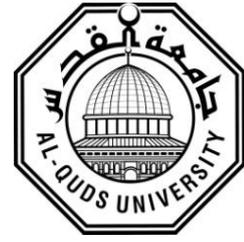


**Deanship of Graduate Studies**

**Al-Quds University**



**Determinants of Colorectal Cancer among Palestinians**

**Nidal Eid Mohammad Al-Jebrini**

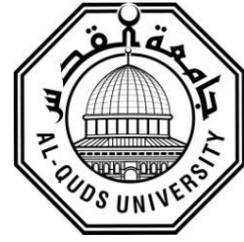
**M.Sc. Thesis**

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**M.Sc. Thesis**

**Jerusalem-Palestine**

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# **Determinants of Colorectal Cancer among Palestinians**

**Prepared By:**

**Nidal Eid Mohammad Al-Jebrini**

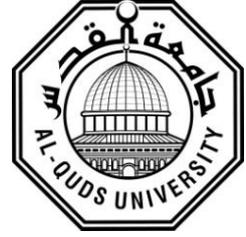
**B. Sc. in General Medicine – The Crimea State Medical  
University / Ukraine**

**Supervisor: Dr. Rania Abu Seir**

Thesis submitted in partial fulfillment of the requirement of  
the degree of Master of Public Health / Faculty of Graduate  
Studies / Al-Quds University

**1442/2021**

**Al-Quds University**  
**Deanship of Graduate Studies**  
**Faculty of Public Health**



## **Thesis Approval**

### **Determinants of Colorectal Cancer among Palestinians**

Prepared By: Nidal Eid Mohammad Al-Jebrini  
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Supervisor: Dr. Rania Abu Seir

Master thesis submitted and accepted: 08.05.2021

The names and signatures of the examining committee members are as follows:

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**Jerusalem-Palestine**

**1442 / 2021**

## **Dedication**

To my almighty God, who gave me strength and knowledge  
throughout my life

To Dr. Rania, the friend, the great teacher, and the exceptional  
human

To the memory of my father, who inspired me to be strong despite  
all the obstacles

To my mother, to my wife, for their understanding and  
overwhelming support

I dedicate this work...

Nidal Eid Mohammad Al-Jebrini

**Declaration:**

I certify that this thesis submitted for the degree of Master, is the result of my own research, except where otherwise acknowledged, and that this study (or any part of the same) has not been submitted for a higher degree to any other university or institution.

Signed .....



Nidal Eid Mohammad Al-Jebrini

Date: 08.05.2021

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I would also like to thank everyone at the Faculty of Public Health Faculty at Al-Quds University for the experience I received from my professors, the help and support of my colleagues, and the great times we shared.

I take this opportunity to acknowledge the people who put their time and experience into this project.

Last but not least, I would like to thank my dearest family for their sacrifices and the person they brought me to be, which allowed me to follow my dream. My gratitude and appreciation are beyond any words.

## **Abstract**

### **Background**

Worldwide, incidence and mortality rates of colorectal cancer (CRC) have been increasing during the past ten years. This increase is primarily attributed to drastic changes in the lifestyle and food consumption patterns with more Western-style and ready-made food in addition to adopting a sedentary lifestyle in daily life and other related activities. In this study, we aimed to describe the clinical and pathological characteristics of CRC and understand the role of lifestyle factors and dietary intake in CRC etiology.

### **Methodology**

A case-control study of 131 pathologically confirmed CRC cases and 104 cancer-free controls was conducted. Cases were ascertained through two hospitals; Beit-Jala Hospital in the South and Augusta Victoria Hospital in Jerusalem. Data were collected using an extensive interview-based questionnaire focused on several risk factors of the disease.

### **Results**

Among CRC cases, 52.7% were females and the median age at diagnosis was 56 years (interquartile range 48-64 years). The majority of cases were diagnosed at advanced stages of the disease. Body mass index (BMI) was not associated with CRC, but a history of diabetes, hypertension, or cardiovascular disease was significantly more common among cases. Furthermore, unexpectedly, physical activity was associated with an increased risk of CRC. Regarding dietary intake, highest intake of fish, fruits, nuts, and sweets were positively associated with an increased risk of CRC.

### **Conclusions**

The rising incidence and mortality could be explained by lifestyle and dietary factors; however, the findings of this study require further investigation.

Keywords: colorectal cancer, case-control study, prevalence, risk factors.

# Table of Contents

## Dedication

<b>Declaration</b> .....	<b>i</b>
<b>Acknowledgments</b> .....	<b>ii</b>
<b>Abstract</b> .....	<b>iii</b>
<b>Table of Contents</b> .....	<b>iv</b>
<b>List of Tables</b> .....	<b>vii</b>
<b>List of Figures</b> .....	<b>viii</b>
<b>List of Appendices</b> .....	<b>ix</b>
<b>List of Abbreviations</b> .....	<b>x</b>

## Chapter One: Introduction

<b>1.1. Background</b> .....	<b>1</b>
<b>1.2. Problem Statement</b> .....	<b>3</b>
<b>1.3. Study Justification</b> .....	<b>4</b>
<b>1.4. Aim and Objectives</b> .....	<b>5</b>
<b>1.5. Summary of Thesis Chapters</b> .....	<b>5</b>

## Chapter Two: Literature Review

<b>2.1. Epidemiology of Colorectal Cancer (CRC)</b> .....	<b>6</b>
<b>2.2. Classification and Staging of Colorectal Cancer (CRC)</b> .....	<b>8</b>
<b>2.2.1. Histopathology of Colorectal Cancer (CRC)</b> .....	<b>8</b>
<b>2.2.2. Staging of Colorectal Cancer (CRC)</b> .....	<b>8</b>
<b>2.3. Pathogenesis of Colorectal Cancer (CRC)</b> .....	<b>9</b>
<b>2.3.1. Traditional Adenoma-Carcinoma Pathway</b> .....	<b>10</b>
<b>2.3.2. The Serrated Neoplasia Pathway</b> .....	<b>11</b>
<b>2.4. Etiology of Colorectal Cancer (CRC)</b> .....	<b>11</b>
<b>2.4.1. Modifiable Risk Factors</b> .....	<b>12</b>
<b>2.4.1.1. Dietary intake</b> .....	<b>12</b>
<b>2.4.1.1.1. Diet high in fats</b> .....	<b>12</b>
<b>2.4.1.1.2. Red and processed meat</b> .....	<b>12</b>
<b>2.4.1.1.3. Fibers</b> .....	<b>13</b>

2.4.1.1.4.	Fruits and vegetables .....	13
2.4.1.1.5.	Cereals and whole grains.....	13
2.4.1.1.6.	Dairy products .....	14
2.4.1.2.	Physical activity .....	14
2.4.1.3.	Body mass index (BMI) and obesity .....	14
2.4.1.4.	Heavy alcohol consumption .....	15
2.4.1.5.	Smoking .....	16
2.4.2.	Non-Modifiable Risk Factors .....	17
2.4.2.1.	Age .....	17
2.4.2.2.	Inflammatory bowel disease .....	17
2.4.2.3.	Familial risk factors of colorectal cancer (CRC) .....	18
2.4.2.3.1.	Family history of colorectal cancer (CRC) .....	18
2.4.2.3.2.	Hereditary colorectal cancer (CRC) syndromes .....	18
2.4.2.4.	Infections .....	19

### **Chapter Three: Study Framework**

3.1.	Conceptual Framework .....	21
3.2.	Study Variables .....	22

### **Chapter Four: Methodology**

4.1.	Study Design and Power .....	24
4.2.	Study Settings .....	25
4.3.	Study Population .....	25
4.4.	Study Tools .....	26
4.4.1.	Pathology questionnaire .....	26
4.4.2.	Study questionnaire .....	26
4.5.	Ethical Considerations .....	27
4.6.	Statistical Analysis .....	27

### **Chapter Five: Results**

5.1.	Clinical and Pathological Characteristics of Colorectal Cancer (CRC) Patients .....	30
------	--	----

<b>5.2.</b>	<b>Demographic Characteristics of Study Subjects .....</b>	<b>33</b>
<b>5.3.</b>	<b>Risk Factors of Colorectal Cancer (CRC) among Palestinians .....</b>	<b>34</b>
<b>5.3.1.</b>	<b>Family history .....</b>	<b>34</b>
<b>5.3.2.</b>	<b>Body mass index (BMI), smoking, and physical activity .....</b>	<b>34</b>
<b>5.3.3.</b>	<b>Dietary intake .....</b>	<b>35</b>
<b>5.3.4.</b>	<b>Medical history .....</b>	<b>38</b>
 <b>Chapter Six: Discussion, Conclusions, Limitations and Recommendations</b>		
<b>6.1.</b>	<b>Discussion .....</b>	<b>39</b>
<b>6.1.1.</b>	<b>Clinical and pathological characteristics of colorectal cancer (CRC) patients .....</b>	<b>39</b>
<b>6.1.2.</b>	<b>Risk factors of colorectal cancer (CRC) .....</b>	<b>42</b>
<b>6.1.2.1.</b>	<b>Family history .....</b>	<b>43</b>
<b>6.1.2.2.</b>	<b>Body mass index (BMI) .....</b>	<b>44</b>
<b>6.1.2.3.</b>	<b>Smoking .....</b>	<b>45</b>
<b>6.1.2.4.</b>	<b>Physical activity .....</b>	<b>46</b>
<b>6.1.2.5.</b>	<b>Dietary intake .....</b>	<b>47</b>
<b>6.1.2.6.</b>	<b>Medical history .....</b>	<b>50</b>
<b>6.1.2.6.1.</b>	<b>Infections and gastrointestinal-related health problems .....</b>	<b>50</b>
<b>6.1.2.6.2.</b>	<b>Hypertension, diabetes, and cardiovascular disease (CVD) .....</b>	<b>53</b>
<b>6.2.</b>	<b>Limitations .....</b>	<b>55</b>
<b>6.3.</b>	<b>Conclusions .....</b>	<b>56</b>
<b>6.4.</b>	<b>Recommendations .....</b>	<b>56</b>
	<b>References .....</b>	<b>58</b>
	<b>Appendices .....</b>	<b>76</b>
	<b>الملخص.....</b>	<b>103</b>

## List of Tables

<b>No.</b>	<b>Title</b>	<b>Page No.</b>
3.1	Definitions of study variables.....	22
4.1	Food groupings of food frequency questionnaire (FFQ) items.....	28
5.1	Clinical and pathological characteristics of colorectal Cancer (CRC) among cases.....	31
5.2	Odds ratios (OR) for colorectal cancer (CRC) association with demographic characteristics of study subjects.....	33
5.3	Odds ratios (OR) for colorectal cancer (CRC) associated with family history.....	34
5.4	Odds ratios (OR) for colorectal cancer (CRC) association with BMI, smoking and physical activity.....	35
5.5	Consumption levels of food groups among study subjects against international recommendations.....	36
5.6	Odds ratios (OR) for colorectal cancer (CRC) associated with quartiles of food groupings.....	37
5.7	Odds ratios (OR) for colorectal cancer (CRC) associated with medical history.....	38

## List of Figures

<b>No.</b>	<b>Title</b>	<b>Page No.</b>
1.1	Incidence and mortality rates of colorectal cancer (CRC) in the West Bank, Palestine .....	4
2.1	Estimated age-standardized incidence rates (World) in 2020, colorectum, both sexes, all ages.....	7
2.2	A model of the genetic changes required for progression from adenoma to carcinoma in the development of colorectal cancer (CRC) .....	10
3.1	Conceptual framework of the study.....	22
5.1	Distribution of colorectal cancer (CRC) cases by age at diagnosis.....	31
5.2	Distribution of age among colorectal cancer (CRC) cases and controls....	33

## List of Appendices

<b>No.</b>	<b>Title</b>	<b>Page No.</b>
<b>4.1</b>	Pathology Questionnaire .....	<b>76</b>
<b>4.2</b>	Study Questionnaire-English .....	<b>79</b>
<b>4.3</b>	Study Questionnaire-Arabic .....	<b>89</b>
<b>4.4</b>	Ethical Approval .....	<b>99</b>
<b>4.5</b>	Ministry of Health (MOH) Approval .....	<b>100</b>
<b>4.6</b>	Consent Form.....	<b>102</b>

## List of Abbreviations

ASR	Age standardized rate
AVH	Augusta Victoria Hospital
BJH	Biet-Jala Hospital
BMI	Body-mass index
CRC	Colorectal cancer
CI	Confidence Interval
CIN	Chromosomal instability
CVD	Cardiovascular disease
CD	Crohn's disease
DNA	Deoxyribonucleic acid
DM	Diabetes mellitus
FAP	Familial adenomatous polyposis
FDA	Food and Drug Administration
FFQ	Food-frequency questionnaire
GI	Gastroenterology
HNPCC	Hereditary non-polyposis colorectal cancer
HPP	hyperplastic polyposis
HPV	Human polyomaviruses
IARC	International Agency for Research on Cancer
IBD	Inflammatory bowel disease
IQR	Interquartile range
MAP	MUTYH-associated polyposis
MMR	Mismatch repair
MOH	Ministry of Health
MSI	Microsatellite instability
MLH1	MutL Homolog 1
MSH2	MutS homolog 2
NCD	Non-communicable disease
OR	Odds ratio
OS	Overall survival
PCBS	Palestinian Central Bureau of Statistics

PJS	Peutz-Jeghers syndrome
PMS2	PMS1 Homolog 2
RR	Relative risk
SEER	Surveillance, Epidemiology, and End Results Program
SD	Standard deviation
TNM	Tumor, node, metastasis
UC	Ulcerative colitis
UK	United Kingdom
USA	United States of America
USDA	U.S. Department of Agriculture
WHO	World Health Organization
WCRF	World Cancer research Fund

## Chapter One

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### Introduction

#### 1.1. Background

Colorectal cancer (CRC) is a heterogeneous and complex disease which occurs as a result of a multistep process that is guided by a number of molecular, cellular, and histological alterations, that can transform the normal epithelium to adenoma and ultimately to cancer (Piskol & de Sousa, 2020). Tumors with similar histopathological characteristics have variable clinical course and different responses to treatment (Bedard *et al.*, 2013). CRC originates either from the colon or from the rectum. It is classified according to the WHO by the site of initiation.

CRC is the 3<sup>rd</sup> most common cancer worldwide; the 2<sup>nd</sup> most commonly occurring type of cancer in women and the 3<sup>rd</sup> in men (IARC, 2020a). In addition, CRC is the 3<sup>rd</sup> leading cause of cancer mortality in men and 4<sup>th</sup> in women worldwide (IARC, 2020a). Northern America, Europe and Australia have the highest rates of colorectal cancer, while south eastern Asia, central Africa have the lowest (Macrae, 2016).

Over the past years, the epidemiological trends of CRC has changed due to effective screening measures, early interventions, and better treatment options (Thanikachalam & Khan, 2019), but these changes are not uniform. For instance, the incidence rates of CRC in the United States and the European countries have been stabilizing or even decreasing while they have doubled in high-income countries that recently made transition such as

Singapore and Japan (Bishehsari *et al.*, 2014). In addition, decrease in overall mortality from colorectal cancer have been reported in the USA between 1990-2007; however, among white young adults 20-54 years old, mortality rates increased between 2004-2014 (Thanikachalam & Khan, 2019).

The situation is different in the Arab World; while the incidence of CRC is much lower than that for developed countries, statistics reported an increase in the incidence of CRC in the past ten years by 2.3 folds in males and 2.7 folds in females (Eser *et al.*, 2018). According to the National Cancer Registry in Jordan, during 2012, CRC ranked the second among males with an incidence rate of 12/100,000 population, and the second among females with an incidence rate of 10.7/100,000 population, and the standardized incidence rates increased between 2003-2012 (Nimri & Halasa, 2012). Furthermore, in Lebanon, CRC ranked as the 4<sup>th</sup> most commonly diagnosed cancer among males and remained stable at 15.3/100,000 population, while it was the 2<sup>nd</sup> most-common cancer among females with an incidence rate of 14.1/100,000 that observed a slight decrease over the six-year period (Shamseddine *et al.*, 2014). Similar increase in CRC incidence rates have also been reported in many Arab countries such as Yemen, Egypt, and Saudi Arabia, Algeria, Qatar, Kuwait, Bahrain (Arafa & Farhat, 2015).

Among Palestinians, CRC was reported to be the 2<sup>nd</sup> most commonly diagnosed type of cancer among both males and females during 2018. The incidence of CRC in the West Bank was 13.6/100,000 population (15.2/100,000 among males and 11.9/100,000 among females), contributing with 11.5% to overall cancer cases. Furthermore, CRC was the second leading cause of cancer mortality constituting 13.9% of cancer deaths (MOH, 2019).

Age, genetic and environmental factors contributes largely to the etiology of CRC (Thanikachalam & Khan, 2019). The development of colorectal cancer occurs through three major pathways; chromosomal instability, mismatch repair, and methylator phenotype (Hughes *et al.*, 2017).

The high variability in rates of CRC between high and low incidence areas that might be up to 10-folds and the rapidly increasing incidence among migrants from low-incidence countries to high-incidence countries provide evidence for the role of environmental and

familial factors in the development of CRC (Siegel *et al.*, 2020). Based on epidemiological studies, the most recognizable risk factors of CRC includes dietary factors, exercise, alcohol consumption, smoking, obesity, inflammatory bowel disease, intestinal infection and age (Marley & Nan, 2016; Thanikachalam & Khan, 2019). Furthermore, family history and other familial disorders were also reported to be associated with increased risk of CRC (Migliore *et al.*, 2011; Thanikachalam & Khan, 2019).

## **1.2. Problem Statement**

During the last few decades, a shifting in the burden of disease from communicable to non-communicable diseases (NCDs) has been noticed in many developing countries (Yach *et al.*, 2005). Non-communicable diseases, which are driven by unhealthy consumption patterns, were responsible for almost 70% of reported deaths in Palestine during 2018 and cancer was the second leading cause of mortality (MOH, 2019). According to the WHO, it is estimated that around one-third cancer deaths are caused by modifiable lifestyle factors. These risk factors include tobacco use, high body mass index (BMI), alcohol use, low fruit and vegetable intake, and lack of physical activity (WHO, 2021).

While maintaining a healthy weight and balanced diet, being physically active, and not using tobacco cancer prevent cancer, it is important to understand the driving factors for the increased rates of cancer. The rapid societal and economic changes undergoing in developing nations have resulted in increased cancer burden (Arnold *et al.*, 2017).

CRC and its research is a neglected area in Palestine as other types of cancer. As a result, very few local researchers have been concerned with this cancer. The incidence and mortality rates of CRC have been increasing during the past 10 years (MOH, 2019). This increase must be attributed to drastic changes in the lifestyle and food consumption patterns with more Western-style and ready-made food in addition to adopting a sedentary life style in daily life and other related activities. In addition, familial factors might play a role especially due to high rate if consanguinity among Palestinians.

While preventive strategies can reduce risk of CRC, it is very important to determine the factors that may play a role as risk/protective factors in Palestine. This data is not available

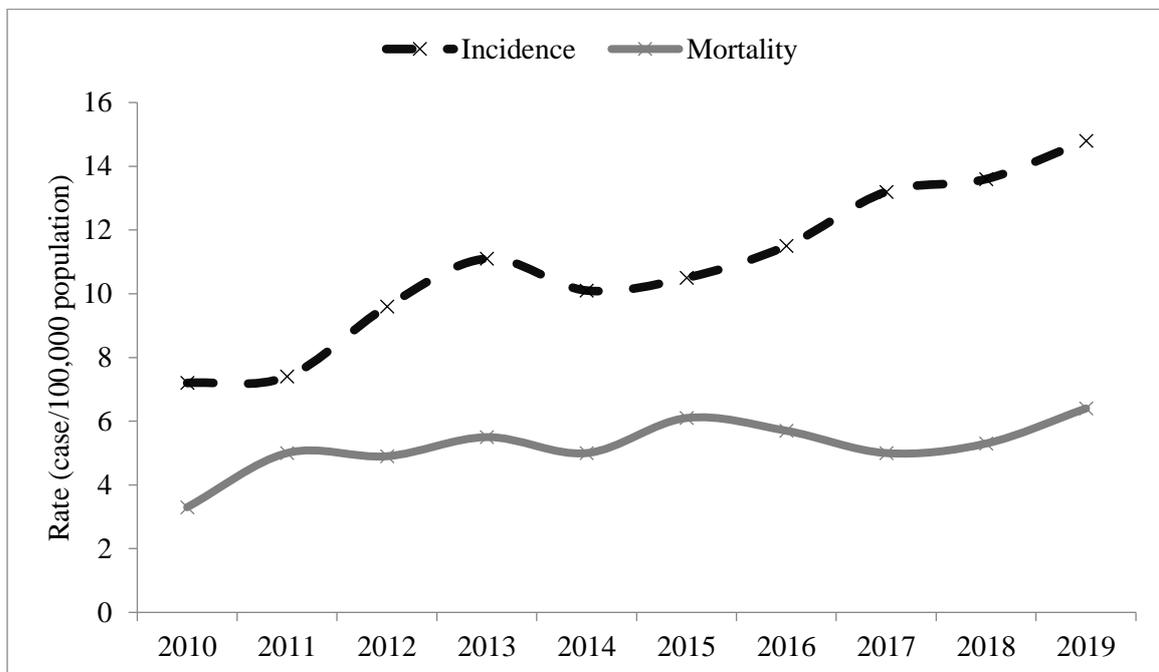
in Palestine, which makes it a rich area for research. Results of this research will formulate baseline data for any plans in the area of prevention of the disease.

### 1.3. Study Justification

CRC is the second most commonly diagnosed cancer and the second leading cause of cancer mortality among Palestinians. Figure 1.1 shows the incidence and mortality rates of CRC in the West Bank. During the last decade, the incidence and mortality rates of CRC has almost doubled. Around 15% of cancer mortality are attributed to CRC (MOH, 2019).

While improved diagnosis undoubtedly contributes to the rise in the incidence of CRC, it has been postulated that the rising incidence reflects the rising prevalence of associated risk factors.

Healthy dietary pattern and active lifestyle factors have been shown to decrease the incidence of CRC (Tayyem *et al.*, 2017). Studies about CRC and its risk factors among Palestinians are scarce. Understanding the etiology of CRC is imperative in order to direct future strategies to reduce the burden of CRC through cancer prevention and care.



**Figure 1.1:** Incidence and mortality rates of colorectal cancer (CRC) in the West Bank, Palestine (MOH, 2020).

#### **1.4. Aim and Objectives**

This study aims to investigate the relationship between lifestyle factors and the risk of CRC in Palestine. The specific objectives of the study are:

1. To set-up a platform to evaluate genetic and environmental determinants of CRC among Palestinians.
2. To describe the pathological characteristics of CRC among Palestinians.
3. To investigate the association between smoking, body-mass index, dietary patterns, physical activity, medical history and the risk of CRC.

#### **1.5. Summary of Thesis Chapters**

The first chapter of this study describes the research problem we investigated and the necessity of it. In chapter two, a review of the available literature on this topic is provided. In chapter three, the study framework and variables of the study are described. Furthermore, chapters four and five illustrate the methodology and the findings of the study. Finally, the major findings of the study are discussed along with the conclusions, limitations of the study, and recommendations in chapter six.

## Chapter Two

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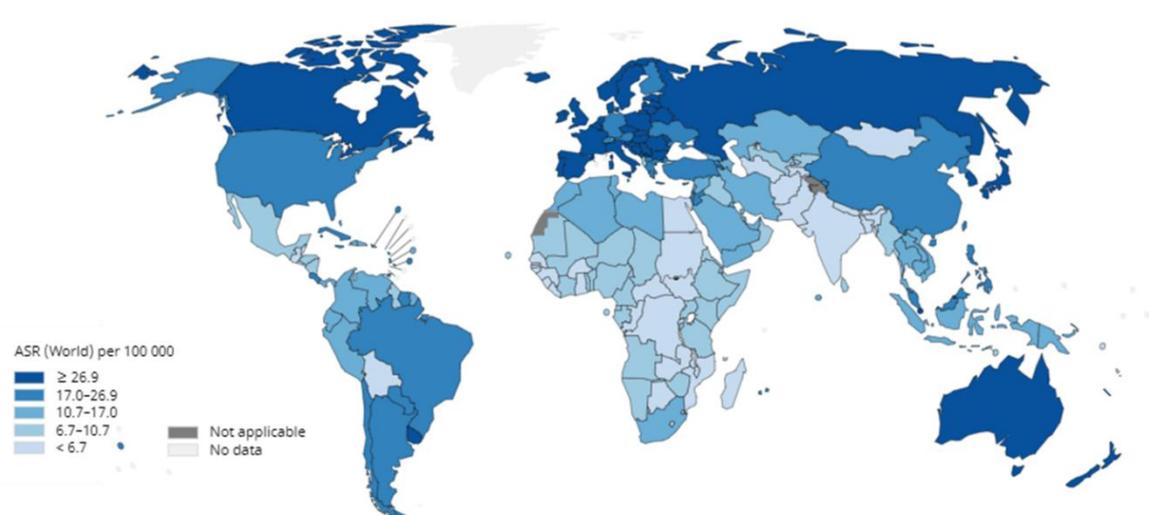
### Literature Review

#### 2.1. Epidemiology of Colorectal Cancer (CRC)

Colorectal cancer (CRC) is the 2<sup>nd</sup> most common cancer in women and 3<sup>rd</sup> in men worldwide with 1.93 million new cases diagnosed in 2020 worldwide and an age-standardized rate (ASR) of 19.5/100,000 population (IARC, 2020a).

In contrast to the United States of America (USA) and some European countries in which the incidence and mortality of CRC have been stabilizing, or even decreasing due to the implementation of preventive strategies, globally, the incidence of CRC has been rising for decades, with more commonly diagnosed among males (Siegel *et al.*, 2015). It is predicted that the number of cases will globally rise from 1.93 million cases in 2020 to 3.15 million in 2040 (IARC, 2020b).

Although the risk of developing CRC increases after the age of 50, different geographic areas have variations in distribution and incidence, the highest incidence being in developed countries (Siegel *et al.*, 2020). Northern America, Europe, and Australia have the highest rates of CRC, while southeastern Asia and central Africa have the lowest (Siegel *et al.*, 2015). Figure 2.1 shows the global estimated age-standardized rates (ASRs) of CRC in 2020.



**Figure 2.1:** Estimated age-standardized incidence rates (World) in 2020, colorectum, both sexes, all ages (IARC, 2020a).

In the Arab world, statistics showed that the CRC incidence is much lower than that of European countries. But the incidence of CRC has been increasing during the last 10 years by 2.3 folds in males and 2.7 folds in females (Arafa & Farhat, 2015). For example, in Jordan; CRC ranked second among males with 16.3/100,000 population, and second among females with 15.9/100,000 during 2012, the trend of age-standardized incidence rates increased through the period 2003-2012 (Nimri & Halasa, 2012). In Lebanon, CRC incidence rates ranked 4<sup>th</sup> among males and remained stable at 15.3/100,000 population, while it was the 2<sup>nd</sup> most common cancer at 14.1/100,000 among females, with a slight decrease over the six-year period (Shamseddine *et al.*, 2014). Similar increase in CRC incidence rates have also been reported in many Arab countries such as Yemen, Egypt, Saudi Arabia, Algeria, Qatar, Kuwait, and Bahrain (Arafa & Farhat, 2015).

Among Palestinians, CRC was reported to be the second most commonly diagnosed type of cancer among both males and females during 2018. The incidence of CRC in the West Bank was 13.6/100,000 population (15.2/100,000 among males and 11.9/100,000 among females), contributing with 11.5% to overall cancer cases. Furthermore, CRC was the second leading cause of cancer mortality constituting 13.9% of cancer deaths (MOH, 2019).

## **2.2. Classification and Staging of Colorectal Cancer (CRC)**

### **2.2.1. Histopathology of Colorectal Cancer (CRC)**

Histopathologically, most of CRCs are carcinomas with more than 90% of them are adenocarcinomas. Adenocarcinoma are further classified into mucinous, signet-ring cell, cribriform-comedo-type, medullary, micropapillary, serrated. Adenosquamous, spindle, squamous and undifferentiated carcinomas are less common types (Ubink *et al.*, 2018). Based on to the percentage of gland formation in the colonic wall, adenocarcinoma can be categorized into well (more than 95%), moderately (more than 50%) and poorly (less than 49%) differentiated, but further divided in two-tier low-grade (well-moderate)/high-grade (poor) with prognostic significance (Di Como *et al.*, 2015; Recio-Boiles & Cagir, 2018; Weerakkody & Gaillard, 2014).

### **2.2.2. Staging of Colorectal Cancer (CRC)**

The tumor, node, metastasis (TNM) staging system is the most widely used and recommended system for CRC staging. TNM staging includes clinical findings (cTNM), radiologic imaging (rTNM) prior to diagnosis, and pathological examination of resected tumor specimens or perioperative findings (pTNM, or ypTNM when staging is made after neoadjuvant treatment). The T stage describes the depth of invasion of the primary tumor through the layers of the intestinal wall, N stage describes the spread to regional lymph nodes, and the M stage describes the occurrence of distant metastases (Karamchandani *et al.*, 2020). TNM stages are classified into stage groups (stage I-IV) where the increasing stage is associated with more advanced disease, e.g. lymph node metastasis (stage III) and metastasis (stage IV)(Yamano *et al.*, 2020). Based on microscopic features, CRC is graded based on the tissue from which it originated and the proportion of gland formation by the tumor. Tumor differentiation grade ranges from highly differentiated tumors with >95% gland formation, to undifferentiated tumors with less than 5% glandular structures. This simple staging system, now at its eighth edition, is widely used, clinically useful, and is highly associated with 5-year overall survival (OS), ranging from 92% in stage I to 11% in stage IV (Edge, 2010; Gospodarowicz *et al.*, 2017).

While the TNM stage nowadays is the most valuable prognostic factor in CRC, TNM stage alone is not optimal for predicting disease outcomes as patients within the same TNM stage may have different prognosis and response to therapy (Moccia *et al.*, 2019). This fact

has motivated the researchers to look for other biomarkers that may have prognostic and predictive value. Despite all efforts, there are no markers or combinations of markers that have been discovered to be unique to provide information on disease outcome and treatment response of CRC. The tumor antigens CEA, CA-19-9 in serum are the most widely used biomarkers in CRC. They are often not elevated in early stages and high levels are found in more advanced stages and associated with poorer prognosis (Thomsen *et al.*, 2018). The tests have low sensitivity and specificity and high rates of false-positive, making it insufficient for early detection and screening. Despite its disadvantages, it can be useful in monitoring CRC progression and recurrence (Compton, 2007; O'Connell *et al.*, 2004).

### **2.3. Pathogenesis of Colorectal Cancer (CRC)**

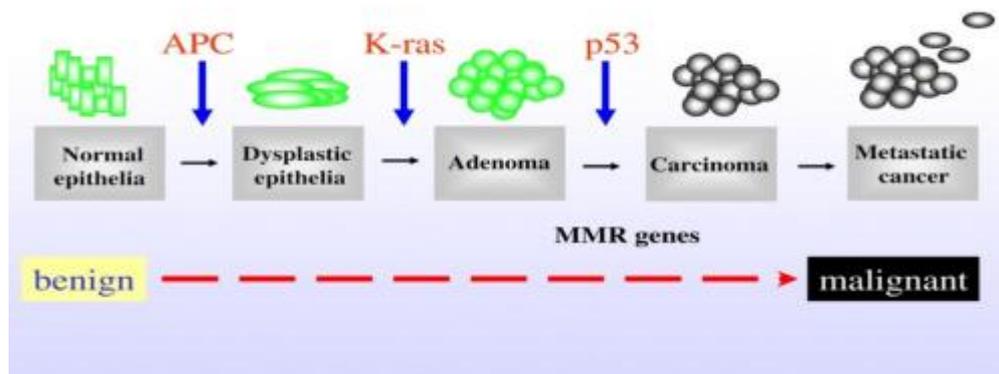
CRC is a heterogeneous and complex disease, which occurs because of a multistep process. Tumors with similar histopathological characteristics have variable clinical course and different responses to treatment that can be driven by a number of molecular, cellular, and histological alterations which can transform the normal epithelium to adenoma and ultimately to cancer (Bedard *et al.*, 2013; Marusyk *et al.*, 2012; Swanton, 2012).

Furthermore, this process requires an accumulation of genetic mutations, either somatic (acquired) and/or germline (inherited) in an approximately 10 to 15 years period. A typical CRC contains at least 11,000 genomic alterations. The Cancer Genome Atlas and consensus molecular subtype classifications have increased the understanding of the genomic and epigenomic landscapes of CRC and have led to the evolution of new classifications according to their distinct molecular pathologies and clinical features (Inamura, 2018). In accordance, several studies have shown that CRC is classified into different subtypes, and each subtype has distinct molecular features and prognosis (Song *et al.*, 2016). As summarized by Song *et al.*, CRC is categorized into 5 distinct subtypes: enterocyte, gobletlike, inflammatory, stem like, and transit amplifying (TA) (Sadanandam *et al.*, 2013), and each subtype is classified into 3 groups: CCS1, CCS2, and CCS3 (de Sousa *et al.*, 2013).

### 2.3.1. Traditional Adenoma-Carcinoma Pathway

There are two morphologic, multi-step pathways to CRC development: the traditional adenoma-carcinoma pathway and the serrated neoplasia pathway. The cancers resulting from each pathway are driven by three molecular carcinogenesis pathways: chromosomal instability (CIN) characterized by abnormal karyotypes, aneuploidy, and loss of heterozygosity; microsatellite instability (MSI) characterized by silencing of DNA repair mechanisms; and epigenetic instability (primarily the CpG island methylator phenotype (CIMP) associated with hypermethylation and silencing of tumor suppressor genes. It is important to understand these pathways to identify disease subtypes, to validate molecular markers for risk assessment, and for early detection, prognosis, and prediction (Bae *et al.*, 2016; Hughes *et al.*, 2017; Peters *et al.*, 2013).

The traditional adenoma-carcinoma pathway accounts for approximately 60–90% of sporadic CRC and begins as preneoplastic lesions including conventional, tubular or tubulovillous adenomas. These types of adenomas are characterized by the presence of CIN, which leads to inactivation of tumor suppressor genes such as Adenomatous Polyposis Coli (APC) or activation of tumor oncogenes such as mutations in the KRAS oncogene, as well as TP53, SMAD4, and PIK3CA genes (Figure 2.2). These changes occur in the early stages of CRC development. Descriptively, tumors that arise from this pathway are more often associated with male sex, and observed in the distal colon (Bae *et al.*, 2016; Hermsen *et al.*, 2002; Hughes *et al.*, 2017; Peters *et al.*, 2013).



**Figure 2.2:** A model of the genetic changes required for progression from adenoma to carcinoma in the development of colorectal cancer. (Smith *et al.*, 2002)

### **2.3.2. The Serrated Neoplasia Pathway**

The serrated neoplasia pathway (10–30% of sporadic CRC) begins with hyperplastic polyps or sessile or traditional serrated adenoma. The histology of these types of tumors are different compared to tumors derived from the traditional adenoma-carcinoma sequence (Kim *et al.*, 2020). They are characterized by a form of genetic instability, which is called MSI, which leads to length alterations of repeated microsatellite sequences of DNA because of defective post-replication mismatch repair system. This will lead to inhibition of normal apoptosis of colonic epithelial cells by the effect of mutation of the BRAF proto-oncogene (Imai & Yamamoto, 2008). The CpG methylator phenotype (CIMP) is the main mechanism, which is involved in the serrated neoplasia pathway. It causes silencing a large variety of tumor suppressor genes, such as MLH1. Loss of MLH1 causes microsatellite instability (MSI) and once MLH1 is inactivated, the rate of progression to malignant transformation is rapid. Tumors with such characteristics are more frequently associated with female sex, and are observed in the proximal colon (Snover, 2011).

### **2.4. Etiology of Colorectal Cancer (CRC)**

Several epidemiological and pathological studies have investigated different factors that may cause mutations and epigenetic changes and have shown that factors such as diet, lifestyle, alcohol consumption, smoking, obesity, and inflammatory bowel disease, may not only play a role in causing mutations and epigenetic changes, but also in enhancing tumor growth in tissues that have already acquired specific (epi) genetic aberrations (Rossello-Tortella *et al.*, 2020). Furthermore, these studies have revealed direct causal associations between diet and lifestyle factors and molecular changes in CRC (S Ogino & Stampfer, 2010; Poynter *et al.*, 2009; Martha L Slattery *et al.*, 2000; Weijenberg *et al.*, 2007).

There are numerous risk factors, which are associated with the development of CRC. CRC risk factors can be modifiable and non-modifiable (Giovannucci, 2002). Those factors that an individual cannot control are non-modifiable factors such as age and hereditary factors. Modifiable risks factors are those that can be controlled by individuals. The importance of knowing and studying modifiable risk factors comes from the fact that these factors can be controlled and used in a way that can prevent CRC (X. Wang *et al.*, 2019b).

### **2.4.1. Modifiable Risk Factors**

Based on epidemiological evidence from the Cancer Research United Kingdom (UK) foundation, 54% of CRC cases are preventable. Furthermore, the estimations show that 28% of cases are caused by low fiber intake, 13% are attributable to eating processed meat and 11% are attributable to obesity (CancerResearchUK, 2018). This section reviews the evidence regarding the role of modifiable risk factors in the etiology of CRC.

#### **2.4.1.1. Dietary intake**

##### **2.4.1.1.1. Diet high in fats**

The risk of colorectal cancer is strongly affected by changes in food habits, which might influence the cancer burden by 70% (Willett, 2005). Diets high in fat, especially animal fat, containing polyunsaturated linoleic acid are considered an important risk factor that induces chronic inflammation and promotes colorectal cancer carcinogenesis by down-regulation of 15-lipoxygenase-1 and upregulation of COX2 (Boyle & Langman, 2000; Yuri *et al.*, 2007), and has been linked to KRAS mutations (Weijenberg *et al.*, 2007). Furthermore, high fats diet, favors the development of an anaerobic bacterial flora responsible for degrading bile salts to potentially carcinogenic N-nitroso compounds (Susanna C Larsson & Wolk, 2006b). Moreover, many studies revealed an increased risk among people of higher socioeconomic status with westernized diet containing high fat diets, low vegetable fats (Bishehsari *et al.*, 2014; Khuhaprema & Srivatanakul, 2008; Stigliano *et al.*, 2014). In another study conducted by involving 88751 women aged 34-59 years who were without IBD or CRC and with a high consumption of animal fats found a significant association between high fat diets and CRC risk (RR: 1.89) (Willett, 1989)

##### **2.4.1.1.2. Red and processed meat**

The consumption of large amounts of meat increases the risk of colon cancer, especially rectal cancer (Susanna C Larsson & Wolk, 2006b). This is related to the presence of heme iron in red meat which can enhance the endogenous formation of carcinogenic N-nitroso-compounds (Santarelli *et al.*, 2008). Furthermore, it has been hypothesized by Gilsing *et al.* that strong association is present between heme and specific point mutations in tumor cells with higher rates of KRAS mutated tumors than KRAS wild-type tumors (Gilsing *et al.*, 2013). In addition to that, there is some evidence revealing that cooking meat at high temperatures resulted in the production of polycyclic aromatic hydrocarbons and

heterocyclic amines, which are approved to have carcinogenic properties (Casella *et al.*, 2018; Sinha, 2002).

Processed meat which is a product obtained by several stages containing salting, curing, smoking, fermentation, to improve taste and preservation time is also associated with increased risk of CRC (Bouvard *et al.*, 2015; Chan *et al.*, 2011). Meat processing can be contaminated by oncogenic thermo-resistant bovine viruses and that when associated with chemical carcinogens developed during procedures of cooking, increases CRC risk (zur Hausen, 2012). Furthermore, the additional factors that can enhance the carcinogenic role of red and processed meat are concomitant dietary factors (e.g., high fat and/ or protein intake) and clinical conditions, such as obesity (Calle & Kaaks, 2004; Jung & Choi, 2014).

#### **2.4.1.1.3. Fibers**

Higher intake of fiber may exert protective effects against CRC by accelerating transit time through the digestive system, thereby reducing exposure of the large intestine to potential carcinogens. Studies have shown that doubling fiber consumption in subjects with low intake reduced colorectal adenomas and CRC by ~30- 40% (Bingham *et al.*, 2003; Peters *et al.*, 2003).

#### **2.4.1.1.4. Fruits and vegetables**

The evidence on the effect of fruits and vegetables on the risk of colon cancer are has been inconsistent. Higher consumption of fruits and vegetables has been associated with a reduced risk of CRC in numerous epidemiologic studies (Rawla *et al.*, 2019). However, a recent meta-analysis conducted by Huxley *et al.*, showed that there is no evidence of a significant association between fruit or vegetable intake and the risk of colorectal cancer (Johnson *et al.*, 2013; Rosato *et al.*, 2016).

#### **2.4.1.1.5. Cereals and whole grains**

Only a small number of studies examined the effects of cereals and grains on CRC risk, and the results were mixed (Donovan *et al.*, 2017). However, one study has demonstrated that cereals and grains have no protective effect for a low CRC-risk population when comparing individuals with higher ( $\geq 267$  g/day) to lower ( $\leq 238$  g/day) intake (Centonze *et al.*, 1994). Another study has found that whole grain intake was associated with a decreased risk for men but not women (Reedy *et al.*, 2008).

#### **2.4.1.1.6. Dairy products**

Cumulative evidence from several studies has demonstrated that consumption of dairy products may be protective (Bamia *et al.*, 2013; Centonze *et al.*, 1994; Rosato *et al.*, 2016). A study on Southern Italian population showed a decreased risk associated with higher ( $\geq 263$  g/day) compared to lower ( $\leq 130$  g/day) dairy consumption (Centonze *et al.*, 1994). Furthermore, a decreased risk was noted for both men and women in individual analyses by gender. However, interesting results were reported in the pooled analysis of Italian case-control studies, in which low consumption of dairy was associated with increased risk of CRC (Rosato *et al.*, 2016).

#### **2.4.1.2. Physical activity**

Physical inactivity and obesity are modifiable and interrelated risk factors that are linked to CRC and may cause the trigger of forth to third of CRC cases (X. Wang *et al.*, 2019b). There is strong evidence that higher levels of frequency, duration, and intensity of physical activity reduces the risk of CRC by approximately 20%–25% among both men and women in a dose-response manner (Harriss *et al.*, 2009; Wolin *et al.*, 2009).

Sustained and regular periods and of physical activity raise the metabolic rate, increase maximal oxygen uptake, increase the body's metabolic efficiency and capacity, as well as reducing blood pressure and insulin resistance (Bazensky *et al.*, 2007). In addition, physical activity increases gut motility. The lack of physical activity in daily routines also can contribute to obesity, all of which play an important role in increasing CRC risk (De Jong *et al.*, 2005; K.-J. Lee *et al.*, 2007a).

A meta-analysis of 21 studies examining the relationship between physical activity and CRC using data from 5994 colon cancer cases and 5099 CRC cases showed a significant negative correlation between CRC risk and physical activity (RR = 0.88 per 2 standard score, 95% CI: 0.86–0.91) (Johnson *et al.*, 2013).

#### **2.4.1.3. Body mass index (BMI) and obesity**

Body mass index or Quetelet index, is defined as weight in kilograms/height in meter square (WHO, 2020). WHO classified individuals as overweight/obese (BMI  $\geq 25.0$  kg/m<sup>2</sup>) and normal weight (BMI  $< 25.0$  kg/m<sup>2</sup>) (WHO, 2020). A BMI  $\geq 30$  kg/m<sup>2</sup> is associated with

higher risk of colon polyps or adenomas (Ashktorab *et al.*, 2014) and CRC (Adams *et al.*, 2007; Lukanova *et al.*, 2006).

A large number of studies have examined the relationship between BMI and the risk of CRC, and have shown a positive and significant association between an increase BMI and CRC (RR = 1.10 per 8 kg/m<sup>2</sup>, 95% CI: 1.08–1.12) (Bostick *et al.*, 1994; Calle & Kaaks, 2004; Kune *et al.*, 1990). A study conducted by the American Cancer Society has been demonstrated a positive association between BMI and CRC and showed that the risk associated with high BMI (above 30 kg/m<sup>2</sup>) was 1.8 for men and 1.2 for women compared with a BMI below 25 kg/m<sup>2</sup>. This association is in general, stronger for males than females (Murphy *et al.*, 2000) and for cancers localized in the distal colon than other localizations (Le Marchand *et al.*, 1997b; Russo *et al.*, 1998).

The mechanism that might link the association between obesity and CRC remain unclear. The two hormonal systems – the insulin/IGF axis and adipokines (adiponectin and leptin) are the most important theories. The first one speaks about the involvement of insulin and IGF-1 in CRC carcinogenesis which has been supported by experimental and clinical studies (Clayton *et al.*, 2011) and supported by the fact that the type 2 DM in which insulin and IGF-1 play an important role in CRC risk (S. C. Larsson *et al.*, 2005). The second one has demonstrated the association of overexpression of fatty acid synthase in adipocytes with the risk of CRC (S. Ogino *et al.*, 2007). Furthermore, increased circulating estrogens and decreased insulin sensitivity because of obesity are believed to influence CRC risk (Vulcan *et al.*, 2017).

#### **2.4.1.4. Heavy alcohol consumption**

While some data have shown either inconsistent or only modest associations between alcohol and CRC (Le Marchand *et al.*, 1997b), most other studies indicate that regular and high intake of alcohol is associated with an increased risk of developing colorectal cancer (Bazensky *et al.*, 2007; Cho *et al.*, 2004a) and is considered as a factor in the onset of CRC at a younger age (Zisman *et al.*, 2006).

These studies have shown a positive association for an increase of five drinks/week. Furthermore, this association is dose-dependent (Johnson *et al.*, 2013). In addition, the International Agency for Research on Cancer (IARC) reports showed that alcohol is a

causal factor for colorectal cancer and revealed that people who consume at least 4 or more drinks per day are at a 50% increased risk for developing this disease (Marley & Nan, 2016; Pelucchi *et al.*, 2011).

The mechanisms of the carcinogenic effect are not fully clear, but some studied mechanisms showed that alcohol might function as a solvent, enhancing penetration of other carcinogenic molecules (such as tobacco carcinogens) into mucosal cells. Additionally, alcohol by its reactive and genotoxic metabolites (acetaldehyde)(Marley & Nan, 2016) enhances the production of prostaglandins, lipid peroxidation, and the generation of free radical oxygen and reactive nitrogen species, leading to affecting the folate synthesis, which cause specific mutations in DNA that are less efficiently repaired (Boffetta & Hashibe, 2006; Marley & Nan, 2016; Tuan & Chen, 2016).

#### **2.4.1.5. Smoking**

Currently, smoking is considered one of the strongest established risk factors for overall cancers (Botteri *et al.*, 2008). In 2011, the International Agency for Research on Cancer classified tobacco smoking as a carcinogenic agent for colon and rectum sites (Cogliano *et al.*, 2011). The ability of the gastrointestinal tract and circulatory system to spread cigarette carcinogens to colorectal mucosa is the major factor that leads to the elevating risk of inflammation, mutagenesis, and carcinogenesis (Harris, 2015).

A meta-analysis of traditional epidemiological studies showed only a modest association between smoking and CRC (i.e., a RR usually below 1.2)(Botteri *et al.*, 2008). However, with the advent of Molecular Pathological Epidemiology Research, an association between tobacco smoking and colorectal cancer incidence and mortality has become established (Hughes *et al.*, 2017). Tobacco smoke significantly increases incidence of colorectal adenomas by two-folds to three-folds which are a precursor lesions of colorectal cancer (Giovannucci, 2001). Furthermore, evidence shows that 12% of colorectal cancer mortality are caused by smoking. The association became stronger with smoking intensity, duration, and the time to start smoking (Giovannucci, 2001; Johnson *et al.*, 2013; Zisman *et al.*, 2006).

## **2.4.2. Non-Modifiable Risk Factors**

### **2.4.2.1. Age**

Age is an established risk factor for CRC. The likelihood of colorectal cancer starts to increase progressively after the age of 40 and rises sharply after age 50. Statistics have shown that more than 90% of CRC cases occur in people older than 50 with more than 50 times higher in persons aged 60 to 79 years compared to younger than 40 years (Fund & Research, 2007; Ries *et al.*, 2008). However, the incidence of colorectal cancer appears to be increasing among younger persons and is considered now one of the 10 most commonly diagnosed cancers among men and women aged 20 to 49 years in the USA (Fairley *et al.*, 2006).

### **2.4.2.2. Inflammatory bowel disease**

Inflammatory bowel disease (IBD) is an idiopathic, lifelong, and frequently remitting/relapsing disease that is caused by continuous and excessive inflammation of the gastrointestinal tract that ultimately lead to inability of the bowel to function in a healthy way (Baumgart & Carding, 2007; Xavier & Podolsky, 2007).

The pathogenesis of IBD is complicated and suggested to be due to multifactorial interactions between genetic, immunological, and environmental factors. It is considered that various environmental factors such as diet and infection trigger the inflammatory process in the intestinal mucosa, in genetically predisposed individuals, leading to changes in gut microbiota and impairment of the regulatory mechanism of the intestinal mucosa immune system (Lichtenstein *et al.*, 2009).

IBD is a term mainly used to describe two diseases, Crohn disease and ulcerative colitis in which the body's own immune system attacks elements of the digestive system. Crohn disease causes inflammation of the bowel wall and may involve any part of the digestive tract from the mouth to the anus, whereas ulcerative colitis primarily affects the colon and the rectum (Kornbluth & Sachar, 2004).

Several studies have reported increased rates of CRC in patients with IBD (Hu *et al.*, 2015; Jawad *et al.*, 2011), in which risk varies widely between studies due to the different methodologies used (Beaugerie *et al.*, 2013). The relative risk of colorectal cancer in patients with IBD increases from 4- to 20-fold. Additionally, the severity, the location and

duration of chronic inflammation, have been described as important factors for both ulcerative colitis (UC) and Crohn's disease (CD) associated with CRC (Triantafyllidis *et al.*, 2009; Xie & Itzkowitz, 2008).

### **2.4.2.3. Familial risk factors of Colorectal Cancer (CRC)**

#### **2.4.2.3.1. Family history of colorectal cancer (CRC)**

Familial CRC cases are an inherited form of the disease accounting for 30% of all CRC cases, but only 5% of these cases are associated with highly penetrant inherited mutations and have well-characterized clinical presentations (Tian *et al.*, 2019). The remaining 25% of familial CRC cases may occur due to the combined contribution of genetics and environmental factors. The etiologies of these 25% of inherited CRCs might be caused by alterations in single genes that are less penetrant. These facts support the significant influence of environmental factors and lifestyle on the development of CRC (Migliore *et al.*, 2011; Nistal *et al.*, 2015; Wogan *et al.*, 2004).

Studies have shown that having a family history of CRC in first-degree relatives (defined as the presence of CRC in a parent, sibling, or child) increases the probability of having a disease in 2-3 folds (Chong *et al.*, 2018; Ramsey *et al.*, 2006). Furthermore, this risk increases with a greater number of affected first-degree relatives, the closer the degree of relation and the younger age at diagnosis (Butterworth *et al.*, 2006; Johns & Houlston, 2001).

#### **2.4.2.3.2. Hereditary colorectal cancer (CRC) syndromes**

A number of genetic syndromes are also associated with higher rates of CRC but have been associated with favorable prognosis (Watson *et al.*, 1998). Highly penetrant hereditary CRC syndromes, including hereditary nonpolyposis colorectal cancer (HNPCC), also called Lynch syndrome, familial adenomatous polyposis (FAP). Other rarer CRC syndromes are MUTYH-associated polyposis, hamartomatous polyposis in Peutz-Jeghers syndrome (PJS), juvenile polyposis syndrome (JPS), and hyperplastic polyposis (HPP) (Snyder & Hampel, 2019).

HNPCC accounts for ~2 to 6% of colorectal cancers (Marmot *et al.*, 2007). It was shown that the lifetime risk of colorectal cancer in people with HNPCC-related mutations is 70 to

80%, and the average age at diagnosis is in the mid-40s (Jeter *et al.*, 2006; Solomon *et al.*, 2002).

FAP is inherited in an autosomal dominant manner and accounts for less than 1% of all colorectal cancer cases (Fund & Research, 2007). People with FAP characteristically have hundreds of polyps, which undergo malignant transformation as early as age 20. By age 40, almost all people with this disorder will have developed cancer if the colon is not removed (Davies *et al.*, 2005).

MUTYH-associated polyposis (MAP) is an autosomal recessive disorder characterized by adenomatous polyps of the colorectum and a very high risk of colorectal cancer. Studies have shown that individuals with this syndrome have an 80% lifetime risk of CRC (Al-Tassan *et al.*, 2002).

The Hamartomatous Polyposis Conditions: Peutz-Jeghers Syndrome, Juvenile Polyposis Syndrome, Mixed Polyposis Syndrome, and Others, all of them have been demonstrated to be a risk factor for CRC (Kopacova *et al.*, 2009).

#### **2.4.2.4. Infections**

It was shown by several studies that some types of bacteria and viruses might increase the risk of CRC. This can occur through direct mutagenesis, secretion of mutagenic products and/or prolonged infection and accompanying inflammation that leads to increased epithelial cell proliferation (Antonic *et al.*, 2013).

The fact that the majority of studies found a much higher prevalence of human polyomaviruses (HPV) (in most instances HPV-16 and HPV-18 alone or combined)(Bodaghi *et al.*, 2005; Liu *et al.*, 2011), human polyomaviruses (Mou *et al.*, 2012), human herpesviruses (Dimberg *et al.*, 2013), in CRC cases and adenomas than in healthy controls may support a potential role of this virus in CRC carcinogenesis (Antonic *et al.*, 2013). Furthermore, several seroprevalence studies assessing antibody titers indicative of viral infections did not find statistically significant differences between CRC cases and healthy controls (H Chen *et al.*, 2015a).

Several studies have shown that the *Streptococcus bovis/galloyticus* bacteria increases the risk of colorectal cancer (Abdulmir *et al.*, 2011). In addition, Boleij *et al.* in 2011 reported a strong association between *S. bovis* biotype I infection and CRC (pooled OR: 7.26; 95% CI: 3.94–13.36)(Boleij *et al.*, 2011). Furthermore, the seroprevalence of *Streptococcus bovis/ galloyticus* is considered as a candidate practical marker for the early prediction of an underlying bowel lesion at high-risk population. It has been suggested that the presence of antibodies to *Streptococcus bovis/galloyticus* antigens or the antigens themselves in the bloodstream may act as markers for carcinogenesis in the colon (Abdulmir *et al.*, 2011).

## **Chapter Three**

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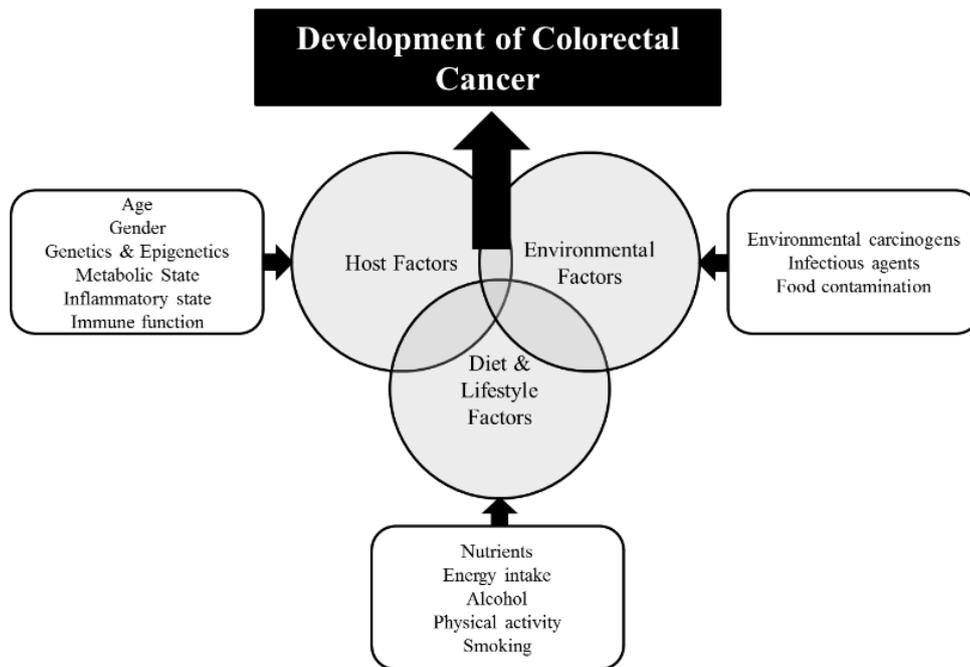
### **Study Framework**

This chapter shows the framework for our study and the dependent and independent variables included along with their definitions.

#### **3.1. Conceptual Framework**

Colorectal cancer (CRC) is one of the most common cancers worldwide. Between 85-90% of CRCs are sporadic (Ghorbanoghli *et al.*, 2018). The cancer process is the result of a complex interaction between lifestyle, environmental factors, and host factors. Host factors influence susceptibility to cancer (WCRF, 2018).

In this study, we hypothesize that the rising incidence of colorectal cancer in Palestine is partly related to the Westernized lifestyle and the emerging epidemic of metabolic disorder.



**Figure 3.1:** Conceptual framework of the study.

### 3.2. Study Variables

In this study, the outcome variable is CRC. In addition, independent variables included demographic characteristics, clinical and pathological characteristics, lifestyle factors, medical history, and family history. The demographic variables included gender, age, region, educational level, and marital status. Moreover, the disease characteristic variables consisted of age at diagnosis, histological subtype, disease stage, and spread. The other independent variables are detailed in Table 3.1.

**Table 3.1-A:** Definitions of study variables.

Study variable	Definition	Categories
Colorectal Cancer (CRC) case	Any man or woman aged 18 years or older with pathological conformation of first diagnosis with CRC	
Control	Any man or woman aged 18 years or older who underwent colonoscopy and their results were free of cancer until the time of the interview	
Gender	Gender of the participants	
Age at recruitment	Number of years between birthdate and interview date	
Age at diagnosis	Number of years between birthdate and date of diagnosis	
Histological diagnosis	The part of the organ where the tumor was found and excised to be microscopically examined to confirm the nature of the tumor	

**Table 3.1-B:** Definitions of study variables.

<b>Study variable</b>	<b>Definition</b>	<b>Categories</b>
Stage of disease	The stage of cancer in patients regarding the invasion of the tumor into the organ's tissue and its spread to other organs	
Educational level	The highest level of education that the subject has successfully completed	
Region	Region where the participant was living in at time of recruitment	Middle: Ramallah, Jericho and Jerusalem
		South: Bethlehem, Hebron
		Others: North (Nablus, Jenin, Tubas, Qalqilya, Tulkarem, Salfit) or Gaza Strip
Marital status	The social status of the participant at time of recruitment	Never married: Single
		Ever married: Married, divorced, or widowed
Family history of cancer	Having first-degree relative (parent, sibling, or child) with any type of cancer	No history
		Any cancer
		CRC
BMI (before 10 years)	The ratio between body mass divided by the square of the body height before 10 years, and is expressed in units of kg/m <sup>2</sup>	Normal: BMI <25 kg/m <sup>2</sup>
		Overweight: BMI 25-29.99 30kg/m <sup>2</sup>
		Obese: BMI ≥ 30kg/m <sup>2</sup>
Smoking	Use of any tobacco product in either smoked or smokeless form on a regular basis for at least 1 year	
Duration of smoking (years)	Number of years	
Cigarette consumption	Number of cigarettes consumed per day	
Occupational physical activity	Type of occupation that the subject was employed at during the last 10 years in terms of physical activity	Sedentary occupation
		Standing occupation
		Manual work
		Heavy manual work

## **Chapter Four**

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### **Methodology**

In this work, we conducted a large multicenter case-control study that included colorectal cancer (CRC) patients from two of the main hospitals that provide cancer care for patients in Palestine to investigate the relationship between lifestyle factors and the risk of CRC in Palestine.

#### **4.1. Study Design and Power**

For the purposes of this study, a multicenter case-control study that included 131 pathologically-confirmed CRC cases and 104 cancer-free controls was conducted. Clinical and pathological data were obtained through medical records. Data regarding CRC risk factors were obtained through an interview-based questionnaire conducted with study subjects by trained interviewers either face-to-face or through phone.

To achieve a study power of at least 80% and detect an OR of 4.0 based on rates of exposure in controls of 5% and a two-sided alpha-level of 0.05, the required sample size was estimated at 102 cases and 102 controls.

## 4.2. Study Settings

The study was conducted during the period between 2018 and 2021 at Beit-Jala Hospital (BJH) which is a governmental hospital located in the southern region of the West Bank and a major provider of cancer care. This hospital has the biggest oncology department, which is one of the three main oncology departments across the West Bank with 26 beds for oncology patients. This department provides oncology services including diagnosis and treatment. In addition, CRC patients were also recruited through Augusta Victoria Hospital (AVH), which is a non-governmental hospital located in Jerusalem and provides care for Palestinian cancer patients on referral basis.

Cancer-free controls were individuals who underwent colonoscopy during the past 12 months and the results of colonoscopy examination showed normal findings. Controls were recruited through gastroenterology (GI) clinics at Beit-Jala Governmental Hospital, Alia Hospital, and Al-Ahli Hospital in Hebron. Due to the COVID-19 pandemic, and to ensure patient safety during the pandemic, we switched to recruitment of controls through phone calls.

## 4.3. Study Population

CRC cases were recruited from outpatient CRC patients visiting the oncology daycare clinic at either BJH or AVH and inpatients admitted to the oncology department at either of the case-recruitment centers. **Inclusion-exclusion criteria:**

- Palestinian adults ( $\geq 18$  years old).
- Incident cases (diagnosis  $\leq 18$  months).
- Pathologically-confirmed CRC.
- Consent to participate in the study.

Controls were cancer-free individuals who underwent colonoscopy and their results were normal. The eligibility criteria for inclusion of controls were:

- Adults ( $\geq 18$  years old).
- CRC-free as determined by the colonoscopy report.
- Consent to participate in the study.

#### **4.4. Study Tools**

In this study, two questionnaires were used. The first was a pathology questionnaire that was used to collect the clinical and pathological data of CRC from medical records of the cases. The second tool was a self-reported, interview-based questionnaire used to collect data regarding risk factors of CRC. The two tools are described here in detail.

##### **4.4.1. Pathology questionnaire**

Clinical and pathological data were obtained through completing a standardized questionnaire that was filled out using data from patients' medical files (Appendix 4.1). Oncologists filled in the data. The questionnaire collected data regarding age at diagnosis, histopathological diagnosis, immunostaining (if any), prognostic markers, disease spread, surgeries, and treatments.

##### **4.4.2. Study questionnaire**

An interview-based questionnaire was used to collect epidemiological data from participants. The questionnaire was designed in English (Appendix 4.2). The questionnaire was reviewed by four reviewers to assess content validity. The questionnaire was translated from English into Arabic (Appendix 4.3) by forward and backward translation and a pilot study (n=30) was conducted to test the questionnaire for local use in Palestine. Amendments to the questionnaire were made according to the feedback from the pilot study. Then interviewers were trained on the interview prior to data collection to ensure the quality of the data.

The questionnaire consisted of five sections. The first section contained demographic data. The second part of the questionnaire focused on lifestyle and habits including body weight and height, smoking, occupational and recreational physical activity, and a semi-quantitative food-frequency questionnaire. The third section of the questionnaire contained questions regarding the bowling habits during the past 12 months (before diagnosis). The fourth section contained questions regarding the medical history of the participants and the fifth and final section contained data regarding consanguinity marriage in the family and a detailed family history of cancer.

Assessment of recreational physical activity was based on the assessment tool used in the European Prospective Investigation into Cancer (EPIC) study (Haftenberger *et al.*, 2002).

Assessment of dietary intake was performed using a semi-quantitative food frequency questionnaire (FFQ). This questionnaire determined the average frequency of consumption and approximate serving size of 49 food items two years prior to diagnosis. This FFQ was developed based on a questionnaire used by Shannon and colleagues (Shannon *et al.*, 1996).

Assessment of bowel habits was established based on the Bowel Disease Questionnaire for assessment of functional gastrointestinal disease (Talley *et al.*, 1990).

#### **4.5. Ethical Considerations**

Ethical approval for this study was obtained from Al-Quds University Ethical Review Board (Appendix 4.4). Permission to conduct the study was also obtained from the Palestinian MOH and AVH (Appendix 4.5).

The participants (cases & controls) signed a consent form (Appendix 4.6) that confirmed the confidentiality and every patient had the freedom to accept or refuse participation in the study without intimidation.

#### **4.6. Statistical Analysis**

All statistical analyses were performed with SPSS statistical software (version 25.0, SPSS Inc). Differences in demographic factors, BMI, lifestyle factors, comorbidity history, and family history between cases and controls were assessed with Pearson's chi-square test. Two-sided  $p < 0.05$  was considered statistically significant.

To calculate the frequency of recreational physical activity, the duration of non-professional activities was solicited by means of various categories. These categories were transformed into continuous values by using the mean of each category.

Regarding analysis of dietary intake, analyses were primarily conducted based on food groupings rather than individual foods. Specific food groupings were determined by traditional food groupings (Table 4.1). The consumption of individual foods was converted to a monthly frequency variable and weighted by the serving size. To create groups of foods, these individual values were summed and divided by 30 to determine an average daily level of consumption. To assess potential trends, each food group was divided into quartiles according to the distribution of consumption in the control group. Because many subjects gave the same responses, not all quartiles contain an equal one-fourth of the control subjects.

**Table 4.1-A:** Food groupings of food frequency questionnaire (FFQ) items.

<b>Main group</b>	<b>Subgroup</b>	<b>Food Item</b>	
Protein	Fish	Fresh Fish	
		Canned fish	
	Red meat	Beef/veal meat	
		Mutton and lamb meat	
	Poultry	Poultry	
	Nuts	Raw Nuts	
		Roasted/salted nuts	
	Legumes	Beans, lentils and peas	
		Eggs	Eggs
	Bread & Grains		White bread
		Bread whole grain, rye	
		French bread	
		Breakfast cereals – low fiber	
		Breakfast cereals –high fiber	
		Oats (cooked)	
		Rice(cooked)	
		Pasta	
Vegetables			Potatoes
			Cabbages
		Mushrooms	
		Leafy vegetables	
		Other vegetables: tomatoes, cucumber, bell pepper, carrots...	
		Mixed salad, raw	
		Vegetable soup/cooked vegetable	
Fruits		Beans, lentils and peas	
		Strawberry	
		Grapes, cherries	
		Figs	
		Melon/ Watermelon	
		Stone fruit: apricot, peach	
		Pit fruit: apple, pear, banana	
	Citrus fruit		

**Table 4.1-B:** Food groupings of food frequency questionnaire (FFQ) items.

<b>Main group</b>	<b>Subgroup</b>	<b>Food Item</b>
Dairy		Milk
		Dairy products (White cheese, labaneh...
		Processed cheese (yellow, triangle, puck..)
		Yoghurt, Butter milk
Sweets		Eastern sweets
		Western sweets

Logistic regression model was used to estimate the effects of these factors on risk for CRC. For each factor, the crude ORs and corresponding 95% CIs were calculated. All ORs were adjusted for age, sex, region, and education level. P-values in all models were calculated using Wald tests.

## Chapter Five

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### Results

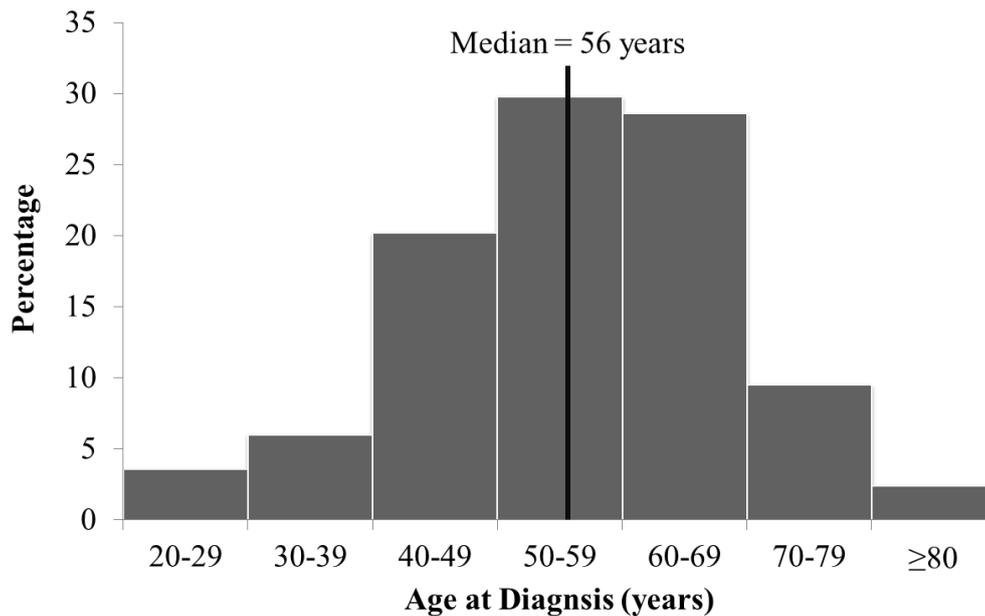
This chapter covers the results of this case-control study.

#### 5.1. Clinical and Pathological Characteristics of Colorectal Cancer Patients

This study consisted of 131 pathologically-confirmed CRC cases that were recruited through Beit-Jala Hospital (80.9%) and Augusta Victoria Hospital (19.1%). Table 5.1 shows the clinical and pathological characteristics of CRC among patients.

The male to female ratio among cases was 0.9:1 and the median age at diagnosis was 56 years (IQR 48-64) (Figure 5.1). Around 30% of the cases were diagnosed before the age of 50 years. The vast majority of cases were diagnosed at stages III & IV (37.0% and 35.8%, respectively). Among the cases, 44% had lymph node involvement and 37% had liver involvement.

The major histological subtype of CRC was sigmoid colon cancer constituting 43.1% of the cases. Rectal cancer was the second most common subtype constituting 15.4%. Other less common subtypes are shown in table 5.1 and included cancer of rectosigmoid junction, cecum, and cancer of the ascending, descending and transverse colon.



**Figure 5.1:** Distribution of colorectal cancer (CRC) cases by age at diagnosis.

Almost all cases underwent hemicolectomy (93%) and/or received chemotherapy (92%) while only 6% of them received radiotherapy. The most common chemotherapy used protocol was FOLFOX (62%). The second most common chemotherapy protocol was CAPEOX (Table 5.1).

A minor group of CRC patients did not report any symptoms during the last year before diagnosis (11.2%). The most frequent complaints among symptomatic patients during the last year before diagnosis were diarrhea and/or constipation (77%) followed by abdominal pain (74%) and rectal bleeding (49%).

**Table 5.1-A:** Clinical and pathological characteristics of colorectal cancer (CRC) among cases.

Variable	Category	Frequency n (%)
Age at Diagnosis (years)	20-29	5 (3.9)
	30-39	8 (6.2)
	40-49	26 (20.2)
	50-59	38 (29.5)
	60-69	37 (28.7)
	70-79	12 (9.3)
	80+	3 (2.3)

**Table 5.1-B:** Clinical and pathological characteristics of colorectal cancer (CRC) among cases.

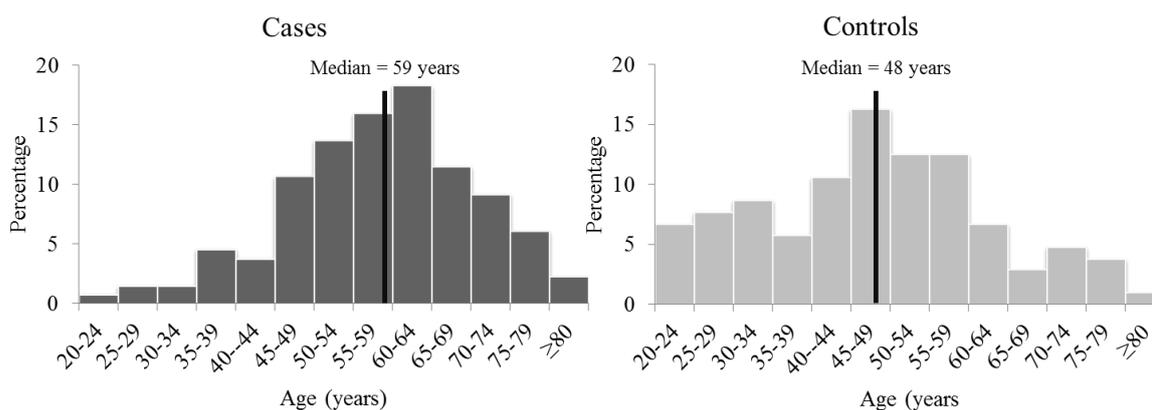
Variable	Category	Frequency n (%)
Histological Diagnosis	Sigmoid colon	56 (43.1)
	Rectum, NOS*	20 (15.4)
	Colon, NOS*	14 (10.8)
	Cecum	8 (6.2)
	Rectosigmoid junction	8 (6.2)
	Ascending colon	6 (4.6)
	Transverse colon	5 (3.8)
	Descending colon	5 (3.8)
	Hepatic flexure of colon	3 (2.3)
	Appendix	3 (2.3)
	Splenic flexure of colon	2 (1.5)
Stage (TNM)	I	2 (1.2)
	II	33 (25.9)
	III	47 (37.0)
	IV	45 (35.8)
Organ involvement	No organ involvement	31 (24.7)
	Liver	47 (37.0)
	Lymph nodes	56 (44.4)
	Lungs	9 (7.4)
	Stomach	5 (3.7)
	Bladder	3 (2.5)
	Brain	2 (1.2)
	Bones	2 (1.2)
	Endometrium	2 (1.2)
	Adrenal gland	2 (1.2)
	Peritoneum	2 (1.2)
Retroperitoneum	2 (1.2)	
Colectomy	Hemicolectomy	78 (92.6)
	Polypectomy during colonoscopy	3 (3.7)
	Partial colectomy	2 (1.9)
	Total colectomy	2 (1.9)
Radiotherapy		8 (6.3)
Chemotherapy <sup>‡</sup>	No chemotherapy	9 (7.6)
	FOLFOX	76 (62.0)
	CAPEOX or CAPOX	33 (26.6)
	Bevacizumab	33 (26.6)
	Capecitabine, with or without a targeted drug	16 (12.7)
	FOLFIRI	9 (7.6)
	Cetuximab [Erbix]	3 (2.5)
	Others	8 (5.2)
Symptoms	Asymptomatic patients	13 (11.2)
	Symptomatic patients	103 (88.8)
Complaints in symptomatic patients	Rectal bleeding	50 (48.5)
	Abdominal pain	76 (73.8)
	Diarrhea/constipation	79 (76.7)

\* NOS: not otherwise specified

<sup>‡</sup> FOLFOX: leucovorin, 5-FU, & oxaliplatin (Eloxatin); CAPEOX or CAPOX : capecitabine (Xeloda) and oxaliplatin; FOLFIRI: leucovorin, 5-FU, and irinotecan (Camptosar)

## 5.2. Demographic Characteristics of Study Subjects

Table 5.2 shows the baseline characteristics of the cases and controls. In this study, slightly more males were recruited in the control group. In addition, compared to cases and controls were significantly younger with a 10-year difference in median age (p-value <0.0001). Furthermore, more than 70% of CRC cases recruited in this study were from southern governorates (78.9% of which were from Hebron) while 18.5% were from the center and 8.5% were from Gaza Strip and northern governorates. On the other hand, around 90% of the controls were from the south. The geographic distribution was significantly different between cases and controls (p-value 0.002). Although more cases lived in urban localities compared to controls (46% versus 37%), the difference was not significant. Moreover, cases were less likely to have a tertiary education compared to controls (16.2% versus 32.4%, p=0.011).



**Figure 5.2:** Distribution of age among colorectal cancer (CRC) cases and controls.

**Table 5.2-A:** Odds ratios (OR) for colorectal cancer (CRC) association with demographic characteristics of study subjects.

Variable	Category	Cases N (%)	Controls N (%)	P-Value	OR (95%CI)
Gender	Male	62 (47.3)	57 (54.8)	0.255	(-)
	Female	69 (52.7)	47 (45.2)		1.4 (0.8 - 2.3)
Age (years)	Median (IQR)	59 (51-67)	48 (36-57)	-	(-)
Age (years)	20-29	3 (2.3)	15 (14.4)	<0.0001	(-)
	30-39	8 (6.1)	15 (14.4)		2.7 (0.6 - 12)
	40-49	19 (14.5)	28 (26.9)		3.4 (0.9 - 13.3)
	50-59	39 (29.8)	26 (25.0)		7.5 (2 - 28.5)
	60-69	39 (29.8)	10 (9.6)		19.5 (4.7 - 80.8)
	70-79	20 (15.3)	9 (8.7)		11.1 (2.6 - 48.2)
	≥80	3 (2.3)	1 (1.0)		15.0 (1.1 - 198)

**Table 5.2-B:** Odds ratios (OR) for colorectal cancer (CRC) association with demographic characteristics of study subjects.

Variable	Category	Cases N (%)	Controls N (%)	P-Value	OR (95%CI)
Type of Locality	Rural	61 (48.4)	58 (56.9)	0.404	(-)
	Urban	58 (46.0)	38 (37.3)		1.5 (0.8 - 2.5)
	Camp	7 (5.6)	6 (5.9)		1.1 (0.4 - 3.5)
Region*	South	95 (73.1)	94 (90.4)	0.002	(-)
	Center	24 (18.5)	9 (8.7)		2.6 (1.2 - 6)
	Other	11 (8.5)	1 (1.0)		10.9 (1.4 - 86)
Educational Level	Illiterate	17 (13.1)	14 (13.7)	0.011	(-)
	0-12 years	92 (70.8)	55 (53.9)		1.4 (0.6 - 3)
	Tertiary education	21 (16.2)	33 (32.4)		0.5 (0.2 - 1.3)
Marital Status	Never Married	7 (5.3)	15 (14.4)	0.018	(-)
	Ever Married	124 (94.7)	89 (85.6)		3 (1.2 - 7.6)

\* South: (Hebron & Bethlehem); Center: (Ramallah, Jericho, Jerusalem)

### 5.3. Risk Factors of Colorectal Cancer (CRC) among Palestinians

#### 5.3.1. Family history

Table 5.3 shows the association between familial factors and the risk of CRC. Although family history of cancer was not found to be significantly associated with CRC, consanguinity among parents was significantly more commonly reported among cases ( $p=0.002$ ) and the association between consanguinity among parents and the risk of CRC was significant for the group with distant cousins compared to the no relationship group (OR=8.0; 95%CI: 2.2-28.4).

**Table 5.3:** Odds ratios (OR) for colorectal cancer (CRC) associated with family history.

Variable	Category	Cases N (%)	Controls N (%)	P-Value	OR (95%CI)	Adjusted OR (95%CI)
Consanguinity among parents	Not related	70 (54.3)	75 (72.1)	0.002	(-)	(-)
	Distant cousins	23 (17.8)	4 (3.8)		6.2 (2.0 - 18.7)	8.0 (2.2 - 28.4)
	1st cousins	36 (27.9)	25 (24.0)		1.5 (0.8 - 2.8)	1.3 (0.6 - 2.6)
History of cancer among 1 <sup>st</sup> degree relatives	No History	80 (61.1)	67 (65.0)	0.693	(-)	(-)
	Any cancer (excl. CRC)	37 (28.2)	24 (23.3)		1.3 (0.7 - 2.4)	1.0 (0.5 - 2.1)
	CRC	14 (10.7)	12 (11.7)		1.0 (0.4 - 2.3)	0.8 (0.3 - 2.1)

#### 5.3.2. Body mass index (BMI), smoking, and physical activity

The prevalence of obesity was around 10% higher among CRC cases in this study (42.3% versus 33.3%). Yet, the association between the risk of CRC and obesity was not significant (Table 5.4).

Regarding smoking, the prevalence of ever smoking among controls was significantly lower than among CRC cases, and after adjusting for confounding factors, ever smoking was found to be associated with reduced CRC risk (OR=0.4; 95%CI: 0.2-0.9), but there was no dose-response relationship with smoking in terms of duration and daily consumption of smoking.

Occupational physical activity was not found to influence the risk of CRC in this study, but the risk of CRC was found to be significantly associated with leisure time activity (OR=3.7; 95%CI: 1.9-7.0). In addition, the risk was found to increase with increased active time. The risk of being active >7 hours/week increased the risk of CRC by 10-folds (95%CI: 3.3 – 31.0) compared to inactive subjects. The mean time dedicated to recreational activities among cases was 4.7±6.2 hours/week compared to 1.8±2.6 hours/week among controls.

**Table 5.4:** Odds ratios (OR) for colorectal cancer (CRC) association with body mass index (BMI), smoking and physical activity.

Variable	Category	Cases N (%)	Controls N (%)	P-Value	OR (95%CI)	Adjusted OR (95%CI)
BMI before 10 years	Normal	29 (23.6)	31 (31.3)	0.304	(-)	(-)
	Overweight	42 (34.1)	35 (35.4)		1.3 (0.7 - 2.5)	0.7 (0.3 - 1.7)
	Obese	52 (42.3)	33 (33.3)		1.7 (0.9 - 3.3)	0.8 (0.3 - 1.8)
Smoking	Never	87 (66.4)	55 (52.9)	0.035	(-)	(-)
	Ever	44 (33.6)	49 (47.1)		0.6 (0.3 – 1.0)	0.4 (0.2 - 0.9)
Duration of smoking (years)	Never	87 (68.0)	55 (55.0)	0.084	(-)	(-)
	<10	7 (5.5)	11 (11.0)		0.4 (0.1 - 1.1)	0.6 (0.2 - 2.3)
	10-19	7 (5.5)	13 (13.0)		0.3 (0.1 - 0.9)	0.3 (0.1 – 1.0)
	20-29	9 (7.0)	10 (10.0)		0.6 (0.2 - 1.5)	0.5 (0.1 - 1.5)
	30-39	9 (7.0)	8 (8.0)		0.7 (0.3 – 2.0)	0.4 (0.1 - 1.4)
	≥40	9 (7.0)	3 (3.0)		1.9 (0.5 - 7.3)	0.6 (0.1 - 3.1)
Cigarette consumption (cigarette/day)	Never	87 (66.9)	55 (59.8)	0.305	(-)	(-)
	1-20	24 (18.5)	25 (27.2)		0.6 (0.3 - 1.2)	0.6 (0.3 - 1.4)
	21+	19 (14.6)	12 (13.0)		1.0 (0.5 - 2.2)	0.6 (0.2 - 1.9)
Occupational physical activity	Sedentary – standing	54 (71.1)	40 (72.7)	0.834	(-)	(-)
	Manual – heavy manual	22 (28.9)	15 (27.3)		1.1 (0.5 - 2.4)	0.9 (0.3 - 2.6)
Leisure time activity	No	36 (27.5)	53 (51.5)	<0.0001	(-)	(-)
	Yes	95 (72.5)	50 (48.5)		2.8 (1.6 - 4.8)	3.7 (1.9 – 7.0)
Leisure time activity (hours/week)	Never	37 (28.2)	53 (51.5)	0.001	(-)	(-)
	<3	30 (22.9)	23 (22.3)		1.9 (0.9 - 3.7)	2.5 (1.1 - 5.5)
	3-4	23 (17.6)	12 (11.7)		2.7 (1.2 - 6.2)	3.0 (1.1 - 8.3)
	5-7	12 (9.2)	9 (8.7)		1.9 (0.7 – 5.0)	3.0 (0.9 - 9.6)
	>7	29 (22.1)	6 (5.8)		6.9 (2.6 - 18.3)	10.0 (3.3 – 31.0)

### 5.3.3. Dietary intake

Table 5.5 shows the median consumption of the main food groups among study participants. Consumption of overall protein was around the daily-recommended intake between both cases and controls while consumption of grains was lower than the daily-recommended intake levels between both groups being higher among controls. In addition, consumption of dairy was lower than the daily-recommended intake but did not differ between study groups. On the other hand, consumption of vegetables was around the daily-recommended intake among controls but slightly lower between CRC cases. As for fruits, between controls, the consumption level was much below the daily-recommended intake while between cases, fruit consumption was almost two times more than the daily-recommended intake.

**Table 5.5:** Consumption levels of food groups among study subjects against international recommendations.

Food Group	Daily Recommended*	Control Median (IQR)	Case Median (IQR)
Protein	6 ounces	5.1 (3.6-7.6)	5.1 (3.3-8.2)
Grains	7 ounces	4.3 (3.1-5.5)	3.5 (2.3-5.7)
Vegetables	3 cups	3.1 (2.0-4.0)	2.6 (1.7-3.7)
Fruits	2 cups	0.8 (0.1-2.4)	6.5 (3.3-11.1)
Dairy	3 cups	2.0 (0.8-3.7)	2.0 (1.1-3.0)

\* U.S. Department of Agriculture Recommendations for ages  $\geq 14$  years at calorie level 2200.

Table 5.6 shows the ORs for the association of food groupings and CRC risk. High intake of fish (OR=5.0 for highest quartile versus lowest quartile; 95%CI: 2.1-11.8), fruits (OR=460.4 for highest quartile versus lowest quartile; 95%CI: 39.0-5431.2), sweets (OR=7.2 for highest quartiles versus lowest quartiles; 95%CI: 3.4-15.1) and nuts (OR=8.0 for highest quartiles versus lowest quartiles; 95%CI: 3.8-16.8) were associated with increased risk of CRC. The OR of CRC increased with increased intake of fish and fruits.

On the other hand, high intake of chicken and associated significantly with a decreased risk of CRC (OR=0.2 for the third quartile versus lowest quartile; 95%CI: 0.1-0.4) while for intake of red meat, higher intake was not found to be associated with risk of CRC, although a significantly decreased association was detected for the second quartile (OR=0.4 for the second quartile versus lowest quartile; 95%CI: 0.2-0.9). Furthermore, the association between dairy intake and the risk of CRC was significantly increased for the second quartile compared to the lowest quartile (OR=2.4; 95%CI: 1.0-5.7). Yet, the association

decreased and was not significant for higher intake of dairy. In addition, consumption of vegetables, water, and grains were not associated with CRC.

**Table 5.6:** Odds ratios (OR) for colorectal cancer (CRC) associated with quartiles of food groupings.

Food Group	Quartile	Case N (%)	Control N (%)	P-Value	OR (95%CI)	Adjusted OR (95%CI)
Protein	Q1	26 (25.0)	40 (30.5)	0.524	(-)	(-)
	Q2	26 (25.0)	28 (21.4)		0.7 (0.3 - 1.4)	0.6 (0.2 - 1.3)
	Q3	26 (25.0)	25 (19.1)		0.6 (0.3 - 1.3)	0.8 (0.3 - 1.9)
	Q4	26 (25.0)	38 (29.0)		1.0 (0.5 - 1.9)	0.9 (0.4 - 2.1)
Fish	Q1	31 (29.8)	23 (17.6)	0.069	(-)	(-)
	Q2	27 (26.0)	22 (16.8)		1.1 (0.5 - 2.4)	0.9 (0.4 - 2.3)
	Q3	21 (20.2)	20 (15.4)		1.3 (0.6 - 2.9)	1.5 (0.6 - 4.0)
	Q4	25 (24.0)	66 (50.4)		3.6 (1.8 - 7.2)	5.0 (2.1 - 11.8)
Red Meat	Q1	26 (25.0)	49 (37.4)	0.069	(-)	(-)
	Q2	35 (33.7)	27 (20.6)		0.4 (0.2 - 0.8)	0.4 (0.2 - 0.9)
	Q3	22 (21.2)	24 (18.3)		0.6 (0.3 - 1.2)	0.6 (0.2 - 1.4)
	Q4	21 (20.2)	31 (23.7)		0.8 (0.4 - 1.6)	0.7 (0.3 - 1.7)
Poultry	Q1	43 (41.3)	86 (65.6)	<0.0001	(-)	(-)
	Q2	26 (25.0)	28 (21.4)		0.5 (0.3 - 1.0)	0.6 (0.3 - 1.2)
	Q3	28 (26.9)	10 (7.6)		0.2 (0.1 - 0.4)	0.2 (0.1 - 0.4)
	Q4	7 (6.7)	7 (5.3)		0.5 (0.2 - 1.5)	0.4 (0.1 - 1.5)
Eggs	Q1	47 (45.2)	69 (52.7)	0.008	(-)	(-)
	Q2	26 (25.0)	40 (30.5)		1.0 (0.6 - 1.9)	1.2 (0.6 - 2.5)
	Q3	22 (21.2)	8 (6.1)		0.2 (0.1 - 0.6)	0.3 (0.1 - 0.8)
	Q4	9 (8.7)	14 (10.7)		1.1 (0.4 - 2.6)	0.9 (0.3 - 2.8)
Nuts	Q1-2	55 (52.9)	20 (15.3)	<0.0001	(-)	(-)
	Q3-4	49 (47.1)	111 (84.7)		6.2 (3.4 - 11.5)	8.0 (3.8 - 16.8)
Vegetables	Q1	28 (26.9)	41 (31.3)	0.605	(-)	(-)
	Q2	24 (23.1)	36 (27.5)		1.0 (0.5 - 2.1)	0.8 (0.4 - 2.0)
	Q3	26 (25.0)	28 (21.4)		0.7 (0.4 - 1.5)	0.6 (0.3 - 1.5)
	Q4	26 (25.0)	26 (19.8)		0.7 (0.3 - 1.4)	0.7 (0.3 - 1.6)
Fruits	Q1	27 (26.0)	1 (0.8)	<0.0001	(-)	(-)
	Q2	25 (24.0)	7 (5.3)		7.6 (0.9 - 65.9)	12.8 (1 - 163.2)
	Q3	26 (25.0)	11 (8.4)		11.4 (1.4 - 94.9)	18.3 (1.4 - 234.8)
	Q4	26 (25.0)	112 (85.5)		116.3 (15.1 - 895.4)	460.4 (39.0 - 5431.2)
Dairy	Q1	27 (26.0)	24 (18.3)	0.056	(-)	(-)
	Q2	26 (25.0)	53 (40.5)		2.3 (1.1 - 4.7)	2.4 (1.0 - 5.7)
	Q3	26 (25.0)	33 (25.2)		1.4 (0.7 - 3.0)	1.7 (0.7 - 4.1)
	Q4	25 (24.0)	21 (16.0)		0.9 (0.4 - 2.1)	0.9 (0.3 - 2.3)
Grains	Q1	26 (25.0)	54 (41.2)	0.006	(-)	(-)
	Q2	26 (25.0)	29 (22.1)		0.5 (0.3 - 1.1)	0.5 (0.2 - 1.2)
	Q3	27 (26.0)	14 (10.7)		0.2 (0.1 - 0.6)	0.3 (0.1 - 0.6)
	Q4	25 (24.0)	34 (26.0)		0.7 (0.3 - 1.3)	0.5 (0.2 - 1.2)
Sweets	Q1-2	54 (51.9)	31 (23.7)	<0.0001	(-)	(-)
	Q3-4	50 (48.1)	100 (76.3)		3.5 (2.0 - 6.1)	7.2 (3.4 - 15.1)
Water	Q1-2	66 (63.5)	86 (65.6)	0.728	(-)	(-)
	Q3-4	38 (36.5)	45 (34.4)		0.9 (0.5 - 1.6)	1.0 (0.6 - 1.9)

### 5.3.4. Medical history

This study showed that history of suffering from diarrhea that lasted more than 2 days, ulcer, stomach infection, and hemorrhoids was associated with significant reduction in CRC risk. On the other hand, history of herpes, periodontal disease, perianal abscesses, and hypertension increased the risk of CRC significantly. Furthermore, the prevalence of diabetes and cardiovascular disease were significantly higher among CRC cases (15.3% and 1.5%, respectively), although we were not able to measure the strength of the association due to absence of subjects in the control group. (Table 5.7)

**Table 5.7:** Odds ratios (OR) for colorectal cancer associated with medical history.

Health Problem	Cases N (%)	Controls N (%)	P-Value	OR (95%CI)	Adjusted OR (95%CI)
Diarrhea lasting >two days	27 (21.8)	28 (38.9)	0.01	0.4 (0.2 - 0.8)	0.4 (0.2 - 0.9)
Herpes	16 (12.3)	1 (1.0)	0.001	14.5 (1.9 - 110.9)	16.8 (1.9 - 145.7)
Enteritis	13 (10.0)	6 (5.8)	0.248	1.8 (0.7 - 4.9)	2.1 (0.6 - 6.9)
Ulcer	9 (6.9)	22 (21.6)	0.001	0.3 (0.1 - 0.6)	0.3 (0.1 - 0.7)
Stomach infection	9 (6.9)	59 (56.7)	<0.0001	0.1 (0.0 - 0.1)	0.1 (0.0 - 0.2)
Periodontal disease	13 (9.9)	2 (1.9)	0.013	5.6 (1.2 - 25.5)	5.4 (1.1 - 26.8)
Brucellosis	1 (0.8)	3 (2.9)	0.208	0.3 (0.0 - 2.5)	0.1 (0.0 - 1.3)
Allergies	13 (9.9)	15 (14.4)	0.29	0.7 (0.3 - 1.4)	0.7 (0.3 - 1.7)
Bowel obstruction	15 (11.5)	7 (6.7)	0.211	1.8 (0.7 - 4.6)	1.1 (0.4 - 3.2)
Appendicitis	8 (6.1)	12 (11.5)	0.138	0.5 (0.2 - 1.3)	0.4 (0.1 - 1.0)
Celiac disease	2 (1.5)	4 (3.8)	0.2671	0.4 (0.1 - 2.2)	0.4 (0.1 - 2.5)
Hemorrhoids	21 (16.0)	39 (37.5)	<0.0001	0.3 (0.2 - 0.6)	0.3 (0.1 - 0.5)
Anal fissures	8 (6.1)	10 (9.6)	0.315	0.3 (0.2 - 0.6)	0.4 (0.1 - 1.2)
Perianal abscesses	9 (6.9)	2 (1.9)	0.075	3.8 (0.8 - 17.8)	8.3 (1.3 - 51.3)
Anal fistulas	2 (1.5)	2 (1.9)	0.822	0.8 (0.1 - 5.8)	0.9 (0.1 - 7.1)
Irritable bowel syndrome	16 (12.2)	8 (7.7)	0.256	1.7 (0.7 - 4.1)	1.7 (0.6 - 4.9)
Ulcerative colitis	2 (1.5)	6 (5.8)	0.075	0.3 (0.1 - 1.3)	( - )
Crohn's disease	0 (0.0)	2 (1.9)	0.111	( - )	( - )
Hypertension	23 (17.6)	2 (1.9)	<0.0001	10.9 (2.5 - 47.2)	8.5 (1.7 - 41.3)
Diabetes	20 (15.3)	0 (0.0)	<0.0001	( - )	( - )
Cardiovascular disease	2 (1.5)	0 (0.0)	<0.0001	( - )	( - )

## **Chapter Six**

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### **Discussion, Conclusions, Limitations and Recommendations**

This study was conducted to investigate the role of lifestyle habits in the etiology of CRC among Palestinians. Furthermore, the findings of this study provide an estimate for the prevalence of several factors that have not been previously studied. This chapter highlights the major findings, recommendations and limitations of the study.

As per our knowledge, this is the first study to investigate factors associated with colorectal cancer in Palestine using confirmed diagnosis as the endpoint. These findings imply that lifestyle and diet could alter the risk of CRC in Palestine, especially in light of the higher prevalence of obesity, hypertension, diabetes, and cardiovascular disease (CVD) among cases. These diseases are directly related to unhealthy lifestyle. Moreover, the clinical and pathological characteristics of CRC point to a familial component that could explain the large proportion of early-onset CRC. This chapter highlights and discusses the major findings of this study. In addition, this chapter also describes the limitations of this study and our further recommendations that are based on our findings.

#### **6.1. Discussion**

##### **6.1.1. Clinical and Pathological Characteristics of CRC**

This study included 131 pathologically-confirmed CRC cases. Cases were recruited from BJH and AVH. These two hospitals are the major providers of cancer care for Palestine in the southern and central regions of Palestine. BJH is a governmental hospital located in

Bethlehem Governorate and provide diagnostic and treatment services for cancer patients. The Oncology Department at BJH is the largest among governmental oncology facility. Furthermore, AVH is a non-governmental hospital that is located in Jerusalem and provide cancer care on referral basis from all over Palestine including Gaza Strip.

Among CRC cases, the male to female ratio in this study was 0.9:1. CRC is more common among males worldwide. In the United States of America (USA) and the United Kingdom (UK), CRC was reported to be more common among males with ratios of 1.1:1 and 1.25:1, respectively (CancerResearchUK, 2019; Siegel *et al.*, 2014). In Jordan, the Jordan cancer registry reported that during the period of 2005–2010, the male to female ratio among CRC cases was 1.3:1 (Sharkas *et al.*, 2017) while in Oman the ratio was 1.4:1 (Kumar *et al.*, 2015), 1.7:1 in Pakistan (Bhurgri *et al.*, 2011), and 2.1:1 in the United Arab Emirates (Al-Shamsi *et al.*, 2003). However, in Iran, the male to female ratio was 1:1 (Hajmanoochehri *et al.*, 2014), and in Egypt, the reported ratio was even lower than that reported in our study (0.8:1) (Gado *et al.*, 2014).

This study showed that the median age at diagnosis was 56 years and around 30% were diagnosed before the age of 50 years. Based on data from the Surveillance, Epidemiology, and End Results Program (SEER), the median age at diagnosis for CRC cases in the USA between 2013-2017 was 67 years, which is 11 years older than the median age reported in this study (SEER, 2017). In the UK, 44% of CRC cases diagnosed between 2015-2017 were aged 75 years and over (CancerResearchUK, 2019). Among Jordanians, the median age at diagnosis was reported to be 62 years among males and 58 years among females. Furthermore, 25% of the cases were below the age of 50 (Sharkas *et al.*, 2017). Among Saudi males, the median age at diagnosis was 60 years and among Saudi females it was 55 years (Alyabsi *et al.*, 2020). However, similar to our results, in Oman, the median age at diagnosis was 56 years with 40% being 50 years old or younger (Kumar *et al.*, 2015), and in Iran the mean age at diagnosis was  $57.3 \pm 14.7$  years with 29% of the cases being younger than the age of 50 (Hajmanoochehri *et al.*, 2014). Furthermore, in the United Arab Emirates, the median age at diagnosis was even younger (47 years)(Al-Shamsi *et al.*, 2003), and in Egypt (mean age at diagnosis  $51 \pm 15$  years) and 25% of the cases were below the age of 40 (Gado *et al.*, 2014). Moreover, supporting these findings, a study conducted in Gaza Strip reported the median age of CRC patients to be 59.5 years (Panato *et al.*, 2018) and another study that was conducted in Israel and aimed to determine the

differences in the characteristics of CRC between Arab and Jews CRC patients in Israel, two populations residing in close proximity yet differ in many social, cultural and nutritional characteristics, it was reported that Arab patients were younger with more than 10 years age difference between the two populations (Shpitz *et al.*, 2006).

Age is one of the major risk factors of CRC since the DNA damage caused by biological processes and exposure to risk factors (CancerResearchUK, 2017). However, early-onset CRC is generally associated with familial cancers and raises questions about the role of hereditary factors in this population. In a case-control study conducted in Japan, it was reported that young CRC patients (<50 years old) had 3.7-folds higher rate of family history compared to the older CRC patients (Nagai *et al.*, 2016). In the study conducted in Israel, evaluating the MMR status among cases showed that Arab patients had higher prevalence of defective MMR expression (20% in Arabs versus 11% in Jews), yet the difference was not significant (Shpitz *et al.*, 2006).

However, the age-structure of the disease with high proportion of early-onset CRC with relatively lower rates among older population is usually observed in countries under epidemiological transition and suggestive of a recent change in the environmental risk factors (Bishehsari *et al.*, 2014).

Another factor that could contribute to the age gap between cases from developing countries compared to cases in developed countries is the younger age structure of the population. Palestinians are young population with a median age of 20.7 years (PCBS, 2019). Furthermore, the role of the Westernized lifestyle and diet in the younger generation and its role in the etiology of CRC should be investigated.

Regarding the histological subtype of CRC, the most common subtypes were sigmoid cancer followed by rectal cancer. Among Israeli Arabs, similar findings were reported with sigmoid CRC being the most common (33.8%), but it was followed by right colon cancer (25.9%) and then rectal cancer (20.0%)(Shpitz *et al.*, 2006). In Jordan, 32.8% of the diagnosed cases between 2005-2010 had rectal cancer (Sharkas *et al.*, 2017) and in Oman between 200-2013, 29.6% of the cases had rectal cancer (Kumar *et al.*, 2015). In Iran, rectum (56%) and sigmoid colon (25%) were the most common subtypes (Hajmanoochehri *et al.*, 2014) while among Yamani CRC patients, 49% of the cases had rectal and

rectosigmoid tumors (Basaleem & Al-Sakkaf, 2004). Rectal cancer was reported to be more common among young CRC patient (Nagai *et al.*, 2016) and to have earlier onset compared to colon cancer (Bhurgri *et al.*, 2011), indicating a familial component to the etiology of rectal cancer.

Further, >70% of the cases had advanced case presentation at diagnosis with lymph nodes and liver being the most common sites of metastasis. Late diagnosis is a phenomena observed in many developing countries, and not only for CRC, but for cancer in general. In Oman, 75% of CRC patients were reported to be diagnosed late stage (Kumar *et al.*, 2015), and the proportion was 68% in Jordan (Abu-Helalah *et al.*, 2016), 53% in Egypt (Metwally *et al.*, 2018). Lower awareness to early screening and to the early symptoms of the disease may be among the possible reasons for the delay in diagnosis of CRC (Qumseya *et al.*, 2014; Shpitz *et al.*, 2006), and early stage at presentation reflects the success of colorectal screening programs (McClements *et al.*, 2012). In addition, late diagnosis is directly associated to survival. A study among CRC in Gaza Strip showed that the 5-year survival for patients with CRC was 50.2% (Panato *et al.*, 2018).

Moreover, due to direct flow of blood from the colon to the liver, metastasis to the liver is very common. CRC can also spread, but less commonly, to lungs and bones (CancerResearchUK, 2018). Moreover, lymph node metastasis is considered an important prognostic factor in predicting disease recurrence and survival in patients with CRC and a key factor in deciding further management (Kim & Choi, 2019; Ong & Schofield, 2016).

Although a significant number of patients presented with advanced-stage disease, the treatment was administered in conformity with the guidelines for the stage (Morales *et al.*, 2020). Surgery was considered adequate if the resection margins were negative and adequate lymph nodes were sampled. Hemicolectomy or sigmoidectomy were the most common surgical procedures for colon cancer, and more than 60% of the patients received FOLFOX chemotherapy (Duran *et al.*, 2014; Morales *et al.*, 2020).

### **6.1.2. Risk Factors of CRC**

Comparing the characteristics of CRC cases and controls, cases were significantly older, with a majority of females. Furthermore, although our assumption in this study was that “urbanization” could explain the increase in CRC, the findings did not show a direct

association between residing in urban localities and the risk of CRC, although higher proportion of cases lived in urban localities. Moreover, CRC cases in this study showed lower education level compared to controls. Several studies reported that globally, the incidence of urbanization is increasing, and is considered one of CRC risk factors, as the urban lifestyle is more sedentary with ongoing transitional changes in diet to westernized modern urban foods including more energy-dense materials such as meat, fats, oil, and sugar, but are low in dietary fiber (Bruce *et al.*, 2000; Katsidzira *et al.*, 2019; Wen *et al.*, 2018). In Palestine, as a high percent of Palestinians still reside in rural areas and are involved in physical work.

Moreover, since the two study centers were located in the south and the center, the majority of the cases were from these regions with underrepresentation for northern governorates in this study. In addition, we were not able to recruit controls from the other regions (especially Gaza Strip), to match the cases, therefore, significantly higher proportion of cases were from there. Furthermore, marital status was also significantly associated with increased risk of CRC. Other studies from some Arab countries did not reveal this association (Alyabsi *et al.*, 2020; Mafiana *et al.*, 2018). On the contrary, many studies showed that marital status provided protective effect for CRC and reduced cancer mortality (Gomez *et al.*, 2016; L. Wang *et al.*, 2011). A possible explanation for the protective effect is that marriage is a source of social support, and could encourage cancer screening, quitting cigarette smoking and excessive alcohol use (Aizer *et al.*, 2013; O'Neill *et al.*, 2012). However, this is not the case in our study. Stress associated with the poor economic situation as well as the Israeli occupation which may generate psychological pressure on families in Palestine could be a possible explanation for this association.

Due to the possible interaction between demographic characteristics and the investigated risk factors, we adjusted the multivariate model for gender, age, educational level, and region.

#### **6.1.2.1. Family history**

This study revealed that having parents that are related by blood was strongly associated with the risk of CRC, but the number of controls having parents from the same family was only low resulting in a limited statistical power. Consanguineous marriage is a very common phenomenon in many Arab countries including Palestine. Consanguinity is

associated with high incidence of genetic diseases (Abdulrazzaq *et al.*, 1997; Bener *et al.*, 2007). On the other hand, this study did not show an association between history of cancer and the risk of CRC regardless of the evidence pointing to the role of familial factors in the etiology of CRC among Palestinian (high proportion of early onset CRC and the association between CRC risk and consanguinity). Contrary to these findings, a previous meta-analysis showed that individuals with a family history of CRC in a first degree relative had two-folds increase in CRC risk (Johnson *et al.*, 2013). Furthermore, several other studies reported a significant association between family history and risk of CRC (Katsidzira *et al.*, 2019; Tian *et al.*, 2019). Further investigation of hereditary and familial CRC-related syndromes is needed in Palestine in order to determine their contribution to CRC burden and take appropriate prevention measures that could reduce the incidence and mortality of CRC.

#### **6.1.2.2. Body mass index (BMI)**

Worldwide, the prevalence of obesity has more than doubled since 1980. Obesity is known to increase the likelihood of diabetes, hypertension, coronary heart disease, stroke, and certain cancers. Overweight (BMI  $\geq 25$  kg/m<sup>2</sup>) and obesity ( $\geq 30$  kg/m<sup>2</sup>) were estimated to account for 3.4 million deaths per year. In 2014, 39% of adults aged 18 years and older were overweight and 11% of men and 15% of women were obese (WHO, 2014).

The prevalence of overweight and obesity among controls in this study were 35.4% and 33.3%, respectively. The National Health and Nutrition Survey (1999-2000) reported the prevalence of overweight and obesity among Palestinian adult to be 38.0% and 24.4%, respectively (Abdeen *et al.*, 2012), which is lower than the reported prevalence in this study. On the other hand, another household survey conducted in the West Bank reported the prevalence of obesity among Palestinian males and females between the ages of 30-65 years to be 31% and 49%, respectively in urban localities, while the prevalence of obesity was significantly lower among residents of rural localities for both males and females (Abdul-Rahim *et al.*, 2003).

However, regarding the association between BMI and CRC risk, the findings here did not support such an association. A differential bias resulting from sampling error among the control group could have nullified the association between obesity and risk of CRC. This error is because the control group (a population that underwent colonoscopy) are high-risk

group for metabolic and gastrointestinal diseases and does not represent the general Palestinian population.

Contrary to these findings, the Physicians' Health Study, which is a 19-years cohort of 22,071 healthy male physicians initially aged 40-84 years, reported that BMI  $\geq 27$  kg/m<sup>2</sup> was associated with 40% increased CRC risk (Sturmer *et al.*, 2006). Furthermore, a recent systemic review and meta-analysis of more than 1000 observational studies showed that high BMI was associated with the CRC risk (Lauby-Secretan *et al.*, 2016). Obesity is associated with inflammation, metabolic, and endocrine abnormalities that promote cell growth and exert anti-apoptotic explaining its role in carcinogenesis (WCRF, 2018).

### **6.1.2.3. Smoking**

Smoking is the cause of 6 million preventable deaths per year globally. In 2012, the global prevalence of current tobacco smoking among adults was estimated to be around 22% (WHO, 2014).

In this study, the prevalence of smoking among controls was very high (47%). The Palestinian Central Bureau of Statistics (PCBS) estimated the prevalence of smoking in Palestine among individuals at age of 18 years and over in 2012 to be 22.5% and reported a decline in the overall prevalence of smoking (PCBS, 2012).

Regarding the association between smoking and the risk of CRC in this study, a significantly decreased risk of CRC associated with ever smoking has been found. However, tobacco is an established carcinogen. Evidence regarding the association between smoking and CRC risk has been inconsistent across epidemiological studies but studies reported either no association or increased risk (Giovannucci, 2002; Hughes *et al.*, 2017; Katsidzira *et al.*, 2019; S. Lee *et al.*, 2019; McCleary *et al.*, 2010).

The most likely explanation for the association found in this study is a sampling bias among controls; controls were younger, more educated compared to cases. Smoking studies among Palestinians showed that the prevalence of smoking is higher among younger adults and among the more educated population (Tucktuck *et al.*, 2017; Zabadi *et al.*, 2018).

#### **6.1.2.4. Physical activity**

Insufficient physical activity is considered one of the ten leading risk factors for global mortality causing around 3.2 million deaths each year (Lim *et al.*, 2012). Globally, it was estimated in 2010 that 20% of adult males and 27% of adult females did not meet WHO recommendations on physical activity for health (which are at least 150 minutes of moderate-intensity physical activity per week) (WHO, 2014). Furthermore, regular physical activity is important for energy balance, weight control and prevention of obesity. Compared to high-income countries, the prevalence of insufficient physical activity is 50% lower in developing countries (WHO, 2014), which is probably due to high levels of occupational and transport activity in these countries (Guthold *et al.*, 2011).

In this study, occupational physical activity and leisure time activity were evaluated separately. Occupational physical activity was classified based on the type of occupation held during last 10 years, ranging from sedentary to heavy manual. On the other hand, leisure time activity included any active time including the time communicating from and to workplace. Although there were no significant differences between cases and controls about to the occupational physical activity, 52% of the controls reported an absence of regular leisure time activity of any form. Furthermore, the majority of reported active time among study subjects consisted of walking. In comparison, it has been previously reported that the majority of physical activity time for Palestinian adults is achieved by occupation or domestic activity and no leisure time have been reported by 42% of Palestinian men and 53% of Palestinian women. Moreover, the study reported that 26% of Palestinian women and 13% of Palestinian men were insufficiently active (Merom *et al.*, 2012).

Regarding the risk of CRC and physical activity, occupational physical activity was not found to be associated with CRC risk. However, regular physical activity was associated with increased risk of CRC and the risk increased with dose-response effect. The risk was 10-folds higher for those maintaining >7 hours physical activity per week. These findings are the opposite of what have been reported regarding the role of physical activity in reducing the risk of CRC (Samad *et al.*, 2005). One possible explanation for these findings is the irregular and non-vigorous intensity during performing physical activity as a previous study estimated that 12–14% of colon cancer could be attributed to lack of frequent involvement in vigorous physical activity (M. L. Slattery, 2004).

Several biological mechanisms have been proposed to explain the association between physical activity and colon cancer including increasing gut motility, enhancing the immune system, decreasing insulin and insulin-like growth factor levels, decreasing obesity; enhancing free radical scavenger systems, and influencing prostaglandin levels (M. L. Slattery, 2004).

#### **6.1.2.5. Dietary intake**

The correlation between diet and CRC has been heavily investigated. Yet, evidence provided by case-control and cohort studies remains controversial. The World Cancer Research Fund (WCRF) concluded in their third expert report that besides obesity and physical inactivity, consuming processed and red meat increases the risk of CRC. On the other hand, consumption of dietary fiber, dairy products, calcium supplements, and whole grains decrease the risk of CRC. The evidence regarding processed meat was considered convincing while the evidence regarding dietary fiber, dairy products, calcium supplements, and whole grains was considered probable. In addition, the WCRF reported limited evidence suggestive of an inverse association between consumption of fish and risk of CRC (WCRF, 2018). Furthermore, a case-control study of 220 CRC subjects and 281 controls analyzed food patterns, which were categorized into healthy pattern, high sugar/high tea pattern, and western pattern, and reported that western pattern was associated with 1.9-folds increased risk of CRC (Tayyem *et al.*, 2017). Moreover, a review of 28 cohort and 21 case-control studies that examined the association between dietary patterns and CRC risk showed that findings differed by study design. The study concluded that a dietary pattern high in fruits and vegetables and low in meats and sweets is protective against CRC risk (Tabung *et al.*, 2017).

In this study, comparison of the median consumption level of CRC cases and controls to the *U.S. Department of Agriculture (USDA)* guidelines for ages of 14 years and above at a calorie level of 2200 (USDA, 2021), which are based on the *Dietary Guidelines for Americans, 2020-2025*, showed that both cases and controls had lower than the recommended intake of dairy, grains, and proteins. Consumption of vegetables among controls was up to the recommended levels while cases' consumption was slightly lower than the recommended. In addition, compared to the recommended level, controls had lower consumption of fruits while cases had much higher consumption.

In this study, a positive association between fish intake and the risk of CRC was found. The risk was 5-folds increased for the highest quartiles compared to the lowest. On the other hand, consumption of red meat, poultry, and eggs were found to be associated with slightly decreased risk of CRC. Furthermore, consumption of sweets and nuts were found to be associated with 7.2-folds and 8-folds increased risk of CRC for the highest consumption levels in reference to the lowest. In addition, consumption of vegetables was not associated with risk of CRC while on the contrary; consumption of fruits was highly associated with increased risk of CRC.

In comparison to these findings, a case-controlled study conducted in Riyadh, Saudi Arabia, reported that consumption of meat high in fat, fried eggs and whole-fat dairy products, and diet low in fibers 2-3 times or above per week increased the risk of CRC. In addition, the study reported that increased consumption of peanuts, walnuts, and almonds to more than 4 times per week was associated with 14-folds increased risk of CRC (Nashar & Almurshed, 2008). Among Kuwaiti population, CRC cases were found to have lower consumption levels of fruits and vegetables and higher consumption levels of red meat compared to controls (Alsheredah & Akhtar, 2018). Another case-control study of 169 CRC patients and 101 controls in Brazil reported that patients had higher average intakes of red and white meat but consumption of fish, vegetables, fruits and whole grains did not differ between cases and controls (Angelo *et al.*, 2016). A population-based case-control study in Hawaii, USA that included 1192 pathologically confirmed CRC cases and 1192 population-based controls evaluated the role of dietary lipids and foods of animal origin on the risk of CRC. The study reported that CRC was not associated with intake of fat, yet there was an inverse association between risk of CRC and the ratio between polyunsaturated and saturated fat. In addition, the findings of the study showed that while red meat, processed meat, and eggs were associated with the risk of CRC, fat-trimmed red meat and fish were not associated with CRC risk, and eating chicken without skin was inversely associated with risk of CRC (Le Marchand *et al.*, 1997a). Furthermore, two meta-analysis studies of prospective cohort studies evaluated the evidence for the association between red meat and processed meat consumption and the risk of colorectal cancer and reported that Consumption of red meat and processed meat was positively associated with risk of CRC (Chan *et al.*, 2011; S. C. Larsson & Wolk, 2006a). Moreover, a pooled analysis of 10 cohort studies in five countries and a meta-analysis of 26,335 cases from 60 observational studies reported that milk and dairy product intake and calcium

intake were associated inversely to the risk of colon cancer (Cho *et al.*, 2004b; Huncharek *et al.*, 2009). In addition, a meta-analysis on five case-control studies and four cohort studies exploring the association between Dietary Inflammatory Index (DII) and CRC showed that increasing DII scores were positively associated with risk of CRC. Energy, carbohydrates, proteins, total fat, trans fat, cholesterol, vitamin B12, saturated fatty acids and iron are considered pro-inflammatory food components (Shivappa *et al.*, 2017).

Diet and nutrition could influence cancer risk in a range of different ways; for example, food and drinks could be vectors for carcinogenic substances (WCRF, 2018). The results of a recent ecological study in Brazil suggested the possibility that pesticide exposure could be a risk factor for colon cancer (Martin *et al.*, 2018). Several studies examined the association between pesticide exposure and the risk of CRC and reported several associations with different types of pesticides (Howsam *et al.*, 2004; W. J. Lee *et al.*, 2007b). Moreover, a study in Spain evaluated the level of contamination by carcinogens in samples of meat and reported that consumption of beef, pork, lamb, and chicken represents a carcinogenic risk for consumers (Hernandez *et al.*, 2015). In Palestine, despite all the efforts to control pesticide importation and use, it has been estimated that up to 50% of pesticides used in the country are illegal. However, there is no reliable data on either contamination of the environment with pesticides or effects on human health in Palestine (Watts *et al.*, 2016). This could explain the positive association between fish and fruit intake and risk of CRC that we observed in this study.

Nuts contain many nutrients that may reduce the risk of cardiovascular diseases (Mohammad Al-Ismail & Aburjai, 2004), type 2 diabetes (Grun *et al.*, 2001; Stintzing *et al.*, 2006), and overall mortality and incidence of colorectal and endometrial cancer (de Souza *et al.*, 2015; Elmadfa & Kornsteiner, 2009). In Palestine, one of the common and traditional ways to present the local cuisine is to top the dishes with fried nuts. Additionally, nuts are also introduced as raw, roasted, fried or as a part of desserts in special occasions and ceremonies. The bioactive compounds of nuts are affected by heat treatments. A study that analyzed the chemical changing of the raw nuts after roasting or frying showed that heat treatment of nuts have a significant impact on nuts properties and essential nutrients that enhance the antioxidant activity and therefore recommended consuming different nuts as raw or as heat-treated (Ghazzawi & Al-Ismail, 2017). Furthermore, salted nut and seeds –which are easily overconsumed- have high levels of

sodium. A recent systematic review that included seven studies reported that high sodium intake can increase the risk of CRC (Yakoob & Baig-ansari, 2019). Several studies have assessed the association between intake of nuts and CRC risk, but results were conflicting. The Nurses' Health Study conducted in the United States suggested a null association between nut consumption and colorectal cancer risk (Yang *et al.*, 2016). On the other hand, a prospective cohort in Taiwan with a 10-year follow-up reported that peanut consumption reduced the risk of colorectal cancer among women significantly, but the association was not significant for men (Yeh *et al.*, 2006). In addition, a case-control study in Korea investigating the relationship between nut intake and risk of colorectal cancer reported that high nut consumption ( $\geq 3$  servings per week) was strongly associated with reduced risk of CRC among both men and women (J. Lee *et al.*, 2018). Moreover, Aflatoxins are a family of toxins produced by certain fungi that are found on agricultural crops such as corn, peanuts, and tree nuts and can contaminate crops in the field, at harvest, and during storage. Aflatoxins are highly carcinogenic mycotoxins that can be absorbed through the gastrointestinal tract after ingestion of the contaminated food and have the ability to penetrate the human and animal cells where it causes a major mutagenic change (Ahmed Adam *et al.*, 2017). Animal studies have reported that exposure to aflatoxin B1 in vitamin A-deficient rats enhanced liver and colon cancer (Suphakarn *et al.*, 1983). Exposure to aflatoxins is associated with liver cancer, but the link between other cancers and exposure to aflatoxins was not extensively investigated (Claeys *et al.*, 2020).

#### **6.1.2.6. Medical history**

##### **6.1.2.6.1. Infections and gastrointestinal-related health problems**

It has been estimated that 20% of all cancer is caused by infectious agents. The human gastrointestinal tract is colonized by  $\geq 100$  trillion bacteria. The link between infectious agents and CRC has not been well described. This might be due to the belief that had prevailed from many years that commensal bacteria is not harmful, but rather have beneficial, symbiotic effects. Over time, several observational and clinical studies indicated that bacteria and viruses might be an etiological link in the development of CRC. With modern molecular biology techniques now available, a new insight has emerged about bacterial and viral involvement in CRC (Tjalsma *et al.*, 2012).

In this study, the association between self-reported history of certain infectious diseases and the risk of CRC was evaluated. These findings showed a significantly increased risk of

CRC associated with Herpes (indication for EBV or CMV viral infections) and periodontal disease (as an indication for infection with *Fusobacterium*), in addition to a non-significant association with history of enteritis. On the contrary, *Helicobacter pylori* was associated with significant inverse relationship with CRC risk.

The number of studies on the association between viral infections and risk of CRC was limited and the evidence was inconclusive. A systematic review of epidemiological studies that investigated the association between viral infections and the risk of CRC reported that human herpesviruses including Cytomegalovirus (CMV), Epstein-Barr virus (EBV), and Varicella-zoster virus (VZV) were more frequently found in CRC cases than in controls but the majority of findings were not statistically significant and the number of participants in each study was small (H. Chen *et al.*, 2015b).

*Fusobacterium* is a genus of anaerobic, Gram-negative bacteria that contribute to several human diseases, including periodontal diseases, Lemierre's syndrome, and topical skin ulcers (Antonic *et al.*, 2013). Several publications correlated its presence with CRC (Castellarin *et al.*, 2012; Kostic *et al.*, 2012). In addition, *Fusobacterium* species has been found to be associated with inflammatory bowel diseases (IBD), a known CRC risk factor (Kostic *et al.*, 2012).

*Helicobacter pylori* is classified as a class I carcinogen by the International Agency for Research in Cancer (IARC). The evidence regarding the association between *H. pylori*-related chronic gastritis and CRC remains inconclusive because of the limited number of epidemiological studies. A recent review of the evidence and two older meta-analysis studies reported that *H. pylori*-related chronic gastritis could be involved in an increased risk of CRC (Inoue *et al.*, 2014; Zhao *et al.*, 2008; Zumkeller *et al.*, 2006). Although we found a significant inverse association between *H. pylori*-related chronic gastritis and the risk of CRC, this association is likely to be a result of the sampling bias in the control group since patient with chronic gastritis undergo endoscopic and colonoscopic examinations on regular basis as part of their follow-up.

Patients with IBD are at an increased risk of developing CRC. Chronic inflammation of the colonic mucosa is likely the cause of this association (E. R. Kim & Chang, 2014; Stidham & Higgins, 2018; Zhiqin *et al.*, 2014). It has been estimated that 2% of the annual CRC

mortality are attributed to IBD-related CRC and that 10-15% of deaths of IBD patients are caused by CRC (Keller *et al.*, 2019). The prevalence of IBD in Palestine is not known, in this study, the prevalence of IBD among controls was 7.7% (5.8% for Ulcerative colitis and 1.9% for Crohn's disease). Patients with IBD are usually followed up regularly by colonoscopic examination, which is the likely explanation for the high prevalence among controls and the negative association between ulcerative colitis and the risk of CRC. However, the incidence and prevalence of IBD have been increasing in many Asian societies (Zhiqin *et al.*, 2014). A large Chinese retrospective case-control study showed that history of inflammatory bowel disease was found to be independently associated with the risk of CRC (Hang *et al.*, 2015).

The results of this study showed that history of inflammatory bowel syndrome (IBS) was non-significantly associated with the risk of CRC. Comparatively, a nationwide cohort study conducted between 1977-2008 in Denmark that included 57851 IBS patients, the risk of colon cancer increased by 8-folds and the risk of rectal cancer increased by 5-folds during the first 3 months after an IBS diagnosis. However, in the period 1–10 years after an IBS diagnosis, the risk of CRC decreased (Norgaard *et al.*, 2011). Another cohort in Taiwan included 91,746 patients with IBS and a control group of 183,492 patients matched by sex, age, and baseline year showed that the risk of CRC during the first 2 years after IBS diagnosis was increased, but not after (Hsiao *et al.*, 2014). These results do not support an association between IBS and CRC risk, but rather, it is thought that the association might have occurred because some CRC patients were initially misclassified as IBS patients.

Celiac disease is a relatively common autoimmune disorder triggered by intestinal exposure to gluten. A meta-analysis including 17 studies reported 1.6-folds increased risk of gastrointestinal malignancies among patients with celiac disease, but there was no significant association between celiac disease and CRC (Han *et al.*, 2015). Another systematic review and meta-analysis that evaluated 3 studies including 367 cases of celiac disease and 682 controls did not find an association between celiac disease and colorectal adenomas (Lasa *et al.*, 2018). Furthermore, a multicenter case-control study in four community hospitals in Buenos Aires, Argentina reported no significant association between celiac disease and risk of CRC (Pereyra *et al.*, 2013). In this study, we found a

non-significant reduction in the risk of CRC in association with celiac disease, however, this could be due to sampling bias of the controls.

The majority of gastrointestinal diseases and health problems are considered indications for colonoscopic examination such as severe diarrhea, hemorrhoids, and inflammatory anal lesions (anal fissures, perianal abscesses, and anal fistulas), therefore, they were commonly reported among controls and affected our ability to detect true associations with risk of CRC. The association between inflammatory anal lesions, hemorrhoids, and risk of CRC has been rarely investigated. A cohort of 45186 Swedish patients hospitalized for inflammatory anal lesions and 79808 hemorrhoid patients between 1965-2002 reported no significant association with the risk of CRC (Nordenvall *et al.*, 2006).

#### **6.1.2.6.2. Hypertension, Diabetes, and CVD**

According to the Global Status Report on Non-communicable Diseases (2014), raised blood pressure is one of the leading risk factors for global mortality. The global prevalence of raised blood pressure in adults aged  $\geq 18$  years was around 22% in 2014. The prevalence of raised blood pressure was higher in low-income countries compared to middle-income and high-income countries (WHO, 2014). Moreover, cardiovascular disease (CVD) was the leading cause of non-communicable disease (NCD) deaths worldwide in 2012. More than 80% of cardiovascular deaths occur in low- and middle-income countries (WHO, 2014). Further, the global prevalence of diabetes was estimated to be 9% being highest in the Eastern Mediterranean Region (14%) (WHO, 2014). The prevalence of diabetes has been increasing globally and has been particularly accelerated in low- and middle-income countries. This rise is partially driven by population aging, but the main drivers are modifiable risk factors; particularly physical activity, overweight and obesity (Finucane *et al.*, 2011). Many factors contribute to the high prevalence of hypertension such as globalization, urbanization, aging, income, education, unhealthy diet, tobacco use, overweight and obesity, harmful use of alcohol, physical inactivity, genetic factors, psychological stress, diabetes, raised blood lipids (WHO, 2014).

In Palestine, diabetes is the fifth leading cause of mortality (7.5%). The incidence of diabetes mellitus in 2018 was 210.7/100,000 population (MOH, 2019). Furthermore, CVD is the leading cause of death among Palestinians causing 31.5% of the mortalities reported in 2018 (MOH, 2019).

The association between hypertension and cancer is complex and it is still unclear since they both are affected by similar risk factors such as smoking, obesity, alcohol consumption, and physical inactivity. Furthermore, no clear mechanism has been proposed to link hypertension to CRC (Seretis *et al.*, 2019). In this study, an 8.5-folds increased risk of CRC has been found among subjects with history of hypertension; however, the low prevalence of hypertension among the control group (1.9%) limited the statistical power of the association. A systematic review and meta-analysis of observational studies that considered evidence from 85 prospective studies investigating the association between hypertension and risk of any cancer reported a positive association between hypertension and CRC (Seretis *et al.*, 2019). Furthermore, a meta-analysis of observational studies that included 25 studies with a pooled 1.95 million participants suggested a positive association between hypertension and risk of CRC with a pooled relative risk of 1.15 (95% CI: 1.08, 1.23) (Xuan *et al.*, 2021). On the other hand, the Physicians' Health Study, which investigated the association between metabolic abnormalities including overweight, diabetes, elevated blood pressure, and hypercholesterolemia with the risk of CRC, reported that elevated blood pressure was not associated with the risk of CRC (Sturmer *et al.*, 2006).

Moreover, diabetes mellitus is a recognized risk factor for CRC independent of diet, physical exercise, smoking, obesity, or metabolic syndrome (Jarvandi *et al.*, 2013; Yuhara *et al.*, 2011). This effect is probably mediated by the high levels of insulin and insulin-like growth factors (Guo *et al.*, 1992; Leitner *et al.*, 1997). On the other hand, CVD and cancer share the same pathophysiology; inflammation, which promote both atherosclerosis and carcinogenesis, and common risk factors such as obesity, tobacco use, hyperglycemia, hypertension, and hyperlipidemia (S. C. Wang *et al.*, 2019a).

Although in this study the association between history of diabetes, CVD, and the risk of CRC could not be measured, there were statistically significant differences in the prevalence of diabetes (15.3% versus 0.0%) and CVD (1.5% versus 0.0%) between cases and controls, respectively ( $p < 0.0001$ ). Comparatively, the Physicians' Health Study estimated that diabetes increased the risk of CRC by 50%, but hypercholesterolemia was not found to be associated with CRC (Sturmer *et al.*, 2006). In addition, the Cancer Prevention Study II Nutrition Cohort reported increased risk of CRC among men with diabetes mellitus whether they were insulin users or not (Campbell *et al.*, 2010). Another

large Chinese retrospective case-control study involving 1144 CRC patients and 60549 community-based controls reported that diabetes and hyperlipidemia were associated with increased risk of CRC (Hang *et al.*, 2015). Furthermore, a follow-up study in Korea reported that the risk of CRC increased with risk of coronary artery disease (J. Y. Lee *et al.*, 2013). Another study reported that right-sided colon cancer had stronger association to hypertension, hyperlipidemia, hypothyroidism and clinical CVD compared to patients with left-sided colon cancer (S. C. Wang *et al.*, 2019a).

## **6.2. Limitations**

Up to our knowledge, this study was the first study to investigate the risk factors of CRC in Palestine using a detailed history of lifestyle factors. The used case-control design is the most convenient study design to investigate the risk factors of CRC in the Palestinian setting since it is hard to maintain follow-up in a fragmented and decentralized healthcare system. However, recall bias remains one of the major limitations of the retrospective data collection. Therefore, to reduce recall bias to a minimum, incident cases (<18 months between diagnosis and recruitment) were recruited. Furthermore, cases may recall their past exposures better than controls. In this study's design, face-to-face interviews were used to reduce the possibility of differential bias rather than self-administered questionnaires.

The use of FFQ for assessment of dietary intake provide a flexible and easy to assessment tool in research settings. In addition, FFQs are one of the most often used instruments to estimate past food consumption or usual consumption over a period of time (especially fruit and vegetables), yet, recall bias might largely affect the data because this method relies on memory.

Moreover, relying on self-reporting rather than biological markers or medical records – especially in assessing medical history – is also one of the major limitations in our study, but there were no other alternatives.

Finally, caution should be taken in the interpretation of these findings given that the control group were high-risk group (mainly for gastrointestinal diseases) and the sample size was relatively small for both cases and controls.

### **6.3. Conclusions**

The findings of this study suggest that the current pattern of CRC could be attributed in part to lifestyle factors, but some of the associations observed here were conflicting with the existing literature. Among the most notable associations in this study were the association of CRC with increased intake of fish, fruits, sweets, and nuts. In addition, the association between physical activity and CRC requires further investigation to understand the deriving factors behind the observed increase in CRC risk. Moreover, although the association between hypertension, diabetes and CVD requires further investigation, it provides a strong evidence regarding the role of metabolic syndrome and the risk of CRC.

### **6.4. Recommendations**

Recommendations for the community:

- CRC is, to an extent, a preventable disease. It can be prevented by maintaining a healthy lifestyle that include regular exercising, healthy diet, smoking prevention, and maintaining healthy body weight.
- CRC screening is the best way to decrease the incidence and mortality rates among Palestinian population. It is recommended for all adult Palestinians greater than 50 years of age and for all high-risk individuals to respond to the advice of doing CRC screening measures.

Recommendations for the future research:

- Conducting more detailed research with larger sample size and including more hospital and healthcare facilities from different regions of Palestine, to achieve more reliable and generalizable findings.
- Patterns of CRC among cases suggest a strong role for genetic factors, therefore, it is important to study the genetics of CRC in our population.
- CRC is a multifactorial disease, therefore, evaluating the combined impact of the different risk factors on CRC risk can provide a model for prediction of the risk of CRC.

Recommendations for policy makers and healthcare team:

- Extensive awareness campaigns should be carried out to explain the importance of maintaining a healthy lifestyle and CRC screening.
- Nutrition education programs about the role of diet in increasing or decreasing the risk of CRC, as well as prevention obesity through the promotion of healthy eating and fostering daily physical activity are greatly needed.
- CRC screening is not yet established in Palestine. Therefore, establishing a national screening program for the early detection of CRC is essential.
- To establish a targeting screening strategy for CRC, it is important to identify patients who are at high risk; i.e. individuals with metabolic abnormalities and genetic predisposition.
- Consanguineous marriage is still very common in Palestine. Advocacy programs should be conducted in Palestine to educate Palestinians on the risk of this issue.
- Improving the quality of the hospital information system and the national cancer registry, and modify to include more details.

## References

- Abdeen, Z., Jildeh, C., Dkeideek, S., Qasrawi, R., Ghannam, I., & Al Sabbah, H. (2012). Overweight and Obesity among Palestinian Adults: Analyses of the Anthropometric Data from the First National Health and Nutrition Survey (1999-2000). *Journal of Obesity*, 2012, 213547. doi:10.1155/2012/213547
- Abdul-Rahim, H. F., Holmboe-Ottesen, G., Stene, L. C., Hussein, A., Giacaman, R., Jervell, J., et al. (2003). Obesity in a rural and an urban Palestinian West Bank population. *Int J Obes Relat Metab Disord*, 27(1), 140-146. doi:10.1038/sj.ijo.0802160
- Abdulmir, A. S., Hafidh, R. R., & Bakar, F. A. (2011). The association of *Streptococcus bovis/galloyticus* with colorectal tumors: the nature and the underlying mechanisms of its etiological role. *Journal of Experimental & Clinical Cancer Research*, 30(1), 11.
- Abdulrazzaq, Y. M., Bener, A., al-Gazali, L. I., al-Khayat, A. I., Micallef, R., & Gaber, T. (1997). A study of possible deleterious effects of consanguinity. *Clin Genet*, 51(3), 167-173. doi:10.1111/j.1399-0004.1997.tb02447.x
- Abu-Helalah, M. A., Alshraideh, H. A., Da'na, M., Al-Hanaqtah, M., Abuseif, A., Arqoob, K., et al. (2016). Delay in Presentation, Diagnosis and Treatment for Colorectal Cancer Patients in Jordan. *J Gastrointest Cancer*, 47(1), 36-46. doi:10.1007/s12029-015-9783-3
- Adams, K. F., Leitzmann, M. F., Albanes, D., Kipnis, V., Mouw, T., Hollenbeck, A., et al. (2007). Body mass and colorectal cancer risk in the NIH-AARP cohort. *Am J Epidemiol*, 166(1), 36-45. doi:10.1093/aje/kwm049
- Ahmed Adam, M. A., Tabana, Y. M., Musa, K. B., & Sandai, D. A. (2017). Effects of different mycotoxins on humans, cell genome and their involvement in cancer (Review). *Oncol Rep*, 37(3), 1321-1336. doi:10.3892/or.2017.5424
- Aizer, A. A., Chen, M. H., McCarthy, E. P., Mendu, M. L., Koo, S., Wilhite, T. J., et al. (2013). Marital status and survival in patients with cancer. *J Clin Oncol*, 31(31), 3869-3876. doi:10.1200/JCO.2013.49.6489
- Al-Shamsi, S. R., Bener, A., Al-Sharhan, M., Al-Mansoor, T. M., Azab, I. A., Rashed, A., et al. (2003). Clinicopathological pattern of colorectal cancer in the United Arab Emirates. *Saudi Med J*, 24(5), 518-522.
- Al-Tassan, N., Chmiel, N. H., Maynard, J., Fleming, N., Livingston, A. L., Williams, G. T., et al. (2002). Inherited variants of MYH associated with somatic G: C→ T: A mutations in colorectal tumors. *Nature genetics*, 30(2), 227.
- Alsheredah, N., & Akhtar, S. (2018). Diet, obesity and colorectal carcinoma risk: results from a national cancer registry-based middle-eastern study. *BMC Cancer*, 18(1), 1227. doi:10.1186/s12885-018-5132-9
- Alyabsi, M., Alhumaid, A., Allah-Bakhsh, H., Alkelya, M., & Aziz, M. A. (2020). Colorectal cancer in Saudi Arabia as the proof-of-principle model for implementing strategies of predictive, preventive, and personalized medicine in healthcare. *EPMA J*, 11(1), 119-131. doi:10.1007/s13167-019-00186-x

- Angelo, S. N., Lourenco, G. J., Magro, D. O., Nascimento, H., Oliveira, R. A., Leal, R. F., *et al.* (2016). Dietary risk factors for colorectal cancer in Brazil: a case control study. *Nutr J*, *15*, 20. doi:10.1186/s12937-016-0139-z
- Antonic, V., Stojadinovic, A., Kester, K. E., Weina, P. J., Brucher, B. L., Protic, M., *et al.* (2013). Significance of infectious agents in colorectal cancer development. *J Cancer*, *4*(3), 227-240. doi:10.7150/jca.5835
- Arafa, M. A., & Farhat, K. (2015). Colorectal Cancer in the Arab World--Screening Practices and Future Prospects. *Asian Pac J Cancer Prev*, *16*(17), 7425-7430.
- Arnold, M., Sierra, M. S., Laversanne, M., Soerjomataram, I., Jemal, A., & Bray, F. (2017). Global patterns and trends in colorectal cancer incidence and mortality. *Gut*, *66*(4), 683-691. doi:10.1136/gutjnl-2015-310912
- Ashktorab, H., Paydar, M., Yazdi, S., Namin, H. H., Sanderson, A., Begum, R., *et al.* (2014). BMI and the risk of colorectal adenoma in African-Americans. *Obesity (Silver Spring)*, *22*(5), 1387-1391. doi:10.1002/oby.20702
- Bae, J. M., Kim, J. H., & Kang, G. H. (2016). Molecular subtypes of colorectal cancer and their clinicopathologic features, with an emphasis on the serrated neoplasia pathway. *Archives of pathology & laboratory medicine*, *140*(5), 406-412.
- Bamia, C., Lagiou, P., Buckland, G., Grioni, S., Agnoli, C., Taylor, A. J., *et al.* (2013). Mediterranean diet and colorectal cancer risk: results from a European cohort. *European journal of epidemiology*, *28*(4), 317-328.
- Basaleem, H. O., & Al-Sakkaf, K. A. (2004). Colorectal cancer among Yemeni patients. Characteristics and trends. *Saudi Med J*, *25*(8), 1002-1005.
- Baumgart, D. C., & Carding, S. R. (2007). Inflammatory bowel disease: cause and immunobiology. *The Lancet*, *369*(9573), 1627-1640.
- Bazensky, I., Shoobridge-Moran, C., & Yoder, L. H. (2007). Colorectal cancer: an overview of the epidemiology, risk factors, symptoms, and screening guidelines. *Medsurg Nursing*, *16*(1), 46.
- Beaugerie, L., Svrcek, M., Seksik, P., Bouvier, A. M., Simon, T., Allez, M., *et al.* (2013). Risk of colorectal high-grade dysplasia and cancer in a prospective observational cohort of patients with inflammatory bowel disease. *Gastroenterology*, *145*(1), 166-175. e168.
- Bedard, P. L., Hansen, A. R., Ratain, M. J., & Siu, L. L. (2013). Tumour heterogeneity in the clinic. *Nature*, *501*(7467), 355-364. doi:10.1038/nature12627
- Bener, A., Hussain, R., & Teebi, A. S. (2007). Consanguineous marriages and their effects on common adult diseases: studies from an endogamous population. *Med Princ Pract*, *16*(4), 262-267. doi:10.1159/000102147
- Bhurgri, Y., Khan, T., Kayani, N., Ahmad, R., Usman, A., Bhurgri, A., *et al.* (2011). Incidence and current trends of colorectal malignancies in an unscreened, low risk Pakistan population. *Asian Pac J Cancer Prev*, *12*(3), 703-708.
- Bingham, S., Day, N., Luben, R., Ferrari, P., Slimani, N., Norat, T., *et al.* (2003). European Prospective Investigation into Cancer and Nutrition. Dietary fibre in food and protection

against colorectal cancer in the European Prospective Investigation into Cancer and Nutrition (EPIC): an observational study. *Lancet*, 361(9368), 1496-1501.

- Bishehsari, F., Mahdavinia, M., Vacca, M., Malekzadeh, R., & Mariani-Costantini, R. (2014). Epidemiological transition of colorectal cancer in developing countries: environmental factors, molecular pathways, and opportunities for prevention. *World J Gastroenterol*, 20(20), 6055-6072. doi:10.3748/wjg.v20.i20.6055
- Bodaghi, S., Yamanegi, K., Xiao, S.-Y., Da Costa, M., Palefsky, J. M., & Zheng, Z.-M. (2005). Colorectal papillomavirus infection in patients with colorectal cancer. *Clinical Cancer Research*, 11(8), 2862-2867.
- Boffetta, P., & Hashibe, M. (2006). Alcohol and cancer. *Lancet Oncol*, 7(2), 149-156. doi:10.1016/S1470-2045(06)70577-0
- Boleij, A., van Gelder, M. M., Swinkels, D. W., & Tjalsma, H. (2011). Clinical Importance of *Streptococcus gallolyticus* infection among colorectal cancer patients: systematic review and meta-analysis. *Clinical Infectious Diseases*, 53(9), 870-878.
- Bostick, R. M., Potter, J. D., Kushi, L. H., Sellers, T. A., Steinmetz, K. A., McKenzie, D. R., et al. (1994). Sugar, meat, and fat intake, and non-dietary risk factors for colon cancer incidence in Iowa women (United States). *Cancer Causes Control*, 5(1), 38-52.
- Botteri, E., Iodice, S., Bagnardi, V., Raimondi, S., Lowenfels, A. B., & Maisonneuve, P. (2008). Smoking and colorectal cancer: a meta-analysis. *Jama*, 300(23), 2765-2778.
- Bouvard, V., Loomis, D., Guyton, K. Z., Grosse, Y., Ghissassi, F. E., Benbrahim-Tallaa, L., et al. (2015). Carcinogenicity of consumption of red and processed meat. *Lancet Oncol*, 16(16), 1599-1600. doi:10.1016/S1470-2045(15)00444-1
- Boyle, P., & Langman, J. S. (2000). ABC of colorectal cancer: Epidemiology. *BMJ*, 321(7264), 805-808.
- Bruce, W. R., Giacca, A., & Medline, A. (2000). Possible mechanisms relating diet and risk of colon cancer. *Cancer Epidemiol Biomarkers Prev*, 9(12), 1271-1279.
- Butterworth, A. S., Higgins, J. P., & Pharoah, P. (2006). Relative and absolute risk of colorectal cancer for individuals with a family history: a meta-analysis. *European journal of cancer*, 42(2), 216-227.
- Calle, E. E., & Kaaks, R. (2004). Overweight, obesity and cancer: epidemiological evidence and proposed mechanisms. *Nature Reviews Cancer*, 4(8), 579.
- Campbell, P. T., Deka, A., Jacobs, E. J., Newton, C. C., Hildebrand, J. S., McCullough, M. L., et al. (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
- CancerResearchUK. (2017). Bowel cancer incidence statistics. Retrieved from <https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/bowel-cancer/incidence#heading-One>
- CancerResearchUK. (2018). What is bowel cancer? Retrieved from <https://www.cancerresearchuk.org/about-cancer/bowel-cancer/about-bowel-cancer>

- CancerResearchUK. (2019). Bowel cancer incidence statistics (2015-2017). Retrieved from <https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/bowel-cancer/incidence#ref-1>
- Cascella, M., Bimonte, S., Barbieri, A., Del Vecchio, V., Caliendo, D., Schiavone, V., *et al.* (2018). Dissecting the mechanisms and molecules underlying the potential carcinogenicity of red and processed meat in colorectal cancer (CRC): an overview on the current state of knowledge. *Infect Agent Cancer*, 13, 3. doi:10.1186/s13027-018-0174-9
- Castellarin, M., Warren, R. L., Freeman, J. D., Dreolini, L., Krzywinski, M., Strauss, J., *et al.* (2012). *Fusobacterium nucleatum* infection is prevalent in human colorectal carcinoma. *Genome Res*, 22(2), 299-306. doi:10.1101/gr.126516.111
- Centonze, S., Boeing, H., Leoci, C., Guerra, V., & Misciagna, G. (1994). Dietary habits and colorectal cancer in a low-risk area. Results from a population-based case-control study in southern Italy.
- Chan, D. S., Lau, R., Aune, D., Vieira, R., Greenwood, D. C., Kampman, E., *et al.* (2011). Red and processed meat and colorectal cancer incidence: meta-analysis of prospective studies. *PLoS One*, 6(6), e20456. doi:10.1371/journal.pone.0020456
- Chen, H., Chen, X. Z., Waterboer, T., Castro, F. A., & Brenner, H. (2015a). Viral infections and colorectal cancer: a systematic review of epidemiological studies. *International journal of cancer*, 137(1), 12-24.
- Chen, H., Chen, X. Z., Waterboer, T., Castro, F. A., & Brenner, H. (2015b). Viral infections and colorectal cancer: a systematic review of epidemiological studies. *Int J Cancer*, 137(1), 12-24. doi:10.1002/ijc.29180
- Cho, E., Smith-Warner, S. A., Ritz, J., van den Brandt, P. A., Colditz, G. A., Folsom, A. R., *et al.* (2004a). Alcohol intake and colorectal cancer: a pooled analysis of 8 cohort studies. *Ann Intern Med*, 140(8), 603-613.
- Cho, E., Smith-Warner, S. A., Spiegelman, D., Beeson, W. L., van den Brandt, P. A., Colditz, G. A., *et al.* (2004b). Dairy foods, calcium, and colorectal cancer: a pooled analysis of 10 cohort studies. *J Natl Cancer Inst*, 96(13), 1015-1022. doi:10.1093/jnci/djh185
- Chong, D. Q., Banbury, B. L., Phipps, A. I., Hua, X., Kocarnik, J., Peters, U., *et al.* (2018). Association of family history and survival in patients with colorectal cancer: a pooled analysis of eight epidemiologic studies. *Cancer medicine*.
- Claeys, L., Romano, C., De Ruyck, K., Wilson, H., Fervers, B., Korenjak, M., *et al.* (2020). Mycotoxin exposure and human cancer risk: A systematic review of epidemiological studies. *19(4)*, 1449-1464. doi:<https://doi.org/10.1111/1541-4337.12567>
- Clayton, P. E., Banerjee, I., Murray, P. G., & Renehan, A. G. (2011). Growth hormone, the insulin-like growth factor axis, insulin and cancer risk. *Nat Rev Endocrinol*, 7(1), 11-24. doi:10.1038/nrendo.2010.171
- Coglianò, V. J., Baan, R., Straif, K., Grosse, Y., Lauby-Secretan, B., El Ghissassi, F., *et al.* (2011). Preventable exposures associated with human cancers. *Journal of the National Cancer Institute*, 103(24), 1827-1839.
- Compton, C. C. (2007). Optimal pathologic staging: defining stage II disease. *Clinical Cancer Research*, 13(22), 6862s-6870s.

- Davies, R. J., Miller, R., & Coleman, N. (2005). Colorectal cancer screening: prospects for molecular stool analysis. *Nature Reviews Cancer*, 5(3), 199.
- De Jong, A. E., Morreau, H., Nagengast, F. M., Mathus-Vliegen, E. M., Kleibeuker, J. H., Griffioen, G., *et al.* (2005). Prevalence of adenomas among young individuals at average risk for colorectal cancer. *The American Journal of Gastroenterology*, 100(1), 139.
- de Sousa, E., Walter, L. T., Higa, G. S. V., Casado, O. A. N., & Kihara, A. H. (2013). Developmental and functional expression of miRNA-stability related genes in the nervous system. *PLoS One*, 8(5), e56908.
- de Souza, R. J., Mente, A., Maroleanu, A., Cozma, A. I., Ha, V., Kishibe, T., *et al.* (2015). Intake of saturated and trans unsaturated fatty acids and risk of all cause mortality, cardiovascular disease, and type 2 diabetes: systematic review and meta-analysis of observational studies. *BMJ*, 351, h3978. doi:10.1136/bmj.h3978
- Di Como, J. A., Mahendraraj, K., Lau, C. S., & Chamberlain, R. S. (2015). Adenosquamous carcinoma of the colon and rectum: a population based clinical outcomes study involving 578 patients from the Surveillance Epidemiology and End Result (SEER) database (1973-2010). *Journal of the American College of Surgeons*, 221(4), e56.
- Dimberg, J., Hong, T. T., Skarstedt, M., Löfgren, S., Zar, N., & Matussek, A. (2013). Detection of cytomegalovirus DNA in colorectal tissue from Swedish and Vietnamese patients with colorectal cancer. *Anticancer research*, 33(11), 4947-4950.
- Donovan, M. G., Selmin, O. I., Doetschman, T. C., & Romagnolo, D. F. (2017). Mediterranean Diet: Prevention of Colorectal Cancer. *Frontiers in nutrition*, 4, 59.
- Duran, A. O., Karaca, H., Besiroglu, M., Bayoglu, I. V., Menekse, S., Yapici, H. S., *et al.* (2014). XELOX plus bevacizumab vs. FOLFIRI plus bevacizumab treatment for first-line chemotherapy in metastatic colon cancer: a retrospective study of the Anatolian Society of Medical Oncology. *Asian Pac J Cancer Prev*, 15(23), 10375-10379. doi:10.7314/apjcp.2014.15.23.10375
- Edge, S. B. (2010). AJCC cancer staging manual. *Springer*, 7, 97-100.
- Elmadfa, I., & Kornsteiner, M. (2009). Fats and fatty acid requirements for adults. *Ann Nutr Metab*, 55(1-3), 56-75. doi:10.1159/000228996
- Eser, S., Chang, J., Charalambous, H., Silverman, B., Demetriou, A., Yakut, C., *et al.* (2018). Incidence patterns of colorectal cancers in four countries of the Middle East Cancer Consortium (Cyprus, Jordan, Israel, and Izmir, Turkey) compared with those in the United States Surveillance, Epidemiology, and End Results Program. *Turk J Gastroenterol*, 29(1), 36-44. doi:10.5152/tjg.2018.17263
- Finucane, M. M., Stevens, G. A., Cowan, M. J., Danaei, G., Lin, J. K., Paciorek, C. J., *et al.* (2011). National, regional, and global trends in body-mass index since 1980: systematic analysis of health examination surveys and epidemiological studies with 960 country-years and 9.1 million participants. *Lancet*, 377(9765), 557-567. doi:10.1016/S0140-6736(10)62037-5
- Fund, W. C. R., & Research, A. I. f. C. (2007). *Food, nutrition, physical activity, and the prevention of cancer: a global perspective* (Vol. 1): Amer Inst for Cancer Research.

- Gado, A., Ebeid, B., Abdelmohsen, A., & Axon, A. (2014). Colorectal cancer in Egypt is commoner in young people: Is this cause for alarm? *Alexandria Journal of Medicine*, 50(3), 197-201. doi:<https://doi.org/10.1016/j.ajme.2013.03.003>
- Ghazzawi, H. A., & Al-Ismail, K. (2017). A Comprehensive Study on the Effect of Roasting and Frying on Fatty Acids Profiles and Antioxidant Capacity of Almonds, Pine, Cashew, and Pistachio. *Journal of Food Quality*, 2017, 9038257. doi:10.1155/2017/9038257
- Ghorbanoghli, Z., Jabari, C., Sweidan, W., Hammoudeh, W., Cortas, G., Sharara, A. I., *et al.* (2018). A new hereditary colorectal cancer network in the Middle East and eastern mediterranean countries to improve care for high-risk families. *Fam Cancer*, 17(2), 209-212. doi:10.1007/s10689-017-0018-6
- Gilsing, A. M., Fransen, F., de Kok, T. M., Goldbohm, A. R., Schouten, L. J., de Bruine, A. P., *et al.* (2013). Dietary heme iron and the risk of colorectal cancer with specific mutations in KRAS and APC. *Carcinogenesis*, 34(12), 2757-2766. doi:10.1093/carcin/bgt290
- Giovannucci, E. (2001). An updated review of the epidemiological evidence that cigarette smoking increases risk of colorectal cancer. *Cancer Epidemiology and Prevention Biomarkers*, 10(7), 725-731.
- Giovannucci, E. (2002). Modifiable risk factors for colon cancer. *Gastroenterol Clin North Am*, 31(4), 925-943.
- Gomez, S. L., Hurley, S., Canchola, A. J., Keegan, T. H., Cheng, I., Murphy, J. D., *et al.* (2016). Effects of marital status and economic resources on survival after cancer: A population-based study. *Cancer*, 122(10), 1618-1625. doi:10.1002/cncr.29885
- Gospodarowicz, M. K., Brierley, J. D., & Wittekind, C. (2017). *TNM classification of malignant tumours*: John Wiley & Sons.
- Grun, I. U., Adhikari, K., Li, C., Li, Y., Lin, B., Zhang, J., *et al.* (2001). Changes in the profile of genistein, daidzein, and their conjugates during thermal processing of tofu. *J Agric Food Chem*, 49(6), 2839-2843. doi:10.1021/jf010028+
- Guo, Y. S., Narayan, S., Yallampalli, C., & Singh, P. (1992). Characterization of insulinlike growth factor I receptors in human colon cancer. *Gastroenterology*, 102(4 Pt 1), 1101-1108.
- Guthold, R., Louazani, S. A., Riley, L. M., Cowan, M. J., Bovet, P., Damasceno, A., *et al.* (2011). Physical activity in 22 African countries: results from the World Health Organization STEPwise approach to chronic disease risk factor surveillance. *Am J Prev Med*, 41(1), 52-60. doi:10.1016/j.amepre.2011.03.008
- Haftenberger, M., Schuit, A. J., Tormo, M. J., Boeing, H., Wareham, N., Bueno-de-Mesquita, H. B., *et al.* (2002). Physical activity of subjects aged 50-64 years involved in the European Prospective Investigation into Cancer and Nutrition (EPIC). *Public Health Nutr*, 5(6B), 1163-1176. doi:10.1079/PHN2002397
- Hajmanoochehri, F., Asefzadeh, S., Kazemifar, A. M., & Ebtehaj, M. (2014). Clinicopathological features of colon adenocarcinoma in Qazvin, Iran: a 16 year study. *Asian Pac J Cancer Prev*, 15(2), 951-955. doi:10.7314/apjcp.2014.15.2.951
- Han, Y., Chen, W., Li, P., & Ye, J. (2015). Association Between Coeliac Disease and Risk of Any Malignancy and Gastrointestinal Malignancy: A Meta-Analysis. *Medicine (Baltimore)*, 94(38), e1612. doi:10.1097/MD.0000000000001612

- Hang, J., Cai, B., Xue, P., Wang, L., Hu, H., Zhou, Y., *et al.* (2015). The Joint Effects of Lifestyle Factors and Comorbidities on the Risk of Colorectal Cancer: A Large Chinese Retrospective Case-Control Study. *PLoS One*, 10(12), e0143696. doi:10.1371/journal.pone.0143696
- Harris, R. E. (2015). *Global epidemiology of cancer*: Jones & Bartlett Publishers.
- Harriss, D., Atkinson, G., Batterham, A., George, K., Tim Cable, N., Reilly, T., *et al.* (2009). Lifestyle factors and colorectal cancer risk (2): a systematic review and meta-analysis of associations with leisure-time physical activity. *Colorectal Disease*, 11(7), 689-701.
- Hermsen, M., Postma, C., Baak, J., Weiss, M., Rapallo, A., Sciutto, A., *et al.* (2002). Colorectal adenoma to carcinoma progression follows multiple pathways of chromosomal instability. *Gastroenterology*, 123(4), 1109-1119.
- Hernandez, A. R., Boada, L. D., Almeida-Gonzalez, M., Mendoza, Z., Ruiz-Suarez, N., Valeron, P. F., *et al.* (2015). An estimation of the carcinogenic risk associated with the intake of multiple relevant carcinogens found in meat and charcuterie products. *Sci Total Environ*, 514, 33-41. doi:10.1016/j.scitotenv.2015.01.108
- Howsam, M., Grimalt, J. O., Guino, E., Navarro, M., Marti-Rague, J., Peinado, M. A., *et al.* (2004). Organochlorine exposure and colorectal cancer risk. *Environ Health Perspect*, 112(15), 1460-1466. doi:10.1289/ehp.7143
- Hsiao, C. W., Huang, W. Y., Ke, T. W., Muo, C. H., Chen, W. T., Sung, F. C., *et al.* (2014). Association between irritable bowel syndrome and colorectal cancer: a nationwide population-based study. *Eur J Intern Med*, 25(1), 82-86. doi:10.1016/j.ejim.2013.11.005
- Hu, T., Li, L. F., Shen, J., Zhang, L., & Cho, C. H. (2015). Chronic inflammation and colorectal cancer: the role of vascular endothelial growth factor. *Curr Pharm Des*, 21(21), 2960-2967.
- Hughes, L. A., Simons, C. C., van den Brandt, P. A., van Engeland, M., & Weijenberg, M. P. (2017). Lifestyle, Diet, and Colorectal Cancer Risk According to (Epi) genetic Instability: Current Evidence and Future Directions of Molecular Pathological Epidemiology. *Current colorectal cancer reports*, 13(6), 455-469.
- Huncharek, M., Muscat, J., & Kupelnick, B. (2009). Colorectal cancer risk and dietary intake of calcium, vitamin D, and dairy products: a meta-analysis of 26,335 cases from 60 observational studies. *Nutr Cancer*, 61(1), 47-69. doi:10.1080/01635580802395733
- IARC, I. A. f. R. o. C. (2020a). Cancer Today. Retrieved from [https://gco.iarc.fr/today/online-analysis-table?v=2020&mode=cancer&mode\\_population=continents&population=900&populations=900&key=asr&sex=0&cancer=39&type=0&statistic=5&prevalence=0&population\\_group=0&ages\\_group%5B%5D=0&ages\\_group%5B%5D=17&group\\_cancer=1&include\\_nmssc=1&include\\_nmssc\\_other=1](https://gco.iarc.fr/today/online-analysis-table?v=2020&mode=cancer&mode_population=continents&population=900&populations=900&key=asr&sex=0&cancer=39&type=0&statistic=5&prevalence=0&population_group=0&ages_group%5B%5D=0&ages_group%5B%5D=17&group_cancer=1&include_nmssc=1&include_nmssc_other=1)
- IARC, I. A. f. R. o. C. (2020b). Cancer Tomorrow. Retrieved from [https://gco.iarc.fr/tomorrow/en/dataviz/isotype?cancers=8\\_9\\_10&single\\_unit=50000&group\\_cancers=1&multiple\\_cancers=1](https://gco.iarc.fr/tomorrow/en/dataviz/isotype?cancers=8_9_10&single_unit=50000&group_cancers=1&multiple_cancers=1)
- Imai, K., & Yamamoto, H. (2008). Carcinogenesis and microsatellite instability: the interrelationship between genetics and epigenetics. *Carcinogenesis*, 29(4), 673-680. doi:10.1093/carcin/bgm228

- Inamura, K. (2018). Colorectal Cancers: An Update on Their Molecular Pathology. *Cancers*, 10(1), 26.
- Inoue, I., Kato, J., Tamai, H., Iguchi, M., Maekita, T., Yoshimura, N., *et al.* (2014). Helicobacter pylori-related chronic gastritis as a risk factor for colonic neoplasms. *World J Gastroenterol*, 20(6), 1485-1492. doi:10.3748/wjg.v20.i6.1485
- 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:10.1371/journal.pone.0074616
- Jawad, N., Direkze, N., & Leedham, S. J. (2011). Inflammatory bowel disease and colon cancer. *Recent Results Cancer Res*, 185, 99-115. doi:10.1007/978-3-642-03503-6\_6
- Jeter, J. M., Kohlmann, W., & Gruber, S. B. (2006). Genetics of colorectal cancer. *Genetic testing*, 14(4), 16.
- Johns, L. E., & Houlston, R. S. (2001). A systematic review and meta-analysis of familial colorectal cancer risk. *The American Journal of Gastroenterology*, 96(10), 2992-3003.
- Johnson, C. M., Wei, C., Ensor, J. E., Smolenski, D. J., Amos, C. I., Levin, B., *et al.* (2013). Meta-analyses of colorectal cancer risk factors. *Cancer causes & control*, 24(6), 1207-1222.
- Jung, U. J., & Choi, M.-S. (2014). Obesity and its metabolic complications: the role of adipokines and the relationship between obesity, inflammation, insulin resistance, dyslipidemia and nonalcoholic fatty liver disease. *International journal of molecular sciences*, 15(4), 6184-6223.
- Karamchandani, D. M., Chetty, R., King, T. S., Liu, X., Westerhoff, M., Yang, Z., *et al.* (2020). Challenges with colorectal cancer staging: results of an international study. *Mod Pathol*, 33(1), 153-163. doi:10.1038/s41379-019-0344-3
- Katsidzira, L., Gangaidzo, I. T., Makunike-Mutasa, R., Manyanga, T., Matsena-Zingoni, Z., Thomson, S., *et al.* (2019). A case-control study of risk factors for colorectal cancer in an African population. *Eur J Cancer Prev*, 28(3), 145-150. doi:10.1097/CEJ.0000000000000439
- Keller, D. S., Windsor, A., Cohen, R., & Chand, M. (2019). Colorectal cancer in inflammatory bowel disease: review of the evidence. *Tech Coloproctol*, 23(1), 3-13. doi:10.1007/s10151-019-1926-2
- Kuhuaprema, T., & Srivatanakul, P. (2008). Colon and rectum cancer in Thailand: an overview. *Japanese journal of clinical oncology*, 38(4), 237-243.
- Kim, & Choi, G. S. (2019). Clinical Implications of Lymph Node Metastasis in Colorectal Cancer: Current Status and Future Perspectives. *Ann Coloproctol*, 35(3), 109-117. doi:10.3393/ac.2019.06.12
- Kim, Moon, H. S., Kwon, I. S., Kim, J. S., Kang, S. H., Sung, J. K., *et al.* (2020). The incidence and risk factors of sessile serrated adenomas in left side colon cancer patients after curative surgery. *Medicine (Baltimore)*, 99(29), e20799. doi:10.1097/MD.00000000000020799
- Kim, E. R., & Chang, D. K. (2014). Colorectal cancer in inflammatory bowel disease: the risk, pathogenesis, prevention and diagnosis. *World J Gastroenterol*, 20(29), 9872-9881. doi:10.3748/wjg.v20.i29.9872

- Kopacova, M., Tacheci, I., Rejchrt, S., & Bures, J. (2009). Peutz-Jeghers syndrome: diagnostic and therapeutic approach. *World journal of gastroenterology: WJG*, *15*(43), 5397.
- Kornbluth, A., & Sachar, D. B. (2004). Ulcerative colitis practice guidelines in adults (update): American College of Gastroenterology, Practice Parameters Committee. *The American Journal of Gastroenterology*, *99*(7), 1371.
- Kostic, A. D., Gevers, D., Pedamallu, C. S., Michaud, M., Duke, F., Earl, A. M., *et al.* (2012). Genomic analysis identifies association of Fusobacterium with colorectal carcinoma. *Genome Res*, *22*(2), 292-298. doi:10.1101/gr.126573.111
- Kumar, S., Burney, I. A., Zahid, K. F., PC, D. S., Belushi, M. A., Mufti, T. D., *et al.* (2015). Colorectal Cancer Patient Characteristics, Treatment and Survival in Oman--a Single Center Study. *Asian Pac J Cancer Prev*, *16*(12), 4853-4858. doi:10.7314/apjcp.2015.16.12.4853
- Kune, G. A., Kune, S., & Watson, L. F. (1990). Body weight and physical activity as predictors of colorectal cancer risk. *Nutr Cancer*, *13*(1-2), 9-17. doi:10.1080/01635589009514041
- Larsson, S. C., Orsini, N., & Wolk, A. (2005). Diabetes mellitus and risk of colorectal cancer: a meta-analysis. *J Natl Cancer Inst*, *97*(22), 1679-1687. doi:10.1093/jnci/dji375
- Larsson, S. C., & Wolk, A. (2006a). Meat consumption and risk of colorectal cancer: a meta-analysis of prospective studies. *Int J Cancer*, *119*(11), 2657-2664. doi:10.1002/ijc.22170
- Larsson, S. C., & Wolk, A. (2006b). Meat consumption and risk of colorectal cancer: a meta-analysis of prospective studies. *International journal of cancer*, *119*(11), 2657-2664.
- Lasa, J., Rausch, A., & Zubiaurre, I. (2018). Risk of colorectal adenomas in patients with celiac disease: a systematic review and meta-analysis. *Rev Gastroenterol Mex*, *83*(2), 91-97. doi:10.1016/j.rgmx.2017.05.007
- Lauby-Secretan, B., Scoccianti, C., Loomis, D., Grosse, Y., Bianchini, F., Straif, K., *et al.* (2016). Body Fatness and Cancer--Viewpoint of the IARC Working Group. *N Engl J Med*, *375*(8), 794-798. doi:10.1056/NEJMs1606602
- Le Marchand, L., Wilkens, L. R., Hankin, J. H., Kolonel, L. N., & Lyu, L. C. (1997a). A case-control study of diet and colorectal cancer in a multiethnic population in Hawaii (United States): lipids and foods of animal origin. *Cancer Causes Control*, *8*(4), 637-648. doi:10.1023/a:1018406716115
- Le Marchand, L., Wilkens, L. R., Kolonel, L. N., Hankin, J. H., & Lyu, L. C. (1997b). Associations of sedentary lifestyle, obesity, smoking, alcohol use, and diabetes with the risk of colorectal cancer. *Cancer Res*, *57*(21), 4787-4794.
- Lee, J., Shin, A., Oh, J. H., & Kim, J. (2018). The relationship between nut intake and risk of colorectal cancer: a case control study. *Nutr J*, *17*(1), 37. doi:10.1186/s12937-018-0345-y
- Lee, J. Y., Hong, S. N., Kim, J. H., Choe, W. H., Lee, S. Y., Sung, I. K., *et al.* (2013). Risk for coronary heart disease increases risk for colorectal neoplasm. *Clin Gastroenterol Hepatol*, *11*(6), 695-702. doi:10.1016/j.cgh.2012.10.017
- Lee, K.-J., Inoue, M., Otani, T., Iwasaki, M., Sasazuki, S., Tsugane, S., *et al.* (2007a). Physical activity and risk of colorectal cancer in Japanese men and women: the Japan Public Health Center-based prospective study. *Cancer causes & control*, *18*(2), 199-209.

- Lee, S., Woo, H., Lee, J., Oh, J. H., Kim, J., & Shin, A. (2019). Cigarette smoking, alcohol consumption, and risk of colorectal cancer in South Korea: A case-control study. *Alcohol*, 76, 15-21. doi:10.1016/j.alcohol.2018.06.004
- Lee, W. J., Sandler, D. P., Blair, A., Samanic, C., Cross, A. J., & Alavanja, M. C. (2007b). Pesticide use and colorectal cancer risk in the Agricultural Health Study. *Int J Cancer*, 121(2), 339-346. doi:10.1002/ijc.22635
- Leitner, J. W., Kline, T., Carel, K., Goalstone, M., & Draznin, B. (1997). Hyperinsulinemia potentiates activation of p21Ras by growth factors. *Endocrinology*, 138(5), 2211-2214. doi:10.1210/endo.138.5.5240
- Lichtenstein, G. R., Hanauer, S. B., & Sandborn, W. J. (2009). Management of Crohn's disease in adults. *The American Journal of Gastroenterology*, 104(2), 465.
- Lim, S. S., Vos, T., Flaxman, A. D., Danaei, G., Shibuya, K., Adair-Rohani, H., *et al.* (2012). A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet*, 380(9859), 2224-2260. doi:10.1016/S0140-6736(12)61766-8
- Liu, F., Mou, X., Zhao, N., Lin, J., Teng, L., & Xiang, C. (2011). Prevalence of human papillomavirus in Chinese patients with colorectal cancer. *Colorectal Disease*, 13(8), 865-871.
- Lukanova, A., Bjor, O., Kaaks, R., Lenner, P., Lindahl, B., Hallmans, G., *et al.* (2006). Body mass index and cancer: results from the Northern Sweden Health and Disease Cohort. *Int J Cancer*, 118(2), 458-466. doi:10.1002/ijc.21354
- Mafiana, R. N., Al Lawati, A. S., Waly, M. I., Al Farsi, Y., Al Kindi, M., & Al Moundhri, M. (2018). Association between Dietary and Lifestyle Indices and Colorectal Cancer in Oman: A Case-Control Study. *Asian Pac J Cancer Prev*, 19(11), 3117-3122. doi:10.31557/APJCP.2018.19.11.3117
- Marley, A. R., & Nan, H. (2016). Epidemiology of colorectal cancer. *Int J Mol Epidemiol Genet*, 7(3), 105-114.
- Marmot, M., Atinmo, T., Byers, T., Chen, J., Hirohata, T., Jackson, A., *et al.* (2007). Food, nutrition, physical activity, and the prevention of cancer: a global perspective.
- Martin, F. L., Martinez, E. Z., Stopper, H., Garcia, S. B., Uyemura, S. A., & Kannen, V. (2018). Increased exposure to pesticides and colon cancer: Early evidence in Brazil. *Chemosphere*, 209, 623-631. doi:10.1016/j.chemosphere.2018.06.118
- Marusyk, A., Almendro, V., & Polyak, K. (2012). Intra-tumour heterogeneity: a looking glass for cancer? *Nat Rev Cancer*, 12(5), 323-334. doi:10.1038/nrc3261
- McCleary, N. J., Niedzwiecki, D., Hollis, D., Saltz, L. B., Schaefer, P., Whittom, R., *et al.* (2010). Impact of smoking on patients with stage III colon cancer: results from Cancer and Leukemia Group B 89803. *Cancer*, 116(4), 957-966. doi:10.1002/cncr.24866
- McClements, P. L., Madurasinghe, V., Thomson, C. S., Fraser, C. G., Carey, F. A., Steele, R. J., *et al.* (2012). Impact of the UK colorectal cancer screening pilot studies on incidence, stage distribution and mortality trends. *Cancer Epidemiol*, 36(4), e232-242. doi:10.1016/j.canep.2012.02.006

- Merom, D., Sinnreich, R., Aboudi, V., Kark, J. D., & Nassar, H. (2012). Lifestyle physical activity among urban Palestinians and Israelis: a cross-sectional comparison in the Palestinian-Israeli Jerusalem risk factor study. *BMC Public Health*, 12, 90. doi:10.1186/1471-2458-12-90
- Metwally, I. H., Shetiwy, M., Elalfy, A. F., Abouzid, A., Saleh, S. S., & Hamdy, M. (2018). Epidemiology and survival of colon cancer among Egyptians: a retrospective study %J Journal of Coloproctology (Rio de Janeiro). 38, 24-29.
- Migliore, L., Migheli, F., Spisni, R., & Coppede, F. (2011). Genetics, cytogenetics, and epigenetics of colorectal cancer. *J Biomed Biotechnol*, 2011, 792362. doi:10.1155/2011/792362
- Moccia, F., Tolone, S., Allaria, A., Napolitano, V., Rosa, D., Ilaria, F., et al. (2019). Lymph Node Ratio Versus TNM System As Prognostic Factor in Colorectal Cancer Staging. a Single Center Experience. *Open Med (Wars)*, 14, 523-531. doi:10.1515/med-2019-0058
- MOH. (2019). Health Annual Report, Palestine, 2018. Retrieved from [http://site.moh.ps/Content/Books/fE4zsafxsjNVhJntidJnqnnEHUibMuC1NYu66TNEmoNUJ1ZxeRcCm3\\_Iei1j8d4YesYKxRyEhD6PZqdxzBa4z91plhALGXoDGEhlEIPai9X9O.pdf](http://site.moh.ps/Content/Books/fE4zsafxsjNVhJntidJnqnnEHUibMuC1NYu66TNEmoNUJ1ZxeRcCm3_Iei1j8d4YesYKxRyEhD6PZqdxzBa4z91plhALGXoDGEhlEIPai9X9O.pdf)
- MOH. (2020). Health Annual Report, Palestine, 2019. Retrieved from [http://site.moh.ps/Content/Books/HYM2UGrm8hFDOPe1AW6z2W6ZDvbJbuYGykdfV6B11Eulthrx5QMAyC\\_5WFKDTWWGKW3O7rk4vgIUzRlhJdSYyQXxFKscP6Uqz3UhrxoWLC\\_HIT.pdf](http://site.moh.ps/Content/Books/HYM2UGrm8hFDOPe1AW6z2W6ZDvbJbuYGykdfV6B11Eulthrx5QMAyC_5WFKDTWWGKW3O7rk4vgIUzRlhJdSYyQXxFKscP6Uqz3UhrxoWLC_HIT.pdf)
- Mohammad Al-Ismail, K., & Aburjai, T. (2004). Antioxidant activity of water and alcohol extracts of chamomile flowers, anise seeds and dill seeds. 84(2), 173-178. doi:<https://doi.org/10.1002/jsfa.1625>
- Morales, M. I., Sen, F., Polat, B., Kleine, P., & Buck, A. (2020). T-Staging and Target Volume Definition by Imaging in GI Tumors. In R. G. H. Beets-Tan, W. J. G. Oyen, & V. Valentini (Eds.), *Imaging and Interventional Radiology for Radiation Oncology* (pp. 203-220). Cham: Springer International Publishing.
- Mou, X., Chen, L., Liu, F., Lin, J., Diao, P., Wang, H., et al. (2012). Prevalence of JC virus in Chinese patients with colorectal cancer. *PLoS One*, 7(5), e35900.
- Murphy, T. K., Calle, E. E., Rodriguez, C., Kahn, H. S., & Thun, M. J. (2000). Body mass index and colon cancer mortality in a large prospective study. *Am J Epidemiol*, 152(9), 847-854.
- Nagai, Y., Hata, K., Kawai, K., Murono, K., Yasuda, K., Otani, K., et al. (2016). Clinicopathological Features of Colorectal Cancer Patients Under the Age of 50: Recent Experience and Case-Control Study of Prognosis in a Japanese Cohort. *Digestion*, 93(4), 272-279. doi:10.1159/000446344
- Nashar, R. M., & Almurshed, K. S. (2008). Colorectal cancer: a case control study of dietary factors, king faisal specialist hospital and research center, riyadh, saudi arabia. *J Family Community Med*, 15(2), 57-64.
- Nimri, D. A. A.-S. D. O., & Halasa, D. M. A.-Z. D. K. A. D. W. (2012). *Jordan cancer registry: cancer incidence in jordan 2012*: ministry of health

- Nistal, E., Fernandez-Fernandez, N., Vivas, S., & Olcoz, J. L. (2015). Factors Determining Colorectal Cancer: The Role of the Intestinal Microbiota. *Front Oncol*, 5, 220. doi:10.3389/fonc.2015.00220
- Nordenvall, C., Nyren, O., & Ye, W. (2006). Elevated anal squamous cell carcinoma risk associated with benign inflammatory anal lesions. *Gut*, 55(5), 703-707. doi:10.1136/gut.2005.070201
- Norgaard, M., Farkas, D. K., Pedersen, L., Erichsen, R., de la Cour, Z. D., Gregersen, H., *et al.* (2011). Irritable bowel syndrome and risk of colorectal cancer: a Danish nationwide cohort study. *Br J Cancer*, 104(7), 1202-1206. doi:10.1038/bjc.2011.65
- O'Neill, C. B., Atoria, C. L., O'Reilly, E. M., LaFemina, J., Henman, M. C., & Elkin, E. B. (2012). Costs and trends in pancreatic cancer treatment. *Cancer*, 118(20), 5132-5139. doi:10.1002/cncr.27490
- O'Connell, J. B., Maggard, M. A., & Ko, C. Y. (2004). Colon cancer survival rates with the new American Joint Committee on Cancer sixth edition staging. *Journal of the National Cancer Institute*, 96(19), 1420-1425.
- Ogino, S., Kawasaki, T., Ogawa, A., Kirkner, G. J., Loda, M., & Fuchs, C. S. (2007). Fatty acid synthase overexpression in colorectal cancer is associated with microsatellite instability, independent of CpG island methylator phenotype. *Hum Pathol*, 38(6), 842-849. doi:10.1016/j.humpath.2006.11.018
- Ogino, S., & Stampfer, M. (2010). Lifestyle factors and microsatellite instability in colorectal cancer: the evolving field of molecular pathological epidemiology. In: Oxford University Press.
- Ong, M. L., & Schofield, J. B. (2016). Assessment of lymph node involvement in colorectal cancer. *World J Gastrointest Surg*, 8(3), 179-192. doi:10.4240/wjgs.v8.i3.179
- Panato, C., Abusamaan, K., Bidoli, E., Hamdi-Cherif, M., Pierannunzio, D., Ferretti, S., *et al.* (2018). Survival after the diagnosis of breast or colorectal cancer in the GAZA Strip from 2005 to 2014. *BMC Cancer*, 18(1), 632. doi:10.1186/s12885-018-4552-x
- PCBS, P. C. B. o. S. (2012). *The Palestinian Central Bureau of Statistics (PCBS) and the Ministry of Health (MoH) are issuing a Press Release on the occasion of International Day of Giving up Smoking (Word No Tobacco Day) on 31/5/2012*. Retrieved from [http://www.pcbs.gov.ps/Portals/\\_pcbs/PressRelease/MoH&PCBSSmoke2012E.pdf](http://www.pcbs.gov.ps/Portals/_pcbs/PressRelease/MoH&PCBSSmoke2012E.pdf)
- PCBS, P. C. B. o. S. (2019). *Palestinians at the End of 2019*. Retrieved from <http://www.pcbs.gov.ps/Downloads/book2497.pdf>
- Pelucchi, C., Tramacere, I., Boffetta, P., Negri, E., & Vecchia, C. L. (2011). Alcohol consumption and cancer risk. *Nutrition and cancer*, 63(7), 983-990.
- Pereyra, L., Gonzalez, R., Mohaidle, A., Fischer, C., Mella, J. M., Panigadi, G. N., *et al.* (2013). Risk of colorectal neoplasia in patients with celiac disease: a multicenter study. *J Crohns Colitis*, 7(12), e672-677. doi:10.1016/j.crohns.2013.06.005
- Peters, U., Jiao, S., Schumacher, F. R., Hutter, C. M., Aragaki, A. K., Baron, J. A., *et al.* (2013). Identification of genetic susceptibility loci for colorectal tumors in a genome-wide meta-analysis. *Gastroenterology*, 144(4), 799-807. e724.

- Peters, U., Sinha, R., Chatterjee, N., Subar, A. F., Ziegler, R. G., Kulldorff, M., *et al.* (2003). Dietary fibre and colorectal adenoma in a colorectal cancer early detection programme. *The Lancet*, 361(9368), 1491-1495.
- Piskol, R., & de Sousa, E. M. F. (2020). Colon Cancer Heterogeneity: Welcome to the RiboZone. *Cell Stem Cell*, 26(6), 797-799. doi:10.1016/j.stem.2020.05.005
- Poynter, J. N., Haile, R. W., Siegmund, K. D., Campbell, P. T., Figueiredo, J. C., Limburg, P., *et al.* (2009). Associations between smoking, alcohol consumption, and colorectal cancer, overall and by tumor microsatellite instability status. *Cancer Epidemiology and Prevention Biomarkers*, 18(10), 2745-2750.
- Qumseya, B. J., Tayem, Y. I., Dasa, O. Y., Nahhal, K. W., Abu-Limon, I. M., Hmidat, A. M., *et al.* (2014). Barriers to colorectal cancer screening in Palestine: a national study in a medically underserved population. *Clin Gastroenterol Hepatol*, 12(3), 463-469. doi:10.1016/j.cgh.2013.08.051
- Ramsey, S. D., Yoon, P., Moonesinghe, R., & Khoury, M. J. (2006). Population-based study of the prevalence of family history of cancer: implications for cancer screening and prevention. *Genetics in Medicine*, 8(9), 571.
- Rawla, P., Sunkara, T., & Barsouk, A. (2019). Epidemiology of colorectal cancer: incidence, mortality, survival, and risk factors. *Prz Gastroenterol*, 14(2), 89-103. doi:10.5114/pg.2018.81072
- Recio-Boiles, A., & Cagir, B. (2018). Cancer, Colon. In *StatPearls*. Treasure Island (FL).
- Reedy, J., Mitrou, P., Krebs-Smith, S., Wirfält, E., Flood, A., Kipnis, V., *et al.* (2008). Index-based dietary patterns and risk of colorectal cancer: the NIH-AARP Diet and Health Study. *American journal of epidemiology*, 168(1), 38-48.
- Ries, L., Melbert, D., Krapcho, M., Stinchcomb, D., Howlander, N., Horner, M., *et al.* (2008). SEER Cancer Statistics Review. National Cancer Institute; Bethesda, MD: 1975–2005. In.
- Rosato, V., Guercio, V., Bosetti, C., Negri, E., Serraino, D., Giacosa, A., *et al.* (2016). Mediterranean diet and colorectal cancer risk: a pooled analysis of three Italian case-control studies. *British journal of cancer*, 115(7), 862.
- Rossello-Tortella, M., Llinas-Arias, P., Sakaguchi, Y., Miyauchi, K., Davalos, V., Setien, F., *et al.* (2020). Epigenetic loss of the transfer RNA-modifying enzyme TYW2 induces ribosome frameshifts in colon cancer. *Proc Natl Acad Sci U S A*, 117(34), 20785-20793. doi:10.1073/pnas.2003358117
- Russo, A., Franceschi, S., La Vecchia, C., Dal Maso, L., Montella, M., Conti, E., *et al.* (1998). Body size and colorectal-cancer risk. *Int J Cancer*, 78(2), 161-165.
- Sadanandam, A., Lyssiotis, C. A., Homicsko, K., Collisson, E. A., Gibb, W. J., Wullschleger, S., *et al.* (2013). A colorectal cancer classification system that associates cellular phenotype and responses to therapy. *Nature medicine*, 19(5), 619.
- Samad, A. K., Taylor, R. S., Marshall, T., & Chapman, M. A. (2005). A meta-analysis of the association of physical activity with reduced risk of colorectal cancer. *Colorectal Dis*, 7(3), 204-213. doi:10.1111/j.1463-1318.2005.00747.x

- Santarelli, R. L., Pierre, F., & Corpet, D. E. (2008). Processed meat and colorectal cancer: a review of epidemiologic and experimental evidence. *Nutr Cancer*, 60(2), 131-144. doi:10.1080/01635580701684872
- SEER. (2017). Cancer Stat Facts: Colorectal Cancer. Retrieved from <https://seer.cancer.gov/statfacts/html/colorect.html>
- Seretis, A., Cividini, S., Markozannes, G., Tseretopoulou, X., Lopez, D. S., Ntzani, E. E., *et al.* (2019). Association between blood pressure and risk of cancer development: a systematic review and meta-analysis of observational studies. *Scientific Reports*, 9(1), 8565. doi:10.1038/s41598-019-45014-4
- Shamseddine, A., Saleh, A., Charafeddine, M., Seoud, M., Mukherji, D., Temraz, S., *et al.* (2014). Cancer trends in Lebanon: a review of incidence rates for the period of 2003-2008 and projections until 2018. *Popul Health Metr*, 12(1), 4. doi:10.1186/1478-7954-12-4
- Shannon, J., White, E., Shattuck, A. L., & Potter, J. D. (1996). Relationship of food groups and water intake to colon cancer risk. *Cancer Epidemiol Biomarkers Prev*, 5(7), 495-502.
- Sharkas, G. F., Arqoub, K. H., Khader, Y. S., Tarawneh, M. R., Nimri, O. F., Al-Zaghal, M. J., *et al.* (2017). Colorectal Cancer in Jordan: Survival Rate and Its Related Factors. *J Oncol*, 2017, 3180762. doi:10.1155/2017/3180762
- Shivappa, N., Godos, J., Hebert, J. R., Wirth, M. D., Piuri, G., Speciani, A. F., *et al.* (2017). Dietary Inflammatory Index and Colorectal Cancer Risk-A Meta-Analysis. *Nutrients*, 9(9). doi:10.3390/nu9091043
- Shpitz, B., Millman, M., Ziv, Y., Klein, E., Grankin, M., Gochberg, S., *et al.* (2006). Predominance of younger age, advanced stage, poorly-differentiated and mucinous histology in Israeli Arab patients with colorectal cancer. *Anticancer Res*, 26(1B), 533-537.
- Siegel, R. L., Ma, J., Zou, Z., & Jemal, A. (2014). Cancer statistics, 2014. 64(1), 9-29. doi:<https://doi.org/10.3322/caac.21208>
- Siegel, R. L., Miller, K. D., Goding Sauer, A., Fedewa, S. A., Butterly, L. F., Anderson, J. C., *et al.* (2020). Colorectal cancer statistics, 2020. *CA Cancer J Clin*, 70(3), 145-164. doi:10.3322/caac.21601
- Siegel, R. L., Miller, K. D., & Jemal, A. (2015). Cancer statistics, 2015. *CA: a cancer journal for clinicians*, 65(1), 5-29.
- Sinha, R. (2002). An epidemiologic approach to studying heterocyclic amines. *Mutat Res*, 506-507, 197-204.
- Slattery, M. L. (2004). Physical activity and colorectal cancer. *Sports Med*, 34(4), 239-252. doi:10.2165/00007256-200434040-00004
- Slattery, M. L., Curtin, K., Anderson, K., Ma, K.-N., Ballard, L., Edwards, S., *et al.* (2000). Associations between cigarette smoking, lifestyle factors, and microsatellite instability in colon tumors. *Journal of the National Cancer Institute*, 92(22), 1831-1836.
- Smith, G., Carey, F. A., Beattie, J., Wilkie, M. J. V., Lightfoot, T. J., Coxhead, J., *et al.* (2002). Mutations in APC, Kirsten-ras, and p53—alternative genetic pathways to colorectal cancer. *Proceedings of the National Academy of Sciences*, 99(14), 9433. doi:10.1073/pnas.122612899

- Snover, D. C. (2011). Update on the serrated pathway to colorectal carcinoma. *Hum Pathol*, 42(1), 1-10. doi:10.1016/j.humpath.2010.06.002
- Snyder, C., & Hampel, H. (2019). Hereditary Colorectal Cancer Syndromes. *Seminars in Oncology Nursing*, 35(1), 58-78. doi:<https://doi.org/10.1016/j.soncn.2018.12.011>
- Solomon, C. H., Pho, L. N., & Burt, R. W. (2002). Current status of genetic testing for colorectal cancer susceptibility. *Oncology (Williston Park, NY)*, 16(2), 161-171; discussion 176, 179-180.
- Song, N., Pogue-Geile, K. L., Gavin, P. G., Yothers, G., Kim, S. R., Johnson, N. L., *et al.* (2016). Clinical outcome from oxaliplatin treatment in stage II/III colon cancer according to intrinsic subtypes: secondary analysis of NSABP C-07/NRG oncology randomized clinical trial. *JAMA oncology*, 2(9), 1162-1169.
- Stidham, R. W., & Higgins, P. D. R. (2018). Colorectal Cancer in Inflammatory Bowel Disease. *Clin Colon Rectal Surg*, 31(3), 168-178. doi:10.1055/s-0037-1602237
- Stigliano, V., Sanchez-Mete, L., Martayan, A., & Anti, M. (2014). Early-onset colorectal cancer: a sporadic or inherited disease? *World journal of gastroenterology: WJG*, 20(35), 12420.
- Stintzing, F. C., Hoffmann, M., & Carle, R. (2006). Thermal degradation kinetics of isoflavone aglycones from soy and red clover. *Mol Nutr Food Res*, 50(4-5), 373-377. doi:10.1002/mnfr.200500187
- Sturmer, T., Buring, J. E., Lee, I. M., Gaziano, J. M., & Glynn, R. J. (2006). Metabolic abnormalities and risk for colorectal cancer in the physicians' health study. *Cancer Epidemiol Biomarkers Prev*, 15(12), 2391-2397. doi:10.1158/1055-9965.EPI-06-0391
- Suphakarn, V. S., Newberne, P. M., & Goldman, M. (1983). Vitamin A and aflatoxin: effect on liver and colon cancer. *Nutrition and cancer*, 5(1), 41-50. doi:10.1080/01635588309513777
- Swanton, C. (2012). Intratumor heterogeneity: evolution through space and time. *Cancer Res*, 72(19), 4875-4882. doi:10.1158/0008-5472.CAN-12-2217
- Tabung, F. K., Brown, L. S., & Fung, T. T. (2017). Dietary Patterns and Colorectal Cancer Risk: A Review of 17 Years of Evidence (2000-2016). *Curr Colorectal Cancer Rep*, 13(6), 440-454. doi:10.1007/s11888-017-0390-5
- Talley, N. J., Phillips, S. F., Wiltgen, C. M., Zinsmeister, A. R., & Melton, L. J., 3rd. (1990). Assessment of functional gastrointestinal disease: the bowel disease questionnaire. *Mayo Clin Proc*, 65(11), 1456-1479. doi:10.1016/s0025-6196(12)62169-7
- Tayyem, R. F., Bawadi, H. A., Shehadah, I., Agraib, L. M., AbuMweis, S. S., Al-Jaberi, T., *et al.* (2017). Dietary patterns and colorectal cancer. *Clin Nutr*, 36(3), 848-852. doi:10.1016/j.clnu.2016.04.029
- Thanikachalam, K., & Khan, G. (2019). Colorectal Cancer and Nutrition. *Nutrients*, 11(1). doi:10.3390/nu11010164
- Thomsen, M., Skovlund, E., Sorbye, H., Bolstad, N., Nustad, K. J., Glimelius, B., *et al.* (2018). Prognostic role of carcinoembryonic antigen and carbohydrate antigen 19-9 in

metastatic colorectal cancer: a BRAF-mutant subset with high CA 19-9 level and poor outcome. *Br J Cancer*, 118(12), 1609-1616. doi:10.1038/s41416-018-0115-9

- Tian, Y., Kharazmi, E., Sundquist, K., Sundquist, J., Brenner, H., & Fallah, M. (2019). Familial colorectal cancer risk in half siblings and siblings: nationwide cohort study. *364*, 1803. doi:10.1136/bmj.1803 %J BMJ
- Tjalsma, H., Boleij, A., Marchesi, J. R., & Dutilh, B. E. (2012). A bacterial driver-passenger model for colorectal cancer: beyond the usual suspects. *Nat Rev Microbiol*, 10(8), 575-582. doi:10.1038/nrmicro2819
- Triantafyllidis, J. K., Nasioulas, G., & Kosmidis, P. A. (2009). Colorectal cancer and inflammatory bowel disease: epidemiology, risk factors, mechanisms of carcinogenesis and prevention strategies. *Anticancer Res*, 29(7), 2727-2737.
- Tuan, J., & Chen, Y.-X. (2016). Dietary and lifestyle factors associated with colorectal cancer risk and interactions with microbiota: fiber, red or processed meat and alcoholic drinks. *Gastrointestinal tumors*, 3(1), 17-24.
- Tucktuck, M., Ghandour, R., & Abu-Rmeileh, N. M. E. (2017). Waterpipe and cigarette tobacco smoking among Palestinian university students: a cross-sectional study. *BMC Public Health*, 18(1), 1. doi:10.1186/s12889-017-4524-0
- Ubink, I., van Eden, W. J., Snaebjornsson, P., Kok, N. F. M., van Kuik, J., van Grevenstein, W. M. U., *et al.* (2018). Histopathological and molecular classification of colorectal cancer and corresponding peritoneal metastases. *Br J Surg*, 105(2), e204-e211. doi:10.1002/bjs.10788
- USDA. (2021). My Plate. Retrieved from <https://www.myplate.gov/myplate-plan>
- Vulcan, A., Manjer, J., & Ohlsson, B. (2017). High blood glucose levels are associated with higher risk of colon cancer in men: a cohort study. *BMC Cancer*, 17(1), 842. doi:10.1186/s12885-017-3874-4
- Wang, L., Wilson, S. E., Stewart, D. B., & Hollenbeak, C. S. (2011). Marital status and colon cancer outcomes in US Surveillance, Epidemiology and End Results registries: does marriage affect cancer survival by gender and stage? *Cancer Epidemiol*, 35(5), 417-422. doi:10.1016/j.canep.2011.02.004
- Wang, S. C., Schulman-Marcus, J., Fantauzzi, J., Bevington, T., Sayegh, A., Lee, E., *et al.* (2019a). Colon cancer laterality is associated with atherosclerosis and coronary artery disease. *J Gastrointest Oncol*, 10(1), 30-36. doi:10.21037/jgo.2018.09.18
- Wang, X., O'Connell, K., Jeon, J., Song, M., Hunter, D., Hoffmeister, M., *et al.* (2019b). Combined effect of modifiable and non-modifiable risk factors for colorectal cancer risk in a pooled analysis of 11 population-based studies. *BMJ Open Gastroenterol*, 6(1), e000339. doi:10.1136/bmjgast-2019-000339
- Watson, P., Lin, K. M., Rodriguez-Bigas, M. A., Smyrk, T., Lemon, S., Shashidharan, M., *et al.* (1998). Colorectal carcinoma survival among hereditary nonpolyposis colorectal carcinoma family members. *Cancer*, 83(2), 259-266.
- Watts, M., Lee, T., & Aidy, H. (2016). Pesticides and Agroecology in the Occupied West Bank.

- WCRF, W. C. R. F. I. (2018). Diet, Nutrition, Physical Activity and Cancer: a Global Perspective-The Third Expert Report. Retrieved from <https://www.wcrf.org/dietandcancer>
- Weerakkody, Y., & Gaillard, F. (2014). Colorectal carcinoma. *Radiopaedia. org. Retrieved, 13.*
- Weijenberg, M. P., Luchtenborg, M., De Goeij, A. F., Brink, M., Van Muijen, G. N., De Bruïne, A. P., *et al.* (2007). Dietary fat and risk of colon and rectal cancer with aberrant MLH1 expression, APC or KRAS genes. *Cancer causes & control, 18*(8), 865-879.
- Wen, D., Zou, W., Wen, X., Yang, Y., Chen, Y., He, Y., *et al.* (2018). Urban-rural disparity in colorectal cancer incidence and increasing trend in relation to socioeconomic development and urbanization in China. *J Int Med Res, 46*(10), 4181-4196. doi:10.1177/0300060518791090
- WHO, W. H. O. (2014). Global status report on noncommunicable diseases 2014. Retrieved from <https://www.who.int/publications/i/item/9789241564854>
- WHO, W. H. O. (2020). Obesity. Retrieved from [https://www.who.int/health-topics/obesity#tab=tab\\_1](https://www.who.int/health-topics/obesity#tab=tab_1)
- WHO, W. H. O. (2021). Cancer. Retrieved from <https://www.who.int/news-room/fact-sheets/detail/cancer>
- Willett, W. (1989). The search for the causes of breast and colon cancer. *Nature, 338*(6214), 389-394. doi:10.1038/338389a0
- Willett, W. (2005). Diet and cancer: an evolving picture. *Jama, 293*(2), 233-234.
- Wogan, G. N., Hecht, S. S., Felton, J. S., Conney, A. H., & Loeb, L. A. (2004). Environmental and chemical carcinogenesis. *Semin Cancer Biol, 14*(6), 473-486. doi:10.1016/j.semcancer.2004.06.010
- Wolin, K. Y., Yan, Y., Colditz, G. A., & Lee, I. (2009). Physical activity and colon cancer prevention: a meta-analysis. *British journal of cancer, 100*(4), 611.
- Xavier, R., & Podolsky, D. (2007). Unravelling the pathogenesis of inflammatory bowel disease. *Nature, 448*(7152), 427.
- Xie, J., & Itzkowitz, S. H. (2008). Cancer in inflammatory bowel disease. *World J Gastroenterol, 14*(3), 378-389.
- Xuan, K., Zhao, T., Sun, C., Patel, A. S., Liu, H., Chen, X., *et al.* (2021). The association between hypertension and colorectal cancer: a meta-analysis of observational studies. *Eur J Cancer Prev, 30*(1), 84-96. doi:10.1097/CEJ.0000000000000578
- Yach, D., Kellogg, M., & Voute, J. (2005). Chronic diseases: an increasing challenge in developing countries. *Trans R Soc Trop Med Hyg, 99*(5), 321-324. doi:10.1016/j.trstmh.2005.02.001
- Yakoob, M. Y., & Baig-ansari, N. (2019). Dietary Sodium (salt) Intake and Risk of Colorectal Cancer: A Systematic Review (P05-039-19). *Current Developments in Nutrition, 3*(Supplement\_1). doi:10.1093/cdn/nzz030.P05-039-19
- Yamano, T., Yamauchi, S., Igeta, M., Takenaka, Y., Song, J., Kimura, K., *et al.* (2020). Combination of preoperative tumour markers and lymphovascular invasion with TNM staging

as a cost and labour efficient subtyping of colorectal cancer. *Scientific Reports*, 10(1), 10238. doi:10.1038/s41598-020-66652-z

- Yang, M., Hu, F. B., Giovannucci, E. L., Stampfer, M. J., Willett, W. C., Fuchs, C. S., *et al.* (2016). Nut consumption and risk of colorectal cancer in women. *Eur J Clin Nutr*, 70(3), 333-337. doi:10.1038/ejcn.2015.66
- Yeh, C. C., You, S. L., Chen, C. J., & Sung, F. C. (2006). Peanut consumption and reduced risk of colorectal cancer in women: a prospective study in Taiwan. *World J Gastroenterol*, 12(2), 222-227. doi:10.3748/wjg.v12.i2.222
- 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? *Am J Gastroenterol*, 106(11), 1911-1921; quiz 1922. doi:10.1038/ajg.2011.301
- Yuri, M., Sasahira, T., Nakai, K., Ishimaru, S., Ohmori, H., & Kuniyasu, H. (2007). Reversal of expression of 15-lipoxygenase-1 to cyclooxygenase-2 is associated with development of colonic cancer. *Histopathology*, 51(4), 520-527.
- Zabadi, H. A., Musmar, S., Hassouna, A., & Shtaiwi, D. (2018). Cigarettes and Water Pipe Smoking Prevalence, Knowledge, and Attitudes Among the Palestinian Physicians in the West Bank. *Tob Use Insights*, 11, 1179173X18813369. doi:10.1177/1179173X18813369
- Zhao, Y. S., Wang, F., Chang, D., Han, B., & You, D. Y. (2008). Meta-analysis of different test indicators: Helicobacter pylori infection and the risk of colorectal cancer. *Int J Colorectal Dis*, 23(9), 875-882. doi:10.1007/s00384-008-0479-z
- Zhiqin, W., Palaniappan, S., & Raja Ali, R. A. (2014). Inflammatory Bowel Disease-related Colorectal Cancer in the Asia-Pacific Region: Past, Present, and Future. *Intest Res*, 12(3), 194-204. doi:10.5217/ir.2014.12.3.194
- Zisman, A. L., Nickolov, A., Brand, R. E., Gorchow, A., & Roy, H. K. (2006). Associations between the age at diagnosis and location of colorectal cancer and the use of alcohol and tobacco: implications for screening. *Arch Intern Med*, 166(6), 629-634. doi:10.1001/archinte.166.6.629
- Zumkeller, N., Brenner, H., Zwahlen, M., & Rothenbacher, D. (2006). Helicobacter pylori infection and colorectal cancer risk: a meta-analysis. *Helicobacter*, 11(2), 75-80. doi:10.1111/j.1523-5378.2006.00381.x
- zur Hausen, H. (2012). Red meat consumption and cancer: reasons to suspect involvement of bovine infectious factors in colorectal cancer. *Int J Cancer*, 130(11), 2475-2483. doi:10.1002/ijc.27413

**Appendix 4.1: Pathology Questionnaire**

**CRC Pathology Questionnaire**

**\*Attach a copy of the original Pathology Report to this document.**

**Patient Name:** \_\_\_\_\_

**Patient ID:** \_\_\_\_\_

**1. Date of Birth:** \_\_\_/\_\_\_/\_\_\_

**2. Date of Diagnosis:** \_\_\_/\_\_\_/\_\_\_

**3. Hospital of diagnosis:**

1. Augusta Victoria      two. Nablus (National)

3. Cancer Registry      4. Beit Jala      5. Other: \_\_\_\_\_

**4. Histological diagnosis:**

<input type="checkbox"/> Cecum	<input type="checkbox"/> Splenic flexure of colon	<input type="checkbox"/> Rectosigmoid junction
<input type="checkbox"/> Appendix	<input type="checkbox"/> Descending colon	<input type="checkbox"/> Colon and rectum
<input type="checkbox"/> Ascending colon	<input type="checkbox"/> Sigmoid colon	<input type="checkbox"/> Pelvirectal junction
<input type="checkbox"/> Hepatic flexure of colon	<input type="checkbox"/> Overlapping lesion of colon	<input type="checkbox"/> Rectum, NOS
<input type="checkbox"/> Transverse colon	<input type="checkbox"/> Colon, NOS	

**5. Immunostain:**

	<b>Positive</b>	<b>Negative</b>
1. CK20		
2. CK7		
3. CDX-2		
4. beta-catenin		
5. Cadherin-17		
6. Villin		
7. SATB2		
8. MUC5AC		
9. p27		
10. p53		
11. thymidylate synthase		
12. EGFR		
13. SMAD4 (DPC4)		
14. Microsatellite instability		
15. MLH1		
16. MSH2		
17. MSH6		
18. PMS2		

6. LDH level at diagnosis: \_\_\_\_\_

7. Organ involvement

- 1. Liver
- 2. Peritoneum
- 3. Nasopharynx
- 4. Oropharynx
- 5. Thyroid
- 6. Lungs
- 7. Breast
- 8. Stomach
- 9. Small Intestine
- 10. Pancreas
- 11. Testes
- 12. Ovaries
- 13. Endometrium
- 14. Cervix
- 15. Skin
- 16. Brain
- 17. Bone Marrow
- 18. Lymph nodes
- 19. Others organs: \_\_\_\_\_

8. Stage (TNM):

- 1. I
- 2. II
- 3. III
- 4. IV

9. Treatment Protocol:

- 1. Polypectomy during colonoscopy
- 2. Colectomy:
  - i. partial colectomy
  - ii. hemicolectomy right or left
  - iii. subtotal colectomy
  - iv. rectum extirpation
- 3. Neoadjuvant chemotherapy
- 4. Radiotherapy
- 5. Diverting colostomy
- 6. Immunotherapy
- 7. Chemotherapy
  - i. FOLFOX: leucovorin, 5-FU, and oxaliplatin (Eloxatin)
  - ii. FOLFIRI: leucovorin, 5-FU, and irinotecan (Camptosar)
  - iii. CAPEOX or CAPOX : capecitabine (Xeloda) and oxaliplatin
  - iv. FOLFOXIRI: leucovorin, 5-FU, oxaliplatin, and irinotecan
  - v. Bevacizumab
  - vi. ramucirumab [Cyramza]
  - vii. cetuximab [Erbix]
  - viii. panitumumab [Vectibix]
  - ix. 5-FU and leucovorin, with or without a targeted drug
  - x. Capecitabine, with or without a targeted drug
  - xi. Irinotecan, with or without a targeted drug

10. Presence of Polyps: 1. Yes  2. No

**11. Estimated number of polyps:**

1. 10-19       2. 20-49       3. 50-99       4. 100-199       5.  
     $\geq$ 200

**12. Morphology of polyps:**

1. Sessile       2. Pedunculated       3. Flat       4. Depressed

**13. Histology of Polyps:**

1. Adenomatous       2. Hamartomatous       3. Other/Mixed

**14. Disease outcome:**

1. Under treatment       2. Relapsed       3. Remission       4. Deceased

**Appendix 4.2: Study Questionnaire-English**

**Risk Factors of Colorectal Cancer**

Interviewer Name: \_\_\_\_\_ Code

Date of Interview: \_\_\_\_/\_\_\_\_/\_\_\_\_

Time Started \_\_\_\_: \_\_\_\_ Finished at \_\_\_\_: \_\_\_\_

Site of Interview: 1. Home 2. Hospital \_\_\_\_\_ 3. Clinic 4. Others \_\_\_\_\_

Subject Name: \_\_\_\_\_

**Part I: Demographic Information**

**I would like to ask you about your sociodemographic information including your marital status, education, place of birth, and others**

Q1) ID Number 

--	--	--	--	--	--	--	--	--

Q2) Gender: 1. Male  2. Female

Q3) Date of Birth 

Year		Month		Day			

Q4) Type of Locality: 1. Rural  2. Urban  3. Camp

Q5) Governorate:

- 1. Hebron  2. Bethlehem  3. Ramallah & Al-Bireh  4. Jericho & Al-Aghwar
- 5. Jerusalem  6. Nablus  7. Qalqiliya  8. Tubas  9. Jenin
- 10. Salfit  11. Tulkarem  12. Gaza Strip

Q6) Marital status:

- 1. Single
- 2. First marriage
- 3. Second marriage or more
- 4. Divorced or separated
- 5. Widowed

Q7) How many births did you have? (including all living and dead)

Q8) How many siblings do you have? (excluding you)

Q9) What is your birth order in the family

Q10) What is your religion?

1. Muslim
2. Christian
3. others

Q11) What is your highest diploma?

1. Never went to school <input type="checkbox"/>	2. Partial primary (< 6 <sup>th</sup> grade) <input type="checkbox"/>	3. Primary school completed <input type="checkbox"/>
4. Partial secondary <input type="checkbox"/>	5. High school completed <input type="checkbox"/>	6. Diploma <input type="checkbox"/>
7. Bachelor degree <input type="checkbox"/>	8. Higher research degrees <input type="checkbox"/>	

**Primary school:** 1<sup>st</sup> grade-6<sup>th</sup> grade, **Secondary school:** 7<sup>th</sup> grade-12<sup>th</sup> grade)

## **Part II: Lifestyle and Habits**

Q12) What are your measurements?

Parameter	Current Measurement	Measurement before 5 yrs
Height (cm)		
Weight (Kg)		

Q13) Have you ever smoked? (if never, go to Q18)

1. Yes
2. No

Q14) Are you a smoker now?

1. Yes
2. No

Q15) How many years did you smoke?

Q16) What type of tobacco do/did you smoke?

1. Cigarettes
2. Nargilah
3. Pipes
4. Tobacco/Cigar

Q17) How many cigarettes do (did) you smoke per day?

- A. **Cigarettes:** 1: less than 10  2: 11-20  3: 21-40  4: more than 40

- B. **Other types:** 1: everyday  2:  $\geq$  once/week  3: < once/week

### **Q18) Occupational physical activity**

a. Have you had a job during the last 10 years/before illness? (If no skip to Q19)

1. Yes
2. No

b. We would like to know the type and amount of physical activity involved in your work during the last 10 years/ before your illness. Please check what best corresponds with your present occupation from the following four possibilities:

1. Sedentary occupation. (You spend most of your time sitting (such as in an office))
2. Standing occupation. (You spend most of your time standing and walking. However, your work does not require intense physical effort (e.g. shop assistant, hairdresser, guard, etc.)
3. Manual work. (This involves some physical effort including handling of heavy objects and use of tools (e.g. plumber, electrician, carpenter, etc.)
4. Heavy manual work. (This implies very vigorous physical activity including handling of very heavy objects (e.g. docker, miner, bricklayer, construction worker, etc.)


**Q19) Physical activity during leisure time and transportation between workplace and home.**

The question concerns both activities during leisure time and the way you transport yourself between workplace and home, but not activities during working hours, **during the last 10 years/** before your illness.

Specify in the table below how many hours per week you spend (on average) at different activities.

**If any activity is missing you can add it at the end of the table.**

#	Physical Activities	Never	<3hours /week	3-4 hours/week	5-7 hours/week	>7 hours/week
1.	Walking					
2.	Football, handball, basketball, tennis, or other ball games					
3.	Athletics, gymnastics					
4.	Aerobics / fitness club exercise/Trade mill at home					
5.	Jogging, running					
6.	Karate, Judo taekwondo					
7.	Boxing/Kick boxing					
8.	Weightlifting/Weight-training					
9.	Dancing (Zumba, eastern, dabka)					
10.	Gardening					
11.	Swimming					
12.	Cycling					
13.	Other _____					

Q20) Your dietary habits over the 2 years (before illness):

Item	Never- <1/month	1/ month	2-3/ month	1/ week	2-3/ week	4-6/ week	1/ day	>1/ day	No. of servings
<b>Meat, Poultry &amp; Fish</b>									

1.	Fresh Fish <b>1pc(90g)</b>										
2.	Canned fish <b>(1can)</b>										
3.	Beef/veal meat <b>1pc(120g)</b>										
4.	Mutton and lamb meat <b>1pc(120g)</b>										
5.	Poultry <b>1pc(120g)</b>										
<b>Bread &amp; Grains</b>											
6.	White bread <b>Small bun</b>										
7.	Bread whole grain, rye <b>Small bun</b>										
8.	French bread <b>1 pc</b>										
9.	Breakfast cereals – low fiber <b>Small plate</b>										
10.	Breakfast cereals – high fiber <b>Small plate</b>										
11.	Oats (cooked) <b>1cup(240mL)</b>										
12.	Rice(cooked) <b>1cup(240mL)</b>										
13.	Pasta <b>1cup(240mL)</b>										
<b>Vegetables</b>											
14.	Potatoes <b>Medium size</b>										
15.	Cabbages <b>1cup(240mL)</b>										
16.	Mushrooms <b>1cup(240mL)</b>										
17.	Leafy vegetables <b>1cup(240mL)</b>										
18.	Other vegetables: tomatoes, cucumber, bell pepper, carrots... <b>Medium size</b>										
19.	Mixed salad, raw <b>1cup(240mL)</b>										
20.	Vegetable soup/cooked vegetable <b>1cup(240mL)</b>										
21.	Beans, lentils and peas <b>1cup(240mL)</b>										
	<b>Item</b>	<b>Never- &lt;1/month</b>	<b>1/ month</b>	<b>2-3/ month</b>	<b>1/ week</b>	<b>2-3/ week</b>	<b>4-6/ week</b>	<b>1/ day</b>	<b>&gt;1/ day</b>	<b>No. of servings</b>	
<b>Fruits</b>											
22.	Strawberry <b>10 pc</b>										

23.	Grapes, cherries <b>10 pcs</b>									
24.	Figs <b>3 figs</b>									
25.	Melon/ Watermelon <b>1 slice</b>									
26.	Stone fruit: apricot, peach <b>Medium size</b>									
27.	Pit fruit: apple, pear, banana <b>Medium size</b>									
28.	Citrus fruit <b>Medium size</b>									
29.	Dried fruit <b>Apricot (4)</b> <b>Fig (3)</b> <b>Dates (2 large)</b> <b>Grape (2 tablespoons)</b>									
30.	Fruit juice <b>1cup(240mL)</b>									
<b>Eggs and Dairy Products</b>										
31.	Milk <b>1cup(240mL)</b>									
32.	Dairy products (White cheese, labaneh... <b>Table spoon /1pc</b> <b>(40g)</b>									
33.	Processed cheese (yellow, triangle, puck..) <b>Table spoon/1 triangle</b>									
34.	Yoghurt, Butter milk <b>1cup(240mL)</b>									
35.	Eggs <b>1 egg</b>									
<b>Drinks</b>										
36.	Water <b>1cup(240mL)</b>									
37.	Coffee <b>1cup(240mL)</b>									
38.	Herbal Tea <b>1cup(240mL)</b>									
39.	Sparkle drinks <b>1cup(240mL)</b>									
40.	Energy drinks <b>Can (250 mL)</b>									
	<b>Item</b>	<b>Never- &lt;1/month</b>	<b>1/ month</b>	<b>2-3/ month</b>	<b>1/ week</b>	<b>2-3/ week</b>	<b>4-6/ week</b>	<b>1/ day</b>	<b>&gt;1/ day</b>	<b>No. of servings</b>
41.	Sugar in drinks <b>(Small spoon)</b> White/brown sugar <input type="checkbox"/> Diet sugar <input type="checkbox"/>									
<b>Desserts &amp; Snacks</b>										

42.	Eastern sweets 2pcs baqlava, ghrayba 50-60g knafa, harisa, namora 3pcs awama, asabe'zenb 1pc qatayef/mamoul									
43.	Western sweets 1 slice cake 2 small cookies 1 small muffin/cupcake 5 small wafers ½ cup ice milk, sherbet or frozen yogurt									
44.	Chocolate 1pc 25g									
45.	Chips Small plate									
46.	Raw Nuts 6 pc/ 1 tbsp									
47.	Roosted/salted nuts 6 pc/1tbsp									
<b>Other</b>										
48.	Dietary supplements: 1. _____ 2. _____ 3. _____									-
49.	Deep fried food									<b>Type of oil:</b> 1Olive Oil <input type="checkbox"/> 2Maize oil <input type="checkbox"/> 3Butter <input type="checkbox"/> 4Animal fat <input type="checkbox"/>
50.	Shallow fried food									
51.	Processed meat									-

### **Part III: Boweling Habits and Inflammatory Bowel Diseases**

Q21) Has your bowel habit changed in the last year/before illness ?

1. Yes                       2. No

Q22) How would you describe your usual bowel pattern in the last year/before illness?

1. Normal   
 2. Constipated   
 3. Diarrhea   
 4. Alternating constipation and diarrhea

Q23) How many bowel movements do you usually have in a week/before illness?

1. 1 or less   
 2. 2   
 3. 3-4

4. 5-8
5. 9-12
6. 13-16
7. 17-21
8. 22-26
9. More than 26

Q24) Do you take anything (e.g. bran, fiber, laxatives) because of constipation/before illness?

1. Yes
2. No

Q25) Have you seen **mucus** in your stools in the last year (that is, white or green slimy material) /before illness?

1. Yes
2. No
3. Don't Know

Q26) Have you noticed **any blood** in your stools or in the toilet bowl in the last year? (**If not go to 28**)

1. Yes
2. No
3. Don't Know

Q27) If yes, was the blood:

1. Coating the stools
2. Dark and mixed in the stools
3. On the toilet paper

Q28) Have you had an ache or pain in your stomach or belly (gut) in the last year? (Please do NOT count cramps or pain with menstrual periods, and do NOT count pain in your chest.) (**If not go to Part IV**)

1. Yes
2. No

Q29) How many times did you get this pain in the last year?

1. Less than once a month
2. About once a month
3. About once a week
4. Several times a week
5. Daily

Q30) How bad is the ache or pain usually?

1. **Mild:** can be ignored if you don't think about it
2. **Moderate:** cannot be ignored, but does not affect your life-style
3. **Severe:** affects your life-style
4. **Very severe:** markedly affects your life-style

Q31) Pain can occur mainly in the upper belly (stomach), lower belly, or in both the upper and lower belly. Concerning your primary pain: Has this ache or pain in your belly usually been:

1. **Above** the navel, that is, in the **upper belly**?
2. **Below** the navel, that is, in the **lower belly**?
3. In different places in **both** the upper and lower belly?

Q32) When in your life did this ache or pain first begin as close as you can recall?

1. In the last 6 months
2. 7 months to 1 year ago
3. More than 1 year to 2 years ago
4. More than 2 years to 5 years ago
5. More than 5 years to 10 years ago
6. More than 10 years to 20 years ago
7. More than 20 years ago

Q33) Does this ache or pain often occur:

1. before meals or when hungry
2. immediately after meals (less than 30 minutes)
3. 30 **minutes to 2 hours after** meals

Q34) Is this pain often made better by:

1. burping
2. having a bowel movement
3. eating
4. taking antacids (like Turns, Riopan, Maalox, Gaviscon, etc.)

**Part IV: Health and Disease**

Q35) Have you ever suffered from any serious diarrhea (lasting more than two days) during the last 10 years (before illness)? (if not, go to Q37)

1. Yes                       2. No                       3. Don't Know

Q36) If you answered yes, did you know the causative agent?

1. Yes                       Cause \_\_\_\_\_  
 2. No

Q37) Did you suffer from any of the following disease(s)?

Disease	Yes	No	Don't remember
1. Herpes: lips, nose, ear, other (EBV)			
2. Infectious Mononucleosis (EBV/HCMV)			
3. Enteritis			
4. Ulcer			
5. Endocarditis (S. bovis)			
6. Bacteremia (S. bovis)			
7. Stomach infection (H. pylori)			
8. Periodontal disease (Fusobacterium)			
9. Brucellosis			
10. Cancer			
11. Allergies			
12. Bowel obstruction			
13. Appendicitis			
14. Celiac disease			
15. Hemorrhoids			
16. Anal fissures			
17. Perianal abscesses/infections			
18. Anal fistulas			
19. Colon polyps			
20. Diverticulitis			
21. Irritable bowel syndrome			
22. Ulcerative colitis			
23. Crohn's disease			
24. Other _____			

**Part V: Familial History**

Q38) Consanguinity among parents

1. Yes                       **Type:** 1. first cousins                       2. from the same family   
 2. No

Q39) Consanguinity among grandparents (paternal side)

1. Yes                       **Type:** 1. first cousins                       2. from the same family

2. No

Q40) Consanguinity among grandparents (maternal Side)

1. Yes  **Type:** 1. first cousins  2. from the same family

2. No

Q41) Did any of your **first degree** relatives had cancer?

1. Yes  2. No  3. Don't Know

Q42) if you answered yes to questions 41 please tell us who had cancer, what type and at what age)

		Type of cancer	Age at diagnosis
<b>Parents</b>			
Did they develop cancer?	1. Yes <input type="checkbox"/> 2. No <input type="checkbox"/>		
If yes, who developed cancer and what type of cancer?	Father		
	Mother		
<b>Brothers</b>			
How many brothers do you have?			
Did they develop cancer?	1. Yes <input type="checkbox"/> 2. No <input type="checkbox"/>		
If yes, who developed cancer and what type of cancer?	Brother 1		
	Brother 2		
	Brother 3		
<b>Sisters</b>			
How many sisters do you have?			
Did they develop cancer?	1. Yes <input type="checkbox"/> 2. No <input type="checkbox"/>		
If yes, who developed cancer and what type of cancer?	Sister 1		
	Sister 2		
	Sister 3		
<b>Children</b>			
How many children do you have?			
Did they develop cancer?	1. Yes <input type="checkbox"/> 2. No <input type="checkbox"/>		
If yes, who developed cancer and what type of cancer?	Child 1		
	Child 2		
	Child 3		

Q43) Did any of your **second degree** relatives had cancer?

1. Yes  2. No  3. Don't Know

Q44) if you answered yes to questions 43 please tell us who had cancer, what type and at what age)

		Type of cancer	Age at diagnosis
<b>Family from paternal side</b>			
How many uncles do you have?			
How many aunts do you have?			
Did they develop cancer?	1. Yes <input type="checkbox"/> 2. No <input type="checkbox"/>		
If yes, who developed cancer and what type of cancer?	Uncle 1		
	Uncle 2		
	Aunt 1		
	Aunt 2		
Did grandfather or grandmother develop cancer?	1. Yes <input type="checkbox"/> 2. No <input type="checkbox"/>		
If yes, who developed cancer and what type of cancer?	Grandfather		
	Grandmother		
<b>Family maternal side</b>			
How many uncles do you have?			
How many aunts do you have?			

Did they develop cancer?	1. Yes <input type="checkbox"/> 2. No <input type="checkbox"/>		
If yes, who developed cancer and what type?	Uncle 1		
	Uncle 2		
	Aunt 1		
	Aunt 2		
Did grandfather or grandmother developed cancer?	1. Yes <input type="checkbox"/> 2. No <input type="checkbox"/>		
If yes, who developed cancer and what type of cancer?	Grandfather		
	Grandmother		

### Appendix 4.3: Study Questionnaire-Arabic

#### العوامل المرتبطة بسرطان القولون والمستقيم

- اسم الباحث: \_\_\_\_\_ الرمز
- تاريخ المقابلة: \_\_\_\_/\_\_\_\_/\_\_\_\_
- وقت البدء: \_\_\_\_\_ وقت الانتهاء: \_\_\_\_\_
- مكان المقابلة: 1. المنزل 2. المستشفى 3. عيادة 4. أخرى
- اسم المشارك: \_\_\_\_\_

#### القسم الأول: المعلومات السكانية

أود أن أسألك حول معلوماتك الديموغرافية والتي تتضمن الحالة الاجتماعية، التعليم، مكان الولادة ومعلومات أخرى.

س (1) رقم هوية الشخص  المشارك

س (2) الجنس: 1. ذكر  2. أنثى

س (3) تاريخ الميلاد				اليوم		الشهر		السنة	

س (4) نوع التجمع السكاني: 1. قرية  2. مدينة  3. مخيم

س (5) المحافظة:

1. الخليل  2. بيت لحم  3. رام الله والبيرة  4. أريحا والأغوار  5. القدس
6. نابلس  7. قلقيلية  8. طوباس  9. جنين  10. سلفيت  11. طولكرم  12. قطاع غزة

س (6) الحالة الاجتماعية:

1. أعزب
2. متزوج لمرة واحدة
3. متزوج لمرتين أو أكثر
4. مطلق أو منفصل
5. أرمل

س (7) كم مولود لديك؟ (يتضمن الأحياء منهم والمتوفون ولا يشمل الإجهاض)

س (8) كم من الأشقاء لديك؟ (بدون احتساب المشارك)

س (9) ما هو ترتيبك في العائلة؟

س 10) ما هو دينك؟

1. مسلم  
 2. مسيحي  
 3. آخر

س 11) ما هي أعلى شهادة علمية حصلت عليها؟

<input type="checkbox"/> 1. لم أذهب إلى المدرسة	<input type="checkbox"/> 2. أساسي جزئي (> الصف السادس)	<input type="checkbox"/> 3. أكملت الدراسة الأساسية
<input type="checkbox"/> 4. ثانوي جزئي	<input type="checkbox"/> 5. أكملت الدراسة الثانوية	<input type="checkbox"/> 6. دبلوم
<input type="checkbox"/> 7. درجة البكالوريوس	<input type="checkbox"/> 8. درجات عليا	

المرحلة الأساسية : الصف الأول – الصف السادس ، المرحلة الثانوية : الصف السابع – الصف الثاني عشر

## القسم الثاني: نمط الحياة والعادات

س 12) ما هي قياساتك الجسمية؟

المؤشرات	القياس الحالي	القياس قبل 5 سنوات
الطول (سم)		
الوزن (كغم)		

س 13) هل سبق لك أن دخننت؟ (إذا لم تدخن أبداً، انتقل إلى س 18)

1. نعم  2. لا

س 14) هل أنت مدخن في الوقت الحالي؟

1. نعم  2. لا

س 15) كم سنة دخننت؟

س 16) ما نوع التبغ الذي تدخن/ كنت تدخن؟

1. السجائر  
 2. النرجيلة  
 3. الغليون  
 4. التبغ/سيجار

س 17) كم عدد السجائر التي تدخنها (دخننتها) في اليوم؟

- السجائر:  1: 10 سجائر أو أقل  2: 11-20  3: 21-40  4: أكثر من 40  
 سيجارة

- أنواع أخرى:  1. كل يوم  2: ≤ مرة في الأسبوع  3: أقل من مرة في الأسبوع

س 18) النشاط البدني المهني:  
 أ. هل كان لديك عمل خلال السنوات العشر الماضية/قبل المرض؟ (إذا أجبت ب لا انتقل إلى س19)  
 1. نعم  2. لا

ب. نود أن نعرف نوع ومقدار النشاط البدني الذي تقوم به في عملك خلال السنوات العشر الماضية/قبل مرضك. يرجى التحقق من أفضل ما يتوافق مع مهنتك الحالية من الاحتمالات الأربعة التالية:


1. الأعمال المكتبية: (أنت تقضي معظم وقتك جالسًا كما هو الحال في المكتب).
2. الأعمال في حال الوقوف: (أنت تقضي معظم وقتك في الوقوف والمشي، ومع ذلك لا يتطلب عملك جهدًا جسديًا كبيراً. على سبيل المثال موظف في متجر، مصفف شعر، حارس، إلخ).
3. الأعمال اليدوية: (يتضمن ذلك بعض الجهد البدني بما في ذلك التعامل مع الأشياء الثقيلة واستخدام الأدوات. مثل السباكة والكهربائيين والنجارين، إلخ).
4. الأعمال اليدوية الثقيلة: (وهذا ينطوي على نشاط بدني قوي للغاية بما في ذلك التعامل مع أشياء ثقيلة جداً. مثل عامل ميناء، عامل منجم، عامل بناء، إلخ).

س19) النشاط البدني أثناء وقت الفراغ والتنقل بين مكان العمل والمنزل:

يتعلق السؤال بالأنشطة خلال وقت الفراغ والطريقة التي تنتقل بها نفسك بين مكان العمل والمنزل، ولكن ليس الأنشطة التي تكون خلال ساعات العمل خلال السنوات العشر الماضية/قبل مرضك. حدد في الجدول أدناه عدد الدقائق التي تقضيها في الأسبوع (في المتوسط) من الأنشطة المختلفة. (إذا كان هناك أي نشاط مفقود، يمكنك إضافته في نهاية الجدول).

#	النشاط البدني	أبدا	<3 ساعة/أسبوع	3 – 4 ساعات/أسبوع	5 – 7 ساعات/أسبوع	< 7 ساعات/أسبوع
1	المشي					
2	كرة القدم، كرة اليد، كرة السلة، التنس، أو غيرها من ألعاب الكرة					
3	ألعاب القوى والجمباز					
4	التمارين الرياضية (Aerobics)، نادي اللياقة البدنية، آلة الجري في المنزل					
5	الركض، الجري					
6	الكاراتيه، الجودو التايكواندو					
7	الملاكمة / الملاكمة بالأرجل					
8	رفع الاثقال					
9	الرقص (الزومبا، الرقص الشرقي، الدبكة)					
10	البسنتة أو التشجير					
11	السباحة					
12	ركوب الدراجات					
13	نشاطات أخرى					

س 20) عاداتك الغذائية خلال العامين الماضيين (قبل المرض):

#	البند	ابدا- أفل من مرة/ شهر	مرة/شهر	٢ - ٣ مرات /شهر	مرة /أسبوع	٢ - ٣ مرة/ أسبوع	٤ - ٦ مرة/أسبوع	مرة /يوم	< مرة/ يوم	عدد الحصص
<b>اللحوم والدواجن والأسماك</b>										
1.	سمك طازج قطعة 90غم									
2.	الأسماك المعلبة علبة									
3.	لحم بقر/عجل قطعة 120 غم									
4.	لحم الخروف قطعة 120 غم									
5.	الدواجن قطعة 120 غم									
<b>منتجات الحبوب</b>										
6.	الخبز الأبيض رغيف صغير									
7.	خبز الحبوب الكاملة /الأسمر رغيف صغير									
8.	خبز الباغيت/ حمام باغيت صغير أو شرحة ونصف									
9.	حبوب الإفطار قليلة الألياف صحن صغير									
10.	حبوب الإفطار الغنية بالألياف صحن صغير									
11.	الشوفان كوب (240مل)									
12.	الأرز (مطبوخ) كوب (240مل)									
13.	المعكرونة (مطبوخة) كوب (240مل)									
<b>الخضار</b>										
14.	البطاطا حبة متوسطة									
15.	الكرنب (الملفوف)، زهر، بروكلي، فجل... كوب (240مل)									
16.	الفطر كوب (240مل)									
17.	الخضار الورقية كوب (240مل)									
18.	خضار أخرى (غير مطبوخة) حبة متوسطة									
19.	سلطة كوب (240مل)									
20.	حساء الخضار/خضار مطبوخة كوب (240مل)									
21.	البقوليات (الفول والعدس ... كوب (240مل)									

#	البند	أبدا - أقل من مرة / شهر	مرة/شهر	٢ - ٣ مرات /شهر	مرة /أسبوع	٢ - ٣ مرة/ أسبوع	٤ - ٦ مرة/أسبوع	مرة /يوم	< مرة/ يوم	عدد الحصص
<b>الفواكه</b>										
22.	الفاولة 10 حبات									
23.	عنب، كرز 10 حبات									
24.	تين 3 حبات تين									
25.	البطيخ والشمام شرحة									
26.	الخوخ، الدراق، المشمش،.. حبة متوسطة									
27.	التفاح، الإجاص، الموز حبة متوسطة									
28.	الحمضيات حبة متوسطة									
29.	الفواكه المجففة مشمش (4حبات) قطين (3حبات) زبيب (ملعقتين طعام) تمر (2حبة كبيرة)									
30.	عصير فواكه كوب (240مل)									
<b>البيض و الحليب ومشتقاته</b>										
31.	الحليب كوب (240مل)									
32.	منتجات الحليب (الجبنه البيضاء، اللبنة..) ملعقة طعام /قطعة (40غم)									
33.	الجبن المعالج (الأصفر، المتلث، بوك ..) ملعقة طعام/متلث									
34.	الزبادي/لبن/ لبن أب كوب (240مل)									
35.	البيض بيضة									
<b>المشروبات</b>										
36.	الماء كوب (240مل)									
37.	القهوة كوب (240مل)									
38.	شاي الأعشاب كوب (240مل)									
39.	المشروبات الغازية كوب (240مل)									
40.	مشروبات الطاقة علبة (250 مل)									
41.	إضافة السكر للمشروبات ملعقة صغيرة سكر أبيض/بني <input type="checkbox"/> سكرين <input type="checkbox"/>									

#	البند	أبدا- أقل من مرة/ شهر	مرة/شهر	٢ - ٣ مرات /شهر	مرة /أسبوع	٢ - ٣ مرة/ أسبوع	٤ - ٦ مرة/أسبوع	مرة /يوم	< مرة/ يوم	عدد الحصص
<b>الحلويات والمسلية</b>										
42.	الحلويات الشرقية 2 بقلوة، غريبة 60-50 غم كنافة، هريسة، نمورة 3 قطع عوامة، أصابع زينب حبة قطايف/معمول									
43.	الحلويات الغربية قطعة كيك 2 كوكيز صغيرة 1 كيك صغير 5 ويفر صغيرة 2/1 كوب بوطة									
44.	الشوكولاتة قطعة 25 غم									
45.	الشيبس صحن صغير									
46.	المكسرات النيئة 6 حبات/ملعقة طعام									
47.	المكسرات المحمص، المملحة 6 حبات/ملعقة طعام									
<b>أخرى</b>										
48.	المكملات الغذائية 1 _____ 2 _____ 3 _____									-
49.	القلي بزيت عميق									نوع الدهن المستخدم 1 زيت زيتون <input type="checkbox"/> 2 زيت ذرة <input type="checkbox"/> 3 زبدة نباتية <input type="checkbox"/> 4 سمنة <input type="checkbox"/>
50.	قلي بدهن خفيف									
51.	لحوم معالجة/مصنعة: نقانق، مرتديلا، لحم معلب، حبش....									-

### القسم الثالث: عادات الإخراج وأمراض القولون

س 21) هل لاحظت أي تغييرات في عادات الإخراج لديك في العام الماضي/قبل المرض؟  
1. نعم  2. لا

س 22) كيف تصف نمط الإخراج المعتاد في العام الماضي/قبل المرض؟

1. عادي   
2. إمساك   
3. إسهال   
4. تناوب الإمساك والإسهال

س 23) كم عدد مرات الإخراج لديك عادةً في الأسبوع؟

1. أقل
2.
3. 3-4
4. 4-5
5. 5-9
6. 13-16
7. 17-21
8. 22-26
9. أكثر من 26

س 24) هل تأخذ أي مليّنات (مثل النخالة، والألياف، والمسهلات) بسبب الإمساك؟

1. نعم
2. لا

س 25) هل شاهدت مادة مخاطية (مادة مخاطية لزجة بيضاء أو خضراء) في البراز الخاص بك في العام الماضي / قبل المرض؟

1. نعم
2. لا
3. لا أعرف

س 26) هل لاحظت وجود أي دم في البراز لديك أو في حوض المراض في العام الماضي؟ (إذا أجبت ب لا انتقل إلى س28)

1. نعم
2. لا
3. لا أعرف

س 27) إذا كانت الإجابة نعم، فهل كان الدم:

1. يغطي البراز
2. غامق ومختلط مع البراز
3. على ورق التواليت

س 28) هل كان لديك ألم في معدتك أو بطنك (منطقة الأمعاء) في العام الماضي؟ (يرجى عدم حساب التشنجات أو الألم مع فترات الحيض أو الألم في الصدر. (إذا أجبت ب لا انتقل إلى القسم الرابع)

1. نعم
2. لا

س 29) كم مرة حصل هذا الألم في العام الماضي؟

1. أقل من مرة واحدة في الشهر
2. مرة في الشهر
3. حوالي مرة واحدة في الأسبوع
4. عدة مرات في الأسبوع
5. يوميًا

س30) ما مدى سوء الألم في العادة؟

1. خفيف: يمكن تجاهله إذا كنت لا تفكر في ذلك
2. متوسط: لا يمكن تجاهله، ولكن لا يؤثر على نمط حياتك
3. شديد: يؤثر على نمط حياتك
4. شديد جدًا: يؤثر بشكل ملحوظ على نمط حياتك

س31) يمكن أن يحدث الألم بشكل رئيسي في الجزء العلوي من البطن (المعدة) أو البطن السفلي أو في كل من البطن العلوي والسفلي. فيما يتعلق بالألم الأساسي: كان هذا الألم في منطقة البطن عادةً في:

1. فوق السرة: وهذا هو في الجزء العلوي
2. أدنى السرة: وهذا هو في منطقة البطن السفلي
3. في أماكن مختلفة في كلا الجزء العلوي والسفلي من البطن

س32) متى بدأ هذا الألم في حياتك من أقرب وقت ممكن أن تتذكر؟

1. في آخر 6 أشهر
2. 7 أشهر إلى 1 سنة
3. أكثر من 1 سنة إلى 2 سنة
4. أكثر من 2 سنة إلى 5 سنوات
5. أكثر من 5 سنوات إلى 10 سنوات
6. أكثر من 10 سنوات إلى 20 سنة
7. منذ أكثر من 20 عاما

س33) هل يحدث هذا الألم غالبًا:

1. قبل الوجبات أو عند الجوع
  2. بعد الوجبات (أقل من 30 دقيقة)
  3. من 30 دقيقة إلى ساعتين بعد الوجبات
- س34) هل تشعر بالارتياح من الألم غالباً عند:

1. التجشؤ
2. الإخراج
3. الأكل
4. أخذ مضادات الحموضة مثل (Rolaids، Gaviscon، Maalox، Mylanta، Riopan، Turns)

## القسم الرابع: الصحة والمرض

س35) قبل المرض، هل سبق لك أن عانيت من إسهال دام لأكثر من يومين خلال السنوات العشر الأخيرة قبل المرض؟ (إذا كانت الإجابة "لا"، اذهب إلى س37)

1. نعم
2. لا
3. لا أعرف

س36) إذا أجبت ب نعم، هل عرفت السبب؟

1. نعم  السبب \_\_\_\_\_
2. لا أعرف

س37) هل عانيت من أي من الأمراض الآتية

لا أذكر	لا	نعم	المرض
			1. Herpes (القوباء): الشفتين، الأنف، الأذن، أخرى
			2. داء كثرة الوحيدات العدائية (الخمجية)/الحمى الغدية Infectious EBV/HCM Mononucleosis
			3. التهاب معوي
			4. القرحة
			5. التهاب الشغاف (الغشاء المحيط بالقلب)(S.bovis)
لا أذكر	لا	نعم	المرض
			6. تجرثم الدم البكتيري/تسمم دم (S.bovis)
			7. جرثومة المعدة (H.pylori)
			8. أمراض اللثة (Fusobacterium) Periodontal disease
			9. الحمى المالطية (Brucellosis)
			10. السرطان

			11. الحساسية
			12. انسداد الأمعاء
			13. التهاب الزائدة الدودية
			14. حساسية القمح
			15. البواسير
			16. الشقوق الشرجية
			17. خراجات/التهابات الشرج
			18. الناسور الشرجي anal fistula
			19. السلائل/ أورام القولون الحميدة polyps
			20. التهاب الرداب/الرتاج (Diverticulitis)
			21. متلازمة القولون العصبي (IBS)
			22. التهاب القولون التقرحي ulcerative colitis
			23. مرض كرون/ التهاب الأمعاء الناحي (Crohn's disease)
			24. أمراض أخرى _____

### القسم الخامس: التاريخ العائلي

س 38) هل هناك صلة قرابة بين الوالدين؟

1. نعم  2. لا
- نوع القرابة: 1. أبناء عم/خال  2. من نفس العائلة

س 39) هل هناك صلة قرابة بين جدك وجدتك (من جهة الأب)؟

1. نعم  2. لا
- نوع القرابة: 1. أبناء عم/خال  2. من نفس العائلة

س 40) هل هناك صلة قرابة بين جدك وجدتك (من جهة الأم)؟

1. نعم  2. لا
- نوع القرابة: 1. أبناء عم/خال  2. من نفس العائلة

س 41) هل أحد أقربائك من الدرجة الأولى مصاب بالسرطان؟

1. نعم  2. لا  3. لا أعرف

س 42) إذا أجبت بنعم على 41 من فضلك أخبرنا من لديه السرطان، أي نوع وفي أي سن .

العمر عند التشخيص	نوع السرطان		
			<b>الآباء</b>
		1. نعم <input type="checkbox"/> 2. لا <input type="checkbox"/>	هل أصيبوا بالسرطان؟
		أب	إذا كانت الإجابة نعم، من الذي أصيب بالسرطان، وما نوع السرطان؟
		أم	
			<b>الإخوة</b>
			كم أخ لديك؟
		1. نعم <input type="checkbox"/> 2. لا <input type="checkbox"/>	هل أصيبوا بالسرطان؟
		الأخ 1	إذا كانت الإجابة نعم، من الذي أصيب بالسرطان، وما نوع السرطان؟
		الأخ 2	
		الأخ 3	
			<b>الأخوات</b>
			كم أخت لديك؟

		1. نعم <input type="checkbox"/> لا <input type="checkbox"/>	هل أصيبت بالسرطان؟
	الأخت ١		إذا كانت الإجابة نعم، من الذي أصيب بالسرطان ، وما نوع السرطان؟
	الأخت ٢		
	الأخت ٣		
			<b>الأطفال</b>
			كم طفلا لديك؟
		1. نعم <input type="checkbox"/> لا <input type="checkbox"/>	هل أصيبت بالسرطان؟
	الطفل ١		إذا كانت الإجابة نعم، من الذي أصيب بالسرطان، وما نوع السرطان؟
	الطفل ٢		
	الطفل ٣		

س (43) هل أحد أقربائك من الدرجة الثانية مصاب بالسرطان؟

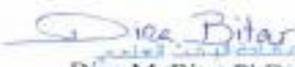
1. نعم  2. لا  3. لا أعرف

س (44) إذا أجبت بنعم على سؤال 43 من فضلك أخبرنا من لديه السرطان، أي نوع وفي أي سن تم تشخيصه .

			<b>الأقارب من جهة الأب</b>
			كم عدد الأعمام لديك؟
			كم عدد العمات لديك؟
		1. نعم <input type="checkbox"/> لا <input type="checkbox"/>	هل أصيبت بالسرطان؟
	العم ١		إذا كانت الإجابة نعم، من الذي أصيب بالسرطان، وما نوع السرطان؟
	العم ٢		
	العمة ١		
	العمة ٢		
		1. نعم <input type="checkbox"/> لا <input type="checkbox"/>	هل أصيب أي من الجد أو الجدة بالسرطان؟
	الجد		إذا كانت الإجابة نعم، من الذي أصيب بالسرطان ، وما نوع السرطان؟
	الجدة		

			<b>الأقارب من جهة الأم</b>
			كم عدد الأخوال لديك؟
			كم عدد الخالات لديك؟
		1. نعم <input type="checkbox"/> لا <input type="checkbox"/>	هل أصيبت بالسرطان؟
	الخال ١		إذا كانت الإجابة نعم، من الذي أصيب بالسرطان ، وما نوع السرطان؟
	الخال ٢		
	الخالة ١		
	الخالة ٢		
		1. نعم <input type="checkbox"/> لا <input type="checkbox"/>	هل أصيب أي من الجد أو الجدة بالسرطان؟
	الجد		إذا كانت الإجابة نعم، من الذي أصيب بالسرطان ، وما نوع السرطان؟
	الجدة		

## Appendix 4.4: Ethical Approval

<p>Al-Quds University Jerusalem Deanship of Scientific Research</p>	<p>بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ</p>  <p>AL-QUDS UNIVERSITY</p>	<p>جامعة القدس القدس عمادة البحث العلمي</p>
<p>Research Ethics Committee Committee's Decision Letter</p>		
<p>Date: July 23, 2018 Ref No: 43/REC/2018</p>		
<p>Dear Dr. Rania Abu Seir,</p>		
<p>Thank you for submitting your application for research ethics approval. After reviewing your application entitled <b>"Evaluation of genetic and environmental risk factors of colorectal cancer among Palestinians"</b> the Research Ethics Committee confirms that it is in accordance with the research ethics guidelines at Al-Quds University.</p>		
<p>Please inform us if there will be any changes in your research methodology, subjects, plan and we would appreciate receiving a copy of your final research report.</p>		
<p>Thank you again and wish you productive research that serves the best interest of your subjects.</p>		
<p> Dina M. Bitar PhD Research Ethics Committee Chair</p>		
<p>Cc. Prof. Imad Abu Kishek - President Cc. Members of the committee Cc. file</p>		
<p>Abu-Dies, Jerusalem P.O.Box 20002 Tel-Fax: #970-02-2791293</p>	<p>research@admin.alquds.edu</p>	<p>ابوديس، القدس ص.ب. 20002 تلفون: #970-02-2791293</p>

## Appendix 4.5: Ministry of Health (MOH) Approval

State of Palestine  
Ministry of Health  
General Directorate  
of Paramedical Services



دولة فلسطين  
وزارة الصحة  
الإدارة العامة  
للخدمات الطبية المساندة



الأخ الدكتور حمدي النابلسي المحترم  
في أ. مدير عام الإدارة العامة للمستشفيات  
الأخ الدكتور أحمد البيتاوي المحترم  
مدير مجمع فلسطين الطبي

الموضوع: تسهيل مهمة إجراء بحث.

عنوان البحث: Evaluation of genetic and environmental risk factors of colorectal cancer among Palestinians

تحية طيبة وبعد ...

لاحظاً لكتابنا رقم GDPS-647 بتاريخ 2018/06/03 بخصوص الدراسة البحثية حول العوامل المسببة لسرطان القولون نود إعلامكم بأنه سيتم تجديد هذا التعاون العلمي وتهدف هذه الدراسة إلى البحث في العوامل البيئية من التغذية والنشاط البدني وتاريخ الإصابة بالأمراض والعوامل الوراثية التي تؤدي للإصابة بسرطان القولون في المجتمع الفلسطيني بالتركيز على تشخيص الأمراض الوراثية ذات العلاقة بسرطان القولون بما فيها سرطان القولون الوراثي والمستقيم غير السلطاني (HNPCC) والمعروفة أيضاً بمتلازمة لينش في نسيج الورم ومرض السلطان الورمي الغدي الوراثي (FAP)

تهدف هذه الدراسة سيتم استقطاب الحالات المشخصة بسرطان القولون في جميع المستشفيات الحكومية إضافة إلى ذلك استقطاب أشخاص أصحاء (غير مصابين بمرض السرطان) كعينة ضابطة في هذه الدراسة، وسيتم استقطابهم عن طريق المستشفيات الحكومية ومراكز الرعاية الصحية الأولية كمرافقين لمرضى يراجعون المركز الصحي لخدمات لا تشمل أقسام الأورام وجر أقسام تطوير الجهاز الهضمي لاستقطاب عينة ضابطة تم مسحها للتأكد من خلوها من أي أورام (حميدة أو خبيثة) في الجهاز الهضمي). وسيتم جمع المعلومات من خلال:

1- استمارة تتم تعبئتها خلال مقابلة شخصية تجرى مع المرضى والعينة الضابطة بواسطة باحث ميداني متدرب: وتهدف إلى البحث في العوامل البيئية بما فيها التغذية والنشاط البدني وتاريخ الإصابة بالأمراض وتاريخ العائلة.

Ministry of Health – Ramallah

تلفاكس: 022964402  
e-mail : labs\_bb@hotmail.com  
تلفاكس: 09-2335821

وزارة الصحة - رام الله

Ministry of Health - Nablus

وزارة الصحة - نابلس



2. جمع عينات دم للحصول على المادة الوراثية DNA للمرضى والعينة الضابطة.

3. جمع شرائح من عينات الأورام المحفوظة لمرضى سرطان القولون والمستقيم - Paraffin-

(embedded blocks) في أرشيف المستشفيات بهدف القيام بعملية تشخيص سرطان

القولون

at QUIDS

القولون الوراثي والمستقيم غير السلانتي (HNPCC) والمعروفة أيضاً بمتلازمة ليتش

وذلك في قسم علم الأمراض في مستشفى بيت جالا الحكومي.

وتعقد هذه الدراسة بمشاركة عدد من الباحثين و المختصين في علم الأورام والتشخيص كما يأتي:

1. الباحث الرئيسي: وتشرف عليها الباحثة الدكتورة رانية أبو سير من جامعة القدس.

2. باحث مشارك: بروفيسور هانس فاسن، المدير الطبي للمؤسسة الهولندية لتشخيص السرطانات

الوراثية.

وتفضلوا بقبول فائق الاحترام...



## Appendix 4.6: Consent Form

### نموذج موافقة

عنوان المشروع: العوامل الوراثية والبيئية لسرطان القولون والمستقيم.

رقم المريض لهذه التجربة: \_\_\_\_\_

- أؤكد أنني قمت بقراءة وفهم ورقة المعلومات الخاصة بالدراسة، ولقد أتيت لي الفرصة بالإجابة بشكلٍ مرضٍ.
- أنا أدرك أن مشاركتي في هذه الدراسة تطوعية، وأنتي حر في الانسحاب في أي وقت دون إبداء أي سبب، بدون أي تأثير على رعايتي الطبية أو حقوقي القانونية.
- أنا أدرك أن المعلومات ذات الصلة بالملاحظات الطبية خاصتي والبيانات التي تم جمعها أثناء الدراسة، يمكن أن ينظر إليها المشاركون في هذا البحث من جامعة القدس، فإنني أعطي إذنًا لهؤلاء الأفراد للوصول إلى سجلاتي.
- أوافق على إعطاء عينات الدم للتحليل الوراثي والمصلي.
- أنا أوافق على إعطاء عينة من أنسجة الورم للاختبار المناعي.
- أوافق على المشاركة في هذه الدراسة.

التوقيع

التاريخ

رقم الهوية

اسم المشارك

التوقيع

التاريخ

اسم الشخص الذي أجرى المقابلة

## محددات سرطان القولون والمستقيم بين الفلسطينيين

إعداد: نضال عيد محمد الجبريني

إشراف: د. رانية أبو سير

### ملخص

### مقدمة

لقد شهدت معدلات الحدوث والوفيات لسرطان القولون والمستقيم في السنوات العشر الأخيرة تزايداً ملحوظاً في جميع أنحاء العالم. تُعزى هذه الزيادة إلى حد كبير إلى التغييرات الجذرية في نمط الحياة وأنماط استهلاك الطعام مع المزيد من الأطعمة ذات النمط الغربي والأطعمة الجاهزة بالإضافة إلى تبني نمط حياة مستقر في الحياة اليومية والأنشطة الأخرى ذات الصلة. هدفت هذه الدراسة إلى وصف الخصائص السريرية والمرضية لسرطان القولون والمستقيم وفهم دور عوامل نمط الحياة والمدخول الغذائي في حدوث سرطان القولون والمستقيم.

### منهجية الدراسة

لقد أجرينا دراسة الحالات والشواهد والتي شملت 131 حالة مؤكدة مرضياً من حالات سرطان القولون والمستقيم و104 من الشواهد الخاليين من السرطان. تم استقطاب الحالات من خلال مستشفيات، مستشفى بيت جالا في الجنوب ومستشفى المطع في القدس. تم جمع البيانات باستخدام استبيان واسع النطاق قائم على المقابلات يركز على العديد من عوامل الخطر للمرض.

## نتائج الدراسة

كانت نسبة الإناث بين حالات سرطان القولون والمستقيم 52.7% وكان متوسط العمر عند التشخيص 56 عامًا (النطاق الربيعي 48-64 عامًا). تم تشخيص غالبية الحالات في مراحل متقدمة من المرض. لم يكن مؤشر كتلة الجسم مرتبطاً بخطورة الإصابة بسرطان القولون والمستقيم، لكن تاريخ الإصابة بمرض السكري وارتفاع ضغط الدم وأمراض القلب والأوعية الدموية كان أكثر شيوعاً بين الحالات. علاوة على ذلك، بشكل غير متوقع، ارتبط النشاط البدني بزيادة خطر الإصابة بسرطان القولون والمستقيم. أما فيما يتعلق بالمدخول الغذائي، فقد ارتبط تناول أعلى كمية من الأسماك والفواكه والمكسرات والحلويات بشكل إيجابي بزيادة خطر الإصابة بسرطان القولون والمستقيم.

## الاستنتاجات

يمكن تفسير ارتفاع معدل الإصابة والوفيات بنمط الحياة والعوامل الغذائية، ومع ذلك، فإن نتائج هذه الدراسة تتطلب مزيداً من البحث.