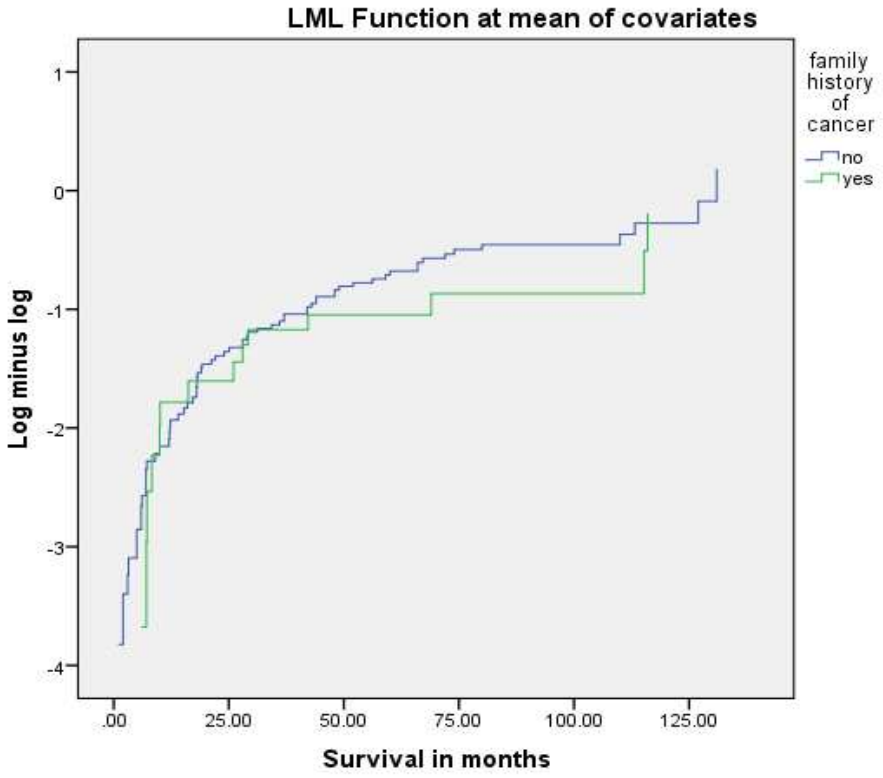


Figure A7 Kaplan Meier Log-Log function for smoking status



FigureA8 Kaplan Meier Log-Log function for family history of CRC