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Colorectal Cancer Survival in Jordan 2003-2007

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ABSTRACT

As in other less developed countries in the region and elsewhere, cancers are becoming a major cause of morbidity and mortality in Jordan. Globally, colorectal cancer (CRC) is the second most common cancer in women and the third most common cancer in men. In Jordan, CRC is the second most common cancer in women and the most common in men. There is little known about survival from CRC in Jordan and few survival studies have been conducted in comparable Eastern Mediterranean countries.

As the first study of its type in Jordan, this thesis aimed at estimating CRC survival among Jordanian patients and comparing them with survival estimates among other populations. The thesis explored the relationship between CRC and socio-demographic characteristics, clinical manifestations, treatment, diabetes mellitus – for which the prevalence in Jordan is very high - and treatment sites. The study augmented existing Jordan Cancer Registry data by gathering additional case mix information and completing missing fields. CRC was classified according to international classification of oncology (ICD-O third edition in addition to the International Classification of Diseases, ICD-10) as C18.0-C20.9. The vital status of the patients was ascertained from Civil Registration Bureau based on use of the unique National Identification number of the patients with follow-up to 31 December, 2010. The survival duration of each case was determined as the time difference (in days) between the date of incidence (index date) and the date of death, date of loss to follow-up or the closing date for follow-up (31 December, 2010). Observed and relative CRC survival rates were calculated among a study population of 1,896 Jordanian colorectal patients aged 15 to 99 years of age, diagnosed with first invasive primary CRC from January 2003 to December 2007. The Kaplan-Meier method was used to determine the

observed survival probability over time. The logrank test was used to estimate whether the difference in survival estimates was statistically significant between the groups. The complete approach of estimation of observed survival probability was used. Cox proportional hazard regression was used to assess the effect of each variable after simultaneously controlling the effects of potential confounders.

With half of the sample aged 60 years and above, males were predominant (55.5 percent) with the majority of the sample (75.4 percent) residing in the central part of Jordan. The vast majority of the cases (63.5 percent) were diagnosed with colon cancer, with regional metastasis present in 58.9 percent. No significant difference was found in the distribution of colon and rectum cancer by sex. Adenocarcinoma was the most commonly found tumor (84.4 percent) compared to mucinous tumors which was found in 7.8 percent of the patients. In addition, 62.7 percent of the cases were classified as moderate and 14.9 percent as poor. The percentages of rectum cancer patients with moderate and poor/anaplastic types of cancer were higher than in colon cancer patients. The majority of patients (77.9 percent) underwent surgery, which was mostly elective (82.0 percent). A significantly higher occurrence of these elective surgeries was found among rectum cancer (87.7 percent) than colon cancer patients (78.7 percent). Curative treatment was found to be a more common form of treatment for colorectal cancer patients (76.5 percent) than palliative (23.5 percent). Of those undergoing surgery, 4.8 percent has died within 30-days of resection, with a significantly lower mortality among patients aged $\leq$ 65 years (2.9 percent) than the over 65 years age group (7.1 percent). Thirty days postoperative mortality was significantly higher among colon cancer patients (5.3 percent), patients with more advanced tumours and those who underwent emergency operations.

Results of this study revealed that the incidence of CRC in the Jordanian population to be low compared to developed countries. However, this low incidence is similar to CRC incidence rates in other countries in the region. During the 5-year study period, the overall crude colorectal cancer incidence rate for males was 5.6 per 100,000 population, and 5.1 per 100,000 populations in females. The overall Age Standardized colorectal incidence rate (ASR) among males was 15.5 per 100,000 populations compared to 12.5 per 100,000 populations among females. For colon cancer, the crude incidence rate was 5.4 per 100,000 populations in males and 4.1 per 100 000 populations in females, while ASR for males was 11.1 and 8.4 for females. Alternatively, the crude incidence rate for rectum cancer was 3.0 per 100,000 population for males and 2.4 per 100,000 population for females, and the respective ASR incidence rates was 6.1 per 100,000 males and 4.9 per 100,000 females. Unexpectedly, results showed a high percentage (13.8 percent) of CRC patients among the young age groups (i.e. less than 40 years of age) with insignificant differences between the sexes. The age specific incidence rates were found to increase with age.

The study revealed that 5-year observed and relative survival probabilities for colorectal cancer to be 57.7 and 61.3 percent respectively, with higher probability for colon cancer. These results showed good survival estimates of colorectal cancer compared to developed countries as well as the most developed countries in the region and across the Asian continent. The slightly higher observed colorectal survival rates among females were found to be insignificantly different than those for males. Patients aged 45 through 59 years had the highest survival estimates among all age groups, and the 75 years and above age group the lowest. The highest survival estimates were found among patients living in the central parts of Jordan, and the poorest was significantly noted in the south. Moreover, the

observed and relative survival estimates were consistently highest during Year 1 and lowest during Year 5.

Mucinous and serous tumors showed the poorest survival rates among the colorectal cancer, with higher 5-year relative survival rates among the mucinous and serous type of colon (52.4 percent) compared to rectum cancer (42.8 percent). With more than half of the colon patients (57.2 percent) and rectal patients (62 percent) having a regional spread; a higher proportion of colon cancers (24.1 percent) were found to have distant metastasis, than rectum cancer patients (20.5) and an equally low (11 percent) had localized CRC at diagnosis. Results also showed that observed and relative survival rates from localized and regional colon cancer were better than survival from rectum cancer in the same stages at 1, 3 and 5-years of diagnosis. Results also indicated that observed survival became poorer with increasing age for both localized and regional tumours. This observation was applicable for both males and females.

In recognizing appropriate surgery as the most important aspect of colorectal cancer treatment, the observed survival probability for colorectal cancer patients who underwent surgery was found significantly higher than that for patients who did not undergo surgery. This scenario was similarly observed for both colon and rectum. Conversely, the overall relative survival rates for patients who underwent surgery declined from 96.2 percent to 62.6 percent between the first and fifth year and from 86.5 percent to 23.5 percent for patients who did not undergo surgery. In addition, no significant difference was found between colorectal survival estimates for patients who underwent elective surgery and those who underwent emergency surgery. This was held true for both colon and rectum cancer.

A multivariable analyses done to examine the adjusted odds of death within 30 days of surgery and selected variables revealed that the odds of dying were significantly higher among colorectal cancer patients older than 65 years (OR 2.3, 95percent CI: 1.3-4.1), those with distant tumors (OR 3.6, 95percent CI: 2.0-6.2); and those who were operated upon as an emergency (OR 2.3, 95percent CI: 1.2-4.1).

Study findings indicated that colorectal cancer patients who received chemotherapy treatment had better survival for almost the first four years. However this was not a statistically significant result. Similarly, colon cancer patients who received chemotherapy treatment had better survival rates for nearly four years, compared to rectum cancer patients had better survival rates for the first two years from receiving chemotherapy.

In terms of treatment sites (hospitals), results showed that 32.4 percent of cases were treated at public health facilities, 23.4 percent at King Hussein Cancer Center (KHCC), 18.4 percent at the teaching hospitals, 16.8 percent at the private health facilities, and only 9.1 percent at other sites. The results of Cox proportional hazards ratios, after adjusting for age, extent of disease, place of residence, surgery, chemotherapy, radiotherapy and intent of treatment, have shown that patients who received treatment in private hospitals as well as in the King Hussein Cancer Center, had better survival rates compared to those who received their treatment in the public sector.

Finally, this study revealed that the mean survival for colorectal cancer patients with diabetes mellitus was significantly lower than that for patients without diabetes (Log-Rank test, p=0.0359). The study also revealed a significant relationship between diabetes

mellitus and colon cancer survival, where diabetic patients with colon cancer were less likely to survive compared to non-diabetic patients with colon cancer. However, no significant association was observed regarding diabetic patients with rectum cancer. In addition, multivariate analysis identified diabetes mellitus as a significant predictor associated with lower observed survival, where diabetic patients were one and one-half times more likely to be at risk of dying compared to non-diabetic patients. Age group 75 years or older, regional and distant metastasis of disease were shown to be independent prognostic factors for observed survival in this multivariate analysis.

The Cox proportional hazard model showed that age, place of residency, extent of disease, and morphology to be significant predictors for colorectal cancer survival. Colon cancer patients aged 75 years and above had 2.2 times higher risk of death than those aged 44 years or less (HR=2.2, 95percent CI: 1.5-3.1). Rectum cancer patients residing in the central region of the country had a 27 percent lower risk of death compared with those who resided in the North (HR=0.73, 95percent CI: 0.56-0.95). Colon and rectum cancer patients with regional metastasis had three times and one and the half times higher risk of death than those with localized disease respectively (Colon: HR=3.3, 95percent CI: 2.0-5.6); (Rectum: HR=1.6, 95percent CI: 1.1-2.5). Moreover, colon patients with distant metastasis had fourteen times higher risk of death and rectum cancer patients portrayed four and the half times higher risk of death than those with localized disease (Colon: HR=14.0, 95percent CI: 8.0-23.8); (Rectum: HR=1.6, 95percent CI: 2.8-7.5). Colon patients with poor or anaplastic grade had almost twice the risk of death than those with well grade (HR=1.9, 95percent CI: 1.1-3.2). On the other hand, patients diagnosed with mucinous rectum cancer had 1.4 times higher risk of death than those with adenocarcinoma (HR=1.4,

95percent CI: 1.1-2.1). Sex, grade and year of diagnosis were insignificant predictors across all three models (CRC, colon and rectum).

The main highlights of the study findings included a higher than expected incidence and a poorer than expected colorectal survival among the younger population, a large variation in survival rates based on the place of residency, and a significantly poorer survival among diabetic patients. Results of this study prompted a set of recommendations to assist national efforts in preventing and improving the survival of colorectal cancer in Jordan. These recommendations included various actions and measures to strengthen health service provision; assure provision of health care by expanding services; improve monitoring by promoting policy and research; and improve and strengthen data quality measures. Specifically, the study recommended screening to be made at a younger age in Jordan than in other developed countries as a result of the high percentage of CRC (13.8percent) among young age groups (<40 year) that was reported in the study. Conducting further research to investigate the reasons for poor survival rates among younger CRC patients is presented as a strong study recommendation.

In addition, introducing managed clinical networks as an approach for reducing the variation in survival between the different hospitals was presented as a worthwhile recommendation. Undoubtedly, improving public health efforts to reduce the prevalence of Diabetes Mellitus, in addition to undertaking further research to explain the increased mortality among diabetic colorectal patients are presented as valuable recommendations in this study. Finally, the study recommended that the Jordan Cancer Registry play a major role in following-up with cancer patients to examine the quality of cancer services that they receive.

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AUTHOR'S DECLARATION

I declare that this thesis and all the work presented, is my own original work, unless indicated otherwise in the text. The Jordan Cancer Registry (JCR) data was used with help from Dr. Omar Al Nemri. Data was handled in compliance with the principles of the Data Protection Act 1988. Secure encrypted electronic storage media was used to handle data, which was made anonymous before analysis by removing all sensitive data such as names and address and replacing them with computer-generated numbers.

Using the data was approved by the national health ethical review board (ERB), Jordan ministry of health as well as by the institutional review board (IRB) of King Hussein Caner Center. Furthermore, the study protocol was approved by the ethics committees of Glasgow University as well as the International Agency for Research on Cancer (IARC). As patients were not directly contacted or involved, the principal ethical consideration in this study was to avoid disclosure of personally identifiable information. After completing the data analysis according to the Study objectives, the data will be provided to the JCR.

I attest that this work has not been submitted previously for the pursuit of any higher degree and was carried out under the supervision of

Mohannad AL-Nsour

March, 2014

DEDICATION

Dedicated to my wonderful mother (Malak Al Azab), who has never failed to nurture me, love me and encourage me through my years of study. Her special ways in supporting me and motivating me throughout my development has given me strength, not only to pursue my dreams, but to do so with passion, desire and strength. I can never pay back my mother for the encouragement and for believing in me……I love you mother.

LIST OF ABBREVIATIONS

Age specific incidence rate (ASIR)

Age-standardized incidence rate (ASR)

American Joint Committee on Cancer (AJCC)

Body Mass Index (BMI)

Cancer in Five Continents (CI5)

Cancer Incidence in Five Continents Volume IX (CI5 IX)

Civil Health Insurance Plan (CHIP)

Civil Registration Bureau (CRB)

Colon cancer (CC)

Colorectal cancer (CRC)

Computed Tomography (CT)

Confidence interval (CI)

Department of Statistics (DOS)

Death certificate only (DCO)

Deoxyribonucleic acid (DNA)

Diabetes mellitus (DM)

Disease-free survival (DFS)

Distal colon cancer (DCC)

Double contrast barium enema (DCBE)

Ethical review board (ERB)

European Standard Population (EASR)

Faecal occult blood testing (FOBT)

Familial Adenomatous Polyposis (FAP)

Gross Domestic Product (GDP)

Hazard Ratio (HR)

Health Care Accreditation Council (HCAC)

Hereditary Nonpolyposis Colon Cancer (HNPCC)

Identification number (ID)

Institutional review board (IRB)

International Agency for Research on Cancer (IARC)

International Cancer Survival Standards (ICSS)

International Classification of Diseases (ICD-10)

International Classification of Diseases for Oncology, 3rd edition (ICD-O3)

International Society for Quality in Healthcare (ISQua)

Joint Commission International (JCI)

Jordan Cancer Registry (JCR)

Jordan University Hospital (JUH)

King Abdullah Hospital (KAH)

King Hussein Cancer Center (KHCC)

Matrix Metalloproteinases 2 (MMP-2)

Metabolic syndrome (MS)

Middle East and North Africa region (MENA)

Middle East Cancer Consortium (MECC)

Ministry of Health (MOH)

Mortality-to-incidence ratio (M/I)

Mucinous adenocarcinoma (MA)

National Cancer Institute (NCI)

Non-communicable diseases (NCDs)

Non-Hodgkin Lymphoma (NHL)

Positron Emission Tomography (PET)

Proximal colon cancer (PCC)

Purchasing Power Parity (PPP)

Rectal cancer (RC)

Ribonucleic acid (RNA)

Royal Medical Services (RMS)

Summary relative risks (SRR)

Surveillance, Epidemiology and End results (SEER)

Total fertility rate (TFR)

Tumour, Node, Metastasis (TNM)

United Nations Relief Works Agency (UNRWA)

Vascular endothelial growth factor (VEGF)

World Health Assembly (WHA)

World Health Organization (WHO)

CHAPTER 1 – INTRODUCTION

1.1 Overview

This chapter aims at introducing the reader to the rationale, aims and objectives of this thesis. The chapter begins by providing an overview of the thesis and its organization by presenting the different chapters and a synopsis for each. This chapter moves on towards identifying the rationale, aims and objectives for undertaking this study. The chapter focuses on the significance of the study and the logical argument for conducting it.

1.2 Thesis Overview

This thesis is organized and presented as follows:

Chapter 1 includes the rationale, the significance of the study, the study's general outline, the study's aims, objectives and the research questions. This chapter provides the logical and systematic construction of the thesis.

Chapter 2 provides a review of the literature starting with background information on Jordan where general information about Jordan's geographical and population characteristics, health care system and mortality system is discussed. In addition, the chapter provides a discussion on the burden of diseases in general, as well as the burden of cancer. The chapter then proceeds to give an overview of cancer and present the problem of CRC with an emphasis on definition, epidemiology, symptoms, risk factors, screening and treatment. Research work describing the different factors that can influence CRC survival rates, namely: age; clinical characteristics of the tumour; type of treatment; comorbidity; country of residence, socio-demographic characteristics (i.e. race and

ethnicity, sex and socio-economic status); health services; and residence-related factors (i.e. country of residence and community-related factors) are depicted and discussed to explain the motivation for pursuing this thesis.

Chapter 3 offers a discussion on the materials and methods used in conducting the study as well as a presentation of the procedures and study design. This chapter focuses on data sources, eligibility and inclusion criteria, study instruments and description of data collection, data quality control, data analysis techniques and procedures, terms and definitions, and human research ethical approvals are also included in this chapter.

Chapter 4 - 9 present the main findings of the study in parallel with the main study objective. These chapters follow a similar presentation pattern where each provides an introduction, presentation of main results, summary and discussion of main findings. Following is a listing and description of these chapters.

Chapter 4 includes a description of the study population in terms its socio-
demographic characteristics, as well as clinical and treatment
characteristics.

Chapter 5 presents incidence rates of CRC in the Jordanian population over the
study period. The chapter also presents results of CRC survival
analysis and findings associated with observed and relative survival
rates related to patients' characteristics: specifically, socio-
demographic characteristics, (age, sex, residency and year of
diagnosis).

Chapter 6 presents and discusses the results of CRC survival analysis in relation to the clinical manifestations (site, histopathology, grade, stage) and treatment and the effect of these factors on the survival rate of CRC.

Chapter 7 presents the results and discussion of CRC survival estimates and the effects of treatment sites on them. It presents differences of CRC survival estimates across treatment sites within Jordan and attempts to explain survival disparities detected between the treatment sites.

Chapter 8 presents the results and discussion of colorectal survival and its association with diabetes mellitus in an attempt to detect the association of diabetes mellitus with CRC survival and rationalize its impact on patient outcome.

Chapter 9 presents an overall discussion and a summary of the main results, implications and recommendations for further related research based on the main study findings. This chapter concludes the study and is followed by a list of references, annexes and appended material.

1.3 Study Rationale

Cancer is considered to be a disease of the developed countries, whereas Jordan, one of the low-middle-income countries, is experiencing an epidemiological transition where infectious diseases are declining and chronic diseases are becoming more predominant (1;2). Sedentary lifestyle, high fat diet, and smoking are becoming common in Jordan

(3;4). As in other less developed countries in the region and elsewhere, cardiovascular diseases (CVD) and cancer are the major causes of morbidity and mortality in Jordan.

Communicable diseases have been the main diseases of the less developed countries. Recent development in less developed countries produced an increase in life expectancy together with changes in lifestyle leading to an epidemic of cancer (5;6). Based on current trends, it is estimated that 70 percent of the new cases of cancer will be diagnosed in people living in developing countries by the year 2020 (7). In addition, recent annotation by the World Health Organization (WHO) and the International Agency for Research on Cancer (IARC) indicated that 12.5 percent of all deaths in less developed countries are caused by cancer. Furthermore, cases in less developed countries are diagnosed with an advanced stage or terminal cancers at the time they are presented to the health system (7-9).

Cancer survival statistics are a means of quantifying the effectiveness of early detection strategies and treatment regimens at the population level (10;11). They are useful as comparative measures between different populations. It is these comparisons that help identify possible reasons for the differences and suggest targets for improvement and a means of monitoring progress towards them (12-14).

Due to the tremendous impact of cancer on the health care system and the escalating cost of health care, strategies for cancer prevention and control are becoming increasingly important. Recently, Jordan launched the National Health Research Priorities Programme (2009-2012) in cooperation with the WHO, which included CRC at the top of its list of priorities (15). However, as other Eastern Mediterranean countries, Jordan still suffers from a scarcity of local studies that investigate the cancers' survival.

Few survival studies have been conducted in developing countries (14;16-18), particularly in Eastern Mediterranean countries. Currently the situation is mainly described through the results of studies conducted in the developed countries (13;19-21). To the best of the author's knowledge, survival statistics of CRC in Jordan are not available. Therefore, results of this study will support the crucial need to better understand the burden of CRC in Jordan, thus contributing to the implementation of the national efforts of cancer prevention and control.

1.4 Study aims and objectives

This is the first CRC survival study in Jordan. The study aimed to establish the estimates of survival among Jordanian patients with CRC and to compare them with survival estimates among other populations. The second major aim of this study was to investigate the possible influence of socio-demographic characteristics, clinical manifestations and treatment on the survival of CRC in Jordan. Another aim of this study was to explore possible survival differences of CRC across treatment sites that provide cancer treatment within Jordan. Finally, the study aimed at determining the possible effect of diabetes mellitus (one of the most prevalent comorbidities in Jordan) on CRC survival among Jordanian patients.

1.4.1 Research questions

Six research questions were formulated based on the review of the relevant literature and to address the gaps found in the literature. These questions were:

RQ1: *What are the observed and relative 5 years survival rates of CRC among Jordanian patients diagnosed in 2003-2007?*

RQ2: *Do survival rates from CRC differ between Jordan and other comparable countries, and if so, how can this be explained?*

RQ3: *Do socio-demographic characteristics (e.g. age, sex, place of residency, etc.) affect the survival rate of CRC in Jordan?*

RQ4: *Do the patient's clinical manifestations (site, histopathology, grade, stage) and treatment of the tumour affect the survival rate of CRC in Jordan?*

RQ5: *Are there differences of CRC survival estimates across treatment sites within Jordan and how could they be explained?*

RQ6: *Does diabetes mellitus – which has very high prevalence in Jordan - affect the survival of CRC among Jordanian patients?*

1.4.2 Study objectives

The Study objectives were developed to answer the research questions. They are the following:

Study objective 1: To produce estimates of observed and relative survival estimates for Jordanian patients diagnosed with CRC in 2003-2007.

Study objective 2: To compare CRC survival among Jordanian patients with other comparable populations, and to explain the possible differences.

Study objective 3: To investigate the possible influence of socio-demographic characteristics (e.g. age, sex, place of residency, etc.) on CRC survival estimates.

Study objective 4: To investigate the effects of the clinical manifestations (e.g. site, histopathology, grade, stage, etc.) and treatment of CRC on survival estimates.

Study objective 5: To explore possible survival differences of CRC between treatment sites within Jordan, and explain the possible differences, if any.

Study objective 6: To investigate the possible effect of diabetes mellitus (as a major co-morbidity factor in Jordan) on CRC survival among Jordanian patients.

1.5 Summary

This chapter introduced the rationale and layout of the thesis as well as the research questions and study objectives. The primary gap in the literature (i.e. the lack of CRC survival statistics in Jordan) along with the deliberate need to focus on preventing and controlling cancer in Jordan were presented in this chapter as key logical elements for motivating the study research questions and study objectives.

CHAPTER 2 – LITERATURE REVIEW

2.1 Introduction

This chapter aims at providing relevant scientific evidence and background information needed to establish a theoretical base for the study. The chapter starts by providing the reader with an overview of Jordan, including a discussion of various characteristics of its health care system, while attempting to compare these characteristics with similar data from other countries. The chapter introduces the reader to the burden of diseases in Jordan by providing a review and discussion on the significance of an epidemiological transition will particular emphasis on the burden of cancer.

The chapter moves on to present a discussion on the development of colorectal cancer (CRC) in patients and its epidemiology. Variations in incidence rates across the globe and the region are compared, and risk factors are introduced with specific focus on the risk factors that are commonly shared with diabetes mellitus. In addition, this chapter discusses identification techniques and treatment of colorectal cancer cases and looks at different factors that can influence colorectal cancer survival rates. These include: age; clinical characteristics of the tumour; type of treatment; comorbidity; socio-demographic characteristics (i.e. race and ethnicity, sex and socio-economic status); health services; and residence-related factors (i.e. country of residence and community-related factors).

The purpose of the literature review provided in this chapter is to help in the preparation of the study tools and to overcome difficulties that were highlighted by previous investigators, as well as provide material that supports the study objectives. The literature review was carried out using IARC library, PubMed, Medline and MSH data bases,

searching for peer-reviewed publications regarding CRC survival and its correlates. IARC library was also used to access many of the selected articles. Key words used in the search process were: "colorectal cancer" used independently or in combination with "survival", "socioeconomic", "social", "deprivation", "comorbidity", "treatment", "radiotherapy" and "chemotherapy".

The search for pertinent references involved a systematic approach. The first step was to look at the title of the article to determine whether to include it or not. In case the title was not clear enough for such a decision, the abstract of the study was read thoroughly. Following the first two steps, relevant studies were saved into a Reference Manager data base. As a third step, a whole-article review was done to determine if the selected articles met the inclusion criteria.

The inclusion criteria for the literature review were mainly studies that: 1) Estimated relative and observed survival rates of CRC; 2) Investigated the associations between survival rates of CRC and socio-demographic characteristics, clinical characteristics, type of treatment and comorbidities; 3) Included the C18-C20 classifications.

Relevant information and reports were referenced through the Ministry of Health and the King Hussein Cancer Center. Many papers prepared by academic researchers were also accessed. Local websites with published and unpublished materials (such as annual reports, some studies) were also examined during the preparation of this review.

2.2 Country Profile

This section presents important demographic and health information about Jordan. Specific information related to Jordan's geography, population, health care system, health profile, and cancer registry is displayed in an attempt to define the study setting.

2.2.1 Jordan's geography and population

Jordan is located in the Middle East region and bordered by Iraq, Syria, Saudi Arabia, the Occupied Palestinian Territory (depicted as West Bank) and Israel (Figure 1). As a small country with limited natural resources and a semi-arid climate, Jordan has a total land territorial area of 89,300 square kilometres, of which only 7.8 percent is arable land. Jordan's population of approximately 5.98 million are mostly Arabs with some Circassians, Chechens and Armenians. More than 92 percent of the population is Muslim and about 6 percent are Christian. Administratively, the country is divided into 12 governorates, which are then grouped into three regions – the North region (Irbid, Jarash, Ajloun and Mafraq), the Central region (Amman, Zarqa, Balqa, and Madaba) and the South region (Karak, Tafielah, Ma'an and Aqaba). The major cities are Amman (the capital), Zarqa and Irbid (22) .

Figure 1: Map of Jordan
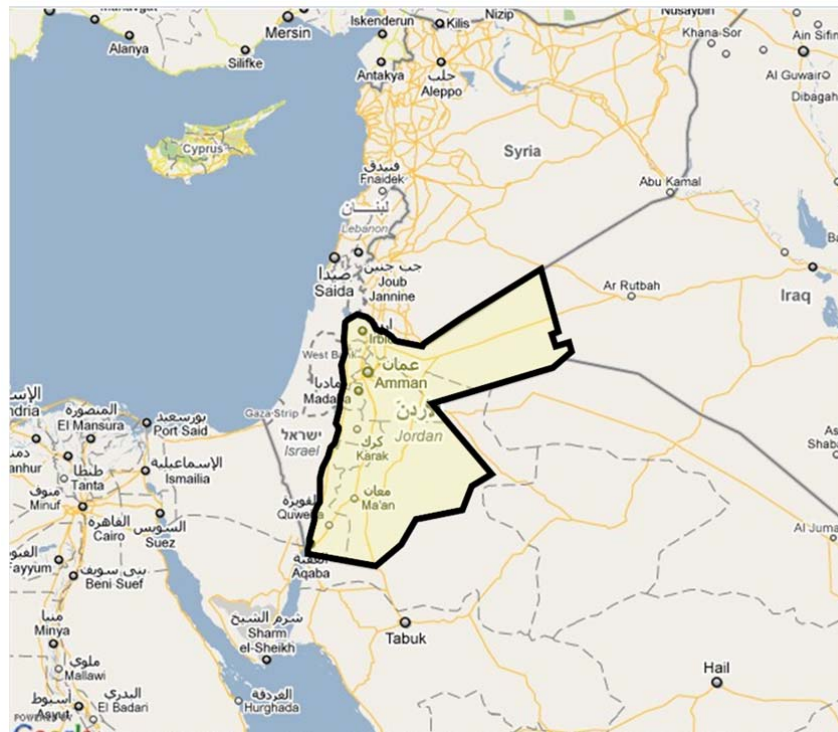
From 2005 through 2008, Jordan's death rate remained constant at less than one percent, while the birth rate continued to climb at nearly 3 percent annually. The significant rise in population growth has seen the national population density increase from 56 to 70 persons per square kilometres in the past decade(22;23). However, population density is far from uniform throughout Jordan. The northern governorates (such as Irbid, Jarash and Ajloun) range from 320 to 660 persons per square kilometres; Amman, in the centre of the country has a population density of slightly less than 300 persons per square kilometres; and in the southern governorates of the country (such as Ma'an and Aqaba), population density is extremely low - between 4 and 19 persons per square kilometres. These figures, though, are strongly influenced by land size. Compared with the whole of the kingdom, the area of the Northern Region represents 33 percent of the total; the Central Region comprises 16 percent; and the Southern Region covers 51 percent of the kingdom (22;23).

The illiteracy rate for those aged 15 years or more is 6.7 percent overall, split as 9.9 percent for females and 3.6 percent for males. Some 41 percent of this age group has completed a secondary education or university; of those completing secondary education (17.7 percent of the group), females slightly outnumber males. The same is true for education of intermediate diploma-stage (8.2 percent of the group); but females more significantly outnumber the males, comprising 9.9 percent of the group versus 6.6 percent, respectively. But this trend is reversed when it comes to completing a bachelor's degree or more; where 14.7 percent of the group aged 15 years or greater have attained a university degree, with 13.7 percent females and 15.7 percent males (22).

Jordan is undergoing a demographic transition. Results from the 2004 census indicate that the age structure of the Jordanian population has changed considerably since 1979 as a result of changes in fertility, mortality and migration dynamics. Consequently, the proportion of the population under 15 years of age declined from 51 percent in 1979 to 37 percent by 2004, while life expectancy continues to increase reaching 74 years for females and 72 for males (1;22).

The total fertility rate (TFR) is relatively high in Jordan, though it has declined steadily in recent years to reach 3.6 in 2009 (1;22). Available data from 2011 shows that the steady mortality rate (of 0.7 percent) combined with the steadily increasing birth rate (presently 2.89 percent) yielded an average annual population growth rate of 2.2 percent in 2008 (1;24). Figure 2 shows the age distribution of Jordan's population in 2009 of 5.98 million total populations with 58 percent were less than 25 years of age. Furthermore, 36.9 percent were under 15 years of age; 59.6 percent were between 15 and 64 years of age; and 3.5

percent were over 65 years of age. The total population was divided into 50.4 percent males and 49.6 percent females.

Figure 2: Age distribution of Jordan population, 2009
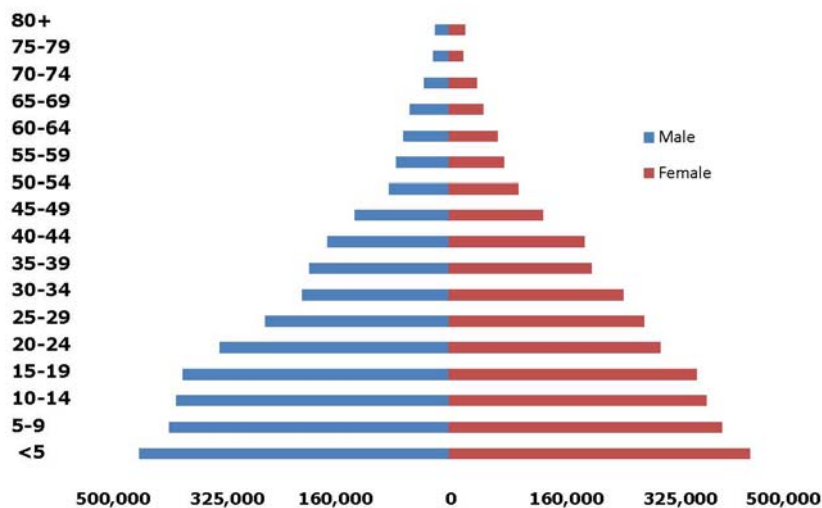
Source: Department of Statistics [Jordan] and ICF. 2010. *Population and family health survey 2009*.

Over the next few years, Jordan's demographics are expected to change significantly. The country's population is growing rapidly, doubling over the last 20 years and likely to almost double again by 2035. Jordan will see the relative size of its working age population more than double, leading to increased demand for infrastructure, quality education and health care. Policies are needed to reduce fertility rates, anticipate future retirement needs and address issues that influence health status and needs. The estimated population of Jordan at the end of the year 2008 was 5.85 million. By 2009, the population was estimated at 6.83 million. This significant increase shows not only the difficulties with

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collecting complete statistics, but also the very large migrations related to conflicts in the region (1;2).

Consequently, the relative size of Jordan's population particularly that of the younger and middle aged group, will more than double in the coming two decades. This denotes an expected sharp increase in the size of the at-risk population for non-communicable diseases, including cancer. Such an increase holds implications for primary and secondary prevention and health care resources needed for screening and treatment services. Therefore, policies are currently needed to reduce fertility rates; anticipate future health needs and health services, and address issues that might impede efficient management of chronic disease, including management of colorectal cancer.

2.2.2 Overview of Health Care System in Jordan

Significant achievements have been made in the health field over the last three decades making Jordan stand as one of the best countries in the region. Jordan was ranked by the World Bank to be the number one medical tourism destination in the Middle East and North Africa region (MENA) and fifth in the world as a top medical tourism destination (25;26).

Despite its modest resources, Jordan has developed an advanced record in terms of caring for the health of its citizens when compared to its neighbouring countries. Jordan's basic health indicators have improved gradually and a variety of national health programmes have significantly cut the risk of infectious disease. For example, there have been no recorded cases of either polio or croup since 1995 and only 59 cases of measles were

recorded in 2008 compared to 1212 cases in 1979. Jordan achieved universal child immunization in 1988 and has made considerable progress in reducing the major health risks to infants and children. Since the early eighties; all national socioeconomic plans have emphasized the right to health and health care. Major progress was achieved in lowering the infant and child mortality rates (1.9 percent and 2.0 percent, respectively), as well as the maternal mortality rate (of 19 per 100,000 live births) (22;24). Currently, Jordan is one of the countries with the lowest infant and maternal mortality rates in the region (2). Further comparisons of main health indicator reveals that in Jordan the Infant Mortality Rate (14.97 infant deaths per 1,000 live births) is not very far off from that of other developed countries with all their lifesaving technology, like the United Kingdom where the average is 4.56 infant deaths per 1,000 live births and the United States (6 per 1,000 live births) (27).

In reviewing the progress made towards achieving the Millennium Development Goal (MDG) targets, utilizing MDG Progress Index and data available from 2011, Jordan's overall MDG progress score (4.5) indicated an overall improved performance (Appendix 1), ranking as top 33 from among 137 countries (28).

2.2.2.1 Epidemiological Transition

The last century has witnessed the most remarkable improvement in health in history for most nations. Life expectancy at birth has increased from a global average of 46 years in 1950 to 66 years in 1998 (29). Socio-economic development has been long associated with the health status and disease profile of human societies. With industrialization, the major causes of death and disability in the more advanced societies, have shifted from a predominance of nutritional deficiencies and infectious diseases, to those classified as

degenerative (i.e. chronic diseases such as cardiovascular disease/CVD, cancer and diabetes). This has come to be known as "the epidemiologic transition" (6). At any given time, different countries in the world or even different regions within a country are at different stages of the epidemiologic transition. This transition can occur between different disease categories (e.g., deaths from childhood diarrhoea and malnutrition giving way to adult chronic diseases), as well as within a specific disease category (e.g., rheumatic heart disease of the young giving way to chronic coronary artery diseases of middle age, degeneration and cancer of the elderly (30;31).

Nowadays worldwide, the burden of non-communicable diseases (NCDs) is increasing posing a major current and future public heath challenge (32-34). Mortality, morbidity and disability attributed to NCDs account for about 60 percent of global deaths and nearly half of the global burden of disease (9;32;34;35). Approximately 80 percent of deaths attributed to NCDs occur in low- and middle-income countries (33;34). In 2005, deaths from all chronic diseases in 23 selected countries accounted to 61 percent of all deaths, it is estimated that this figure will rise to 66 percent in 2015 and to 71 percent in 2030. These 23 selected countries, including Egypt, Turkey, Pakistan and Iran, account for around 80 percent of the total chronic disease mortality burden in developing countries (5). Furthermore, different studies in Colombia, Spain and Brazil indicated ascending trend in the mortality rate from colorectal cancer (36-38). As an example, in Spain the adjusted overall mortality rate of Andalusia increased from 7.7 to 17 deaths per 100,000 person-year in men and 6.6 to 9 deaths/100,000 person-year in women (38).

The Middle East and North Africa (MENA) region faces a dual burden of disease because of decreasing rates of communicable diseases and increasing rates of non-communicable

diseases. According to the World Health Organization (WHO) estimates, in 2010, communicable diseases accounted for 29 percent of the disease burden (down from 40 percent in year 2000) and non-communicable diseases accounted for 53 percent (up from 45 percent in 2000). By 2020, the respective figures are estimated to be 20 percent and 60 percent. Results from the Global Burden of Disease Project 4 dispel the notion that non-communicable diseases are related to affluence: premature mortality rates from non-communicable diseases are higher in populations with high mortality and low income than in industrialized countries. Upper-income and urban areas in middle-income countries of the region are mainly burdened by non-communicable diseases, having largely controlled communicable diseases (38-40).

Jordan is witnessing a demographic transition with expected increase in the elderly population (5 percent of the population by 2025 and 15 percent by 2050 (22), decrease in the burden of communicable diseases and concomitant increase in the burden of non-communicable diseases (3;4). Currently, approximately half of deaths in Jordan are attributed to NCDs, namely, cardiovascular diseases, diabetes and cancer (41). Information from Jordan supports the theory that Jordan is experiencing an epidemiological transition from communicable to non-communicable diseases (3;4;15;41;42). Nowadays (in Jordan) Infectious disease accounted for less than 2 percent of all deaths; however NCDs accounted for more than 50 percent of all deaths in Jordan. Heart disease and stroke (International Statistical Classification of Diseases, 10th Revision, codes I00-I99) accounted for 35 percent of all deaths; malignant neoplasms (C00-C97) were responsible for 13 percent of deaths (15).

Results from the most recent (2007) Jordan Behavioural Risk Factor Survey on a national representative sample above 18 years of age showed that nearly one in three participants smoked cigarettes; two-thirds were overweight or obese; nearly one in five had been diagnosed with high blood pressure; and nearly one in ten had been diagnosed with diabetes mellitus; among participants of the medical evaluation, an estimated 11percent reported having been diagnosed with diabetes by a health professional, and 19 percent were diagnosed with diabetes according to laboratory testing (3). Furthermore, sedentary lifestyle, high fat diet and smoking are becoming common in Jordan (3;4;42-44). Crude projection estimates suggest that approximately 1 to 3 million people in Jordan will have diabetes, hypertension, or high blood cholesterol by 2050 according to changes in disease prevalence and the growth of the population (45).

2.2.2.2 Governance of health system

The healthcare system in Jordan comprises public, private and not for profit organizations, complemented by rising standards of living, housing, education, safe water supply and sanitation. The public sector consists of two major public programs that finance as well as deliver healthcare: the Ministry of Health (MOH) and Royal Medical Services (RMS). Other smaller public programs include several university-based programs, such as Jordan University Hospital (JUH) in Amman and King Abdullah Hospital (KAH) in Irbid. The extensive private sector includes 60 hospitals and many private clinics. Over 1.6 million Palestinian refugees in Jordan get access to primary care through the United Nations Relief Works Agency (UNRWA). Each of the health care sub-sectors has a financing and delivery system of its own. It is worth mentioning that MOH is responsible for all health matters in the country and, in particular, for maintaining public health by offering

preventive, treatment and health control services and organizing and supervising health services offered by both the public and private sectors (46;47).

In addition, the majority of public hospitals are located in the central part of the country as well as the referral hospitals. Furthermore, the governance of MOH hospitals is highly centralized. Senior level executives at headquarters in Amman (the capital of the country which is located in the central region) decide all significant managerial, personnel, budgetary and procurement matters (25) .

2.2.2.3 Health care financing

In 2007, Jordan's total Gross Domestic Product (GDP) per capita represented 3,022 U.S. Dollars. This was considerably higher than the rate of the Lesser Developed Countries (576 U.S. Dollars), considerably less than the OECD Member States (34,092 U.S. Dollars), but in line with the World Bank's set of Middle Income countries (2,923 U.S. Dollars) (48).

In the same year, Jordan's total health expenditure–-both public and private–-was estimated at 1,422 million U.S. Dollars, or 253 U.S. Dollars per capita. This was equivalent to 8.4 percent of GDP. The government share in the financing of health expenditures increased from 43 percent in 1998 to 59.8 percent in 2007. Jordan's healthcare expenditure of 8.4 percent of GDP is similar to that of the U.K. (8.4 percent) and Australia (8.5 percent). When total healthcare expenditures are compared in terms of Purchasing Power Parity (PPP), Jordan's expenditure per capita ($414) is much lower than

the U.K. ($3,007) and Australia ($3,314) but more favourable than Egypt ($259), Syria ($177) and Iraq ($136) but similar to Tunisia ($469) (48).

Secondary care, in Jordan like many other developing countries, takes up a disproportionately large share of public spending on health. During the period 1998-2007, the share of curative care increased from about 79 to 82 percent of the total health expenditure, while the proportion spent on primary health care remained below 20 percent (46;47).

Overall spending has increased in nominal terms over the past six years and has grown slightly more rapidly than Gross Domestic Product (GDP). Nevertheless, Jordan's health spending, whether measured in per capita U.S. dollar terms or as a share of GDP, is high compared to other Middle East and North Africa Region (MENA) and middle-income countries (25).

2.2.2.4 Health insurance

About 79 percent of the population in Jordan is covered by formal health insurance. MOH is the largest health insurer (34 percent) followed by RMS (26 percent), private firms (9 percent), UNRWA (8.5 percent) and university hospitals (1.3 percent) (49). In addition to its general public health functions, the MOH is responsible for administering the Civil Health Insurance Plan (CHIP) that covers civil servants and their dependents. Individual certified as poor, the disabled, children below the age of six years and blood donors, pregnant women and elderly above 60 are also formally covered under the CHIP. In

addition some costly diseases are also insured according to special regulations determined by the Health Insurance bylaw, including cancer and its side effects (46).

2.2.2.5 Health workers

In 2008, the total number of health workers in Jordan was 91,756 (12 percent of the total employees in the public and private sectors). The country has 25 physicians, 38 nurses (all categories), 9 dentists and 13 pharmacists per 10,000 populations (46). The number of physicians per 10,000-population is similar to the numbers found in the U.K. (27), Australia (25) and the U.S. (24). This makes Jordan's rate considerably greater than the number of physicians per 10,000 population found in Syria (5), Iraq (7), Saudi Arabia (9), Tunisia (13) and Turkey (16). But, numbers for UAE (19.3) and Qatar (22.5) approach Jordan's ratio of physicians to 10,000 population, while Egypt (28) exceeds it (50). During the last ten years the number of most health professions and their percentages to population has been increasing (46). The nurse-to-doctor ratio in the health sector (i.e. 1.2 nurses to 1.0 doctor) remains very low and is among the lowest group of countries in the world (46;47). E.g. Jordan's ratio is the same as Mexico, but much lower than the ratios found in the U.K., France and the U.S. (i.e. 3.6, 2.5 and 4.2, respectively) and even lower than Russian Federation and Estonia (both at 1.9) and Poland (at 2.4) (48).

2.2.2.6 Jordan Cancer Registry

The Jordanian Cancer Registry (JCR) is a population based–cancer registry covering six million people at national level. Jordan initiated the Jordan Cancer Registry (JCR) in 1996 in collaboration with National Cancer Institute (NCI-USA) and the Middle East Cancer Consortium (MECC). The main purpose of JCR is to assess the burden of cancer diseases by collecting data on all diagnosed malignancies from all related health facilities. The JCR

receives notification forms from different hospitals representing all health sectors distributed all over the country, (Public, Private, Royal Medical Services and the teaching hospitals). The JCR collects data by a combination of active and passive methods, 1) trained personnel abstract cancer data from patient files and complete notification forms before forwarding them to the JCR, and 2) JCR staff conduct site visits to medical facilities during which; JCR staff monitor the quality of data collection and search for missed cases and missing information (51).

Since 1996 onwards, cancer registration in Jordan was performed in accordance with rules set out by the International Agency for Research on Cancer (52). The JCR started using a specially designed registration form and checking for duplication and consistency using the CANREG IV software developed by IARC specifically for cancer registration (53). All cancer cases are coded using the 3rd revision the International Classification of Diseases for Oncology, 3rd edition (ICD-O3) (54), in addition to the International Classification of Diseases (ICD-10) (55).

When Jordan joined the Middle East Cancer Consortium (MECC) in 1998, further quality control measures were applied and awareness was also raised on notifying staff about the existence and benefits of the registry (56). In 1998, completeness and reliability of The JCR data was assessed by external assessors and registrations were determined to be 88 percent complete. Such a completeness rate was considered excellent for a newly establish registry (57). In 2003, the Jordan Ministry of Health updated its death certificate according to international standards. Improving of quality of death certificate and increasing coverage and utilization of medical death certificates allows mortality statistics to be used with greater confidence for causes of death. However, even mandatory death certification

requires basic additional information to enable verification of the causes of death statistics with other sources. Recently death certificates have been used as a reliable source of information in the JCR (41).

Synopsis: Located in the Middle East Region, Jordan is divided into 12 governorates with a population of 5.85 million. Over the last three decades, Jordan underwent a demographic transition as a result of changes in fertility, mortality and migration dynamics. With a steady low mortality rate and an increasingly high birth rate and TFR, 58 percent of Jordan's population are under 25 years of age. Over the next few decades, Jordan's population is expected to double, leading to increased demand on health care and an expected sharp increase in the size of the at-risk population for non-communicable diseases, including cancer.

Changes in Jordan's health profile brought about significant improvements in health care services, placing Jordan among the top medical destinations in the region. Improvements in health care services in Jordan resulted in improvements in the population's health status which was mainly marked by a reduction in infant mortality rate and maternal mortality. Such improvements were brought about by strengthening the structure and function of Jordan's healthcare delivery system, which is comprised of public, private and non-profit. However, health care expenditure for Jordan remains high when compared to the region. Simultaneously, the demographic transition in Jordan introduced new challenges to health care, particularly the increasing burden of NCDs. Such a transition resulted in a shift in the population's vital status where half of the deaths in Jordan are currently being attributed to NCDs, mainly cardiovascular diseases, diabetes and cancer. Given the evidence provided in the literature that supports the association between diabetes and the increased risk of

colorectal cancer, the change in disease profile in Jordan becomes of utmost importance for this study. Finally, as the main source for collecting data and assessing the burden of cancer diseases, the JCR is the sole population based–cancer registry in Jordan that provides quality data on all cancer cases.

2.3 Overview

This section provides an overview of cancer and its risk factors. The global and regional burden of cancer is presented herewith, with special notation colorectal cancer. Cancer incidence is presented with a focus on Jordan statistics both for cancers in general while explicitly concentrating on colorectal cancer among the Jordan population.

2.3.1 The Global and Regional burden of cancer

Examining the burden of cancer, both globally and regionally, can assist in describing and understanding the problem of cancer, its magnitude and its different correlates when focusing on Jordan. The GLOBOCAN published by the International Agency for Research on Cancer prepared a worldwide estimate of the incidence and mortality rates from 27 cancers for 182 countries. Estimations showed that globally 12.7 million new cancer cases and 7.6 million cancer deaths occurred in 2008. Lung cancer remains the most common cancer in the world, both in term of cases (1.6 million cases, 12.7 percent of total) and deaths (1.4 million deaths, 18.2 percent), followed by breast cancer in terms of cases (1.4 million cases, 10.9 percent) which ranks fifth as cause of death (458,000, 6.1 percent), followed in terms of incidence by colorectal cancer (1.2 million cases, 608,000 deaths) and stomach cancer (990,000 cases, 738,000 deaths) (7).

In West Asia and according to GLOBOCAN the most common cancer among males is lung cancer with an ASR of 30.7, followed by colorectal cancer with an ASR of 13.1, while bladder cancer ranks third with an ASR of 13.2. For females, breast cancer ranks first with an ASR of 32.5, followed by colorectal cancer with an ASR of 10.1, corpus uteri cancer comes next with an ASR of 5.5. As the cause of mortality among males, lung cancer ranks first with an ASR of 28.4, followed by stomach cancer with an ASR at 11.1, and then comes colorectal cancer with an ASR of 8.3. For females, the most common cause of mortality among cancers is breast cancer with an ASR of 14.3, followed by colorectal cancer with an ASR of 6.2 and stomach cancer at 5.8 (7).

In Western Asia, Israel scored the highest age-standardized incidence rate (ASR) for both males (288.0) and females (270.7). In Jordan ASR for males was 132.5 per 100,000 population; lower than in Israel, Turkey (190.6), Cyprus (188.0) and Bahrain (156.0), but higher than in Kuwait (119.9) and Oman (100.9). ASR for females in Jordan was 126.4 per 100,000 population; lower than Israel, Cyprus (171.4), Bahrain (141.4) and Kuwait (127.2) but higher than Turkey (113.6) and Oman (86.5) (7).

The Cancer in Five Continents (CI5) monograph series (published by the International Agency for Research) presents essential incidence data from populations all over the world (58). In CI5 I–IX, periods are generally about 5 years in length. It allows comparative studies between different populations (in terms of geography or ethnicity). In addition, the long-time series of data allows studying risk in different populations over time. Findings from 44 cancer registries in 15 countries in Asia were published as Cancer Incidence in Five Continents Volume IX (CI5 IX); in addition to three other registries (including

Jordan), findings were analysed to provide an overview on the incidence by country/region in Asia for the period 1998-2002 (Figure 3) (59).

Figure 3: Number of person-years, crude and age-standardized cancer incidence rates by sex, 1998-2002

Population	Males				Females			
	PY	Cases	CR	ASR	PY	Cases	CR	ASR
Eastern Asia								
Chinese (Mainland)	27,923	80,757	289.2	223.6	27,077	64,498	238.2	161.7
Japanese	41,349	202,021	488.6	270.7	43,362	43,883	331.8	166.3
Korea	95,726	241,155	251.9	281.9	94,974	83,620	193.3	162.7
Taiwan	56,875	165,445	290.9	254.3	54,349	119,916	220.6	192.1
South-Eastern Asia								
Hong Kong	16,353	56,776	347.2	259.6	16,921	45,492	268.9	190.7
Malaysian	7,769	8,047	103.6	143.0	7,624	8,683	113.9	138.5
Philippines (Manila)	12,991	14,119	108.7	209.8	13,446	18,638	138.6	205.0
Singapore	8,053	17,810	221.2	221.5	8,051	18,185	225.9	189.7
Thai	8,736	12,002	137.4	136.2	8,953	13,116	146.5	134.8
Viet Namese	16,789	13,534	80.6	154.2	17,005	12,349	72.6	111.6
Western Asia								
Bahrain, Bahraini	1,005	929	92.4	156.0	987	944	95.6	141.4
Cyprus	1,716	4,311	251.3	188.0	1,776	4,081	229.8	171.4
Israel	5,153	48,406	319.5	288.0	15,489	52,172	336.8	270.7
Jordan	13,182	9,833	74.6	132.5	12,024	9,215	76.6	126.4
Kuwait, Kuwaitis	2,110	1,294	61.3	119.9	2,167	1,648	76.1	127.2
Oman, Omani	3,568	1,859	52.1	100.9	3,450	1,627	47.2	86.5
Turkish	11,933	20,669	173.2	190.6	1,795	13,317	112.9	113.6
South-Central Asia								
Indian	96,513	69,268	71.8	103.9	82,524	69,607	84.3	108.9
Pakistan (Karachi)	4,643	4,454	95.9	162.3	3,975	4,085	102.8	187.9

PY, Person-years (in thousands); CR, crude rate; ASR, age-standardized rate

Among countries of Eastern and South Eastern Asia, with predominantly Chinese populations, the highest rates for males were seen in the most developed countries of Hong Kong (259.6), Singapore (221.5) and Taiwan (254.3); Mainland China rates for males, though, were slightly higher (223.6) than the rate of Singapore. Females in the same countries fared much better: Hong Kong (190.7), Singapore (189.7), Taiwan (192.1) and Mainland China (161.7). Males in the wealthy countries of Japan (270.7) and Korea (281.9) approached Israeli rates. While for females, Manila in the Philippines (205.0) had the ASR closest to the rate for females in Israel; females in Japan (166.3) and Korea (162.7) had considerably lower rates than both their male counterparts and Israeli females (59).

2.3.2 Burden of Cancer in Jordan

From the publication of the latest Jordan data, since establishment of the cancer registry (in 1996) and until the end of 2005, there were 33,661 cases of cancer reported in Jordan, with 16,981 male cases and 16,680 females. The highest crude incidence rate recorded for males was 74.7 per 100,000 in 1996, as for females the highest crude incidence rate recorded was 75.2 per 100,000 in 1997. In this period of time lung cancer was the most common cancer among males (10.6 percent), followed by colorectal (9.8 percent), leukaemia (9.3 percent), urinary and bladder (8.6 percent) and prostate cancer (7.4 percent). As for females, breast cancer was the most common tumour (32.0 percent), followed by colorectal (9.0 percent), leukaemia (6.7 percent), thyroid (4.9 percent) and corpus uteri cancer (4.6 percent). The overall average of the Age Standardized Incidence Rate adjusted to the world standard population (ASRs) for all cancers was 119 per 100,000 adult males and 116 per 100,000 adult females for the phase between 1996 and 2005 (60).

GLOBOCAN estimates showed that the most common incident cancer among males is lung cancer at an ASR of 16.5, the second most common cancer among males in Jordan is colorectal at an ASR of 15.3, followed by prostate cancer at an ASR of 13. Among Jordanian females breast cancer comes first at an ASR of 42.2, next comes colorectal cancer at an ASR of 11.9 and leukaemia ranks third at an ASR of 8.5. However, the most leading cause of deaths from cancers among Jordanian males is lung cancer at an ASR of 15.3, followed by colorectal cancer at an ASR of 11.4 and prostate cancer at an ASR of 9.6. For Jordanian females the chief cause of death from cancers is breast cancer at an ASR of 22.2, followed by leukaemia at an ASR of 5.8 and thyroid cancer at an ASR of 3.3 (Figure 4) (7).

Figure 4: The top ten cancers among Jordanian population, 2008
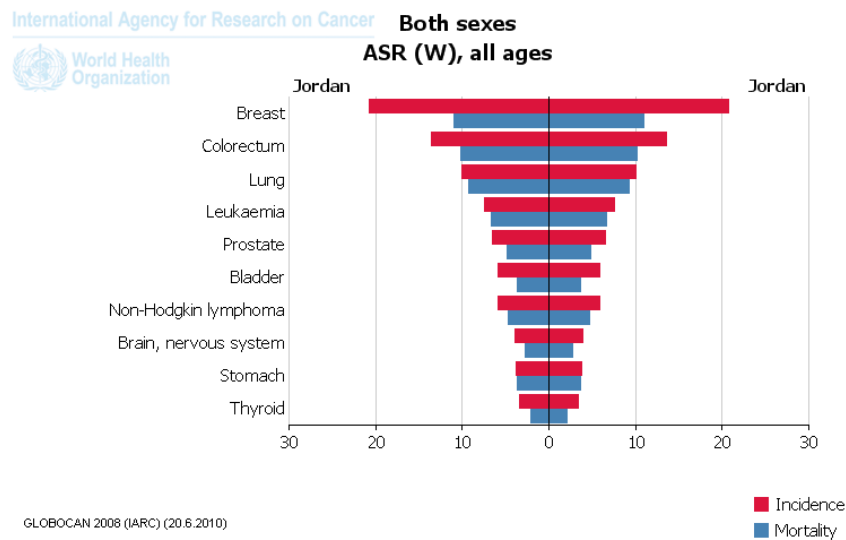
Source: *GLOBOCAN 2008*. Reproduced with permission of GLOBOCAN, 2010.

More recent information (2009) from Jordan has shown the crude incidence rate and ASR for all cancers among Jordanians were increasing to reach 78.7 per 100,000 population (i.e. 75.4 for males and 82.3 for females) and 135.1 per 100,000 population (i.e. 134.7 for males and 136.0 for females, respectively) (51). The Age-Standardized Incidence Rate of cancer has been found to be lower among Jordanians than people in developed countries for both males and females: the Age-Standardized Incidence Rate in the U.S.A. for males was 371.7 and 284.5 for females; in New Zealand, the rate for males was 345.7 and 274.8 for females; in Canada the rate for males was 330.5 and 257.3 for females (51). However, the Age-Standardized Incidence Rate of overall cancer for men in Jordan in 2008 was 134.7 per 100,000 (51). In comparison to other countries in the Middle East and North Africa, it is higher than Kuwait (125.1) and Tunisia (113.0), but lower than Bahrain (162.2), Egypt (161.7), Qatar (165.5) and Lebanon (179.0). In comparison to many countries in Europe and North America, the Age-Standardized Incidence Rate of overall cancer for men is

lower than most of these countries, including Poland (201.0), Norway (328.0), Canada (330.5), Scotland (323.7) and white males in the U.S.A. (371.7), as well as New Zealand (345.7) (51).

Among females, the Age-Standardized Incidence Rate of overall cancer in Jordan is slightly higher than for males at 136 per 100,000 (51). In comparison to many countries in the Middle East and North Africa, this is higher than Tunisia (89.0) and Egypt (120.8), similar to Kuwait (136.6), but lower than Bahrain (150.0), Qatar (164.5) and Lebanon (180.3). In comparison to countries in Europe and North America, it is higher than Poland (107.3), but still lower than Norway (271.0), Canada (257.3), Scotland (268.5) and the rate for white females in the U.S.A. (284.5), as well as New Zealand (274.8). The rank order of cancers for both males and females among Jordanian in 2008 was shown in the below (Figure 5).

Figure 5: The percentage distribution of the most frequent types of cancer by sex in Jordan (all ages), 2008

Source: Jordan Cancer Registry, Ministry of Health. *Cancer Incidence in Jordan 2008*. Amman (JO): Ministry of Health, Jordan; 2010

It is noticed that breast and colorectal cancers are the leading cancers in Jordan in both sexes (51). For males, colorectal cancer at 14.5 percent ranks in the first place followed by lung cancer at 13.1 percent, urinary bladder cancers at 7.5 percent, prostate cancer at 7.2 percent, leukaemia at 6.7 percent, Non-Hodgkin Lymphoma (NHL) at 5.1 percent, stomach cancer at 4.2 percent, brain and CNS cancers at 3.9 percent, cancer of the larynx at 3.8 percent and Hodgkin's Disease at 2.9 percent. However, among Jordanian females the most common cancers are still breast cancer at 36.7 percent, then colorectal cancer at 9.4 percent, corpus uteri cancers at 5.4 percent, thyroid cancer at 4.7 percent, Non-Hodgkin's Lymphoma at 4.6 percent, leukaemia at 4.0 percent, ovarian cancer at 3.6 percent, stomach cancer at 3.1 percent, brain and CNS cancers at 2.8 percent and lung cancer at 2.5 percent (51).

Synopsis: Statistical data indicates that cancer is a predominant global health problem. Data collected from 182 countries in 2008 estimated that there were 12.7 million of new cancer cases and 7.6 million cancer deaths. Overall, the most common cancer in the world is lung cancer (1.6 million cases, 12.7 percent of total), followed by breast cancer (1.4 million cases, 10.9 percent), then colorectal cancer (1.2 million cases, 9.4 percent). In addition, data collected from cancer registries allows comparison of different types of cancer between countries. Results from the GLOBOCAN 2008 project presented indicate that while females retained uniformity in incidence, males of the most developed countries of Asia had the highest rates of age standardized incidence rates of cancer. The Age-Standardized Incidence Rate of cancer among Jordanians is lower than that in developed countries for both males and females. While breast cancer is the leading type of cancer among females in Jordan, colorectal cancers are more common among males. When

compared to other countries in the region, Jordan ranks among countries with relatively moderate Age-Standardized Incidence Rate of overall cancer (7).

2.4 Colorectal Cancer

This section defines colorectal cancer and introduces its aetiology, diagnosis, symptoms and epidemiological profile worldwide while specifically focusing on Jordan. Screening procedures for the early detection of colorectal cancer are discussed as a mechanism for decreasing mortality. In addition, different treatment modalities are presented, and a directed discussion is presented on type 2 Diabetes Mellitus as a major risk factor for colorectal cancer.

Colorectal cancer is a disease in which cancerous growths (tumours) are found in the tissues of the colon and/or rectum. Because colon cancer and rectum cancer have many features in common, they are sometimes referred to together as colorectal cancer. Colorectal cancer usually develops slowly over a period of many years. Before a true cancer develops, it usually begins as a noncancerous polyp, which may eventually change into cancer. A polyp is a growth of tissue that develops on the lining of the colon or rectum. Certain kinds of polyps, called adenomatous polyps or adenomas, are most likely to become cancers, although most adenomas do not become cancerous. More than half of all individuals will eventually develop one or more adenomas. About 96 percent of colorectal cancers are adenocarcinomas, which evolve from glandular tissue. The great majority of colon and rectum cancers arise from an adenomatous polyp. Other types of colon cancer such as lymphoma, carcinoid tumours, melanoma and sarcomas are rare (61-63).

2.4.1 Epidemiology of Colorectal Cancer

As indicated previously, global statistics indicates that colorectal cancer is the second most common cancer in women (570,000 cases, 9.4 percent of the total) and the third most common cancer in men (663,000 cases, 10.0 percent of the total) with almost 60 percent of the cases occur in developed regions. The ASR for males was 20.4 versus 24.6 for females. Estimated deaths from colorectal cancer account for 8 percent of all cancer deaths making colorectal cancer the fourth most common cause of death from cancer (7).

Incidence of colorectal cancer from cancer registries for 1983 through 1987 and 1998 through 2002 show that colorectal cancer increased statistically significantly for both 27 of 51 males and females. This rise in incidence mainly concerned economically transitioning countries in Eastern Europe, most parts of Asia and selected countries of South America. Increases in incidence were more frequent among men than among women. Considerable variations in colorectal cancer incidence trends were detected both within countries and among ethnicities (7;64).

According to information abstracted from cancer registries (1998-2002), the highest worldwide colorectal ASR for males was in the Czech Republic at 59.1 followed by males in New Zealand at 49.3. For females the highest ASR was in New Zealand at 39.5, and followed by Australia (South) at 34.1. The lowest ASR for males was reported in India, Mumbai at 5.9, followed by Ecuador, Quito at 8.4. For females, the lowest ASR was also reported in India, Mumbai at 4.4, followed by Ecuador, Quito at 8.9 (58).

Regionally, using the same source of information, the Israeli non-Jews have the highest ASR of colorectal cancer for both males and females (i.e. 34 and 34.7, respectively). The lowest ASR of colorectal cancer for males was reported in Oman: Omani at 3.7 (57;58;65).

In 2008, there were 548 colorectal cancer cases accounting for 11.9 percent of all newly diagnosed cases among Jordanians. Colorectal cancer ranked second among all types of new cancers, and ranked first among males (14.5 percent) and second among females (9.4 percent), with a male to female ratio of 1.5: 1. The median age at diagnosis was: 61 years for both males and females; 62 years for the colon in the males and 59 for females; and 62 years for the rectum in males and 59 for females. The highest (ASR) was found in the age group 80-84 years in both males (198.9/100,000) and females (128.4/100 000). The overall ASR was 20.9/100 000 for males and 13.9/100 000 for females (66). The trend of Age specific incidence rate (ASIR) and Age standardized Incidence Rate (ASR) for colorectal cancer in Jordan also showed an increase from 1996 through 2009. In 1996, the ASIR was 5.2 and the ASR was 10.1 per 100,000. Both of these trends increased gradually over time with some fluctuation (Figure 6). In 2009, the ASIR and ASR reached 9.3 and 17.3 per 100,000, respectively (51).

*ASIR: Age Specific Incidence Rate per 100,000 population

ASR: a weighted mean of the age-specific rates; the weights are taken from population distribution of the standard population.

Source: Jordan Cancer Registry, Ministry of Health. *Cancer Incidence in Jordan 2009*. Amman (JO): Ministry of Health, Jordan; 2011

2.4.2 Symptoms of Colorectal Cancer

The symptoms of colorectal cancer depend on the stage of the disease and the area of the colon that is involved. The problem with colorectal cancer is that it may present with no symptoms at all in early stages, or its symptoms are also found in other conditions such as ulcers, gallstones, haemorrhoids or reactions to certain foods - conditions far less serious than colorectal cancer. The majority of patients present either with abdominal symptoms such as abdominal discomfort, a persistent (6 weeks) change in bowel habits, particularly looser stools or increased frequency, vomiting, decreased appetite, cramping or gnawing stomach pain, or symptoms of anaemia such as weakness and fatigue, rectum bleeding (especially if it is not associated with anal symptoms such as itching, pain or soreness) or mucus discharge per rectum. Persons whose cancer involves the rectum may experience a feeling of rectal fullness, painful spasms, change in bowel movements, and change in the

diameter of stools. Pain, diarrheal or vomiting may be other symptoms of colorectal cancer (67-69).

2.4.3 Aetiology and risk factors of Colorectal Cancer

Although the exact cause of CRC is still unidentified, researchers have identified a set of variant risk factors. Being above the age 45 to 50 increases the chance of CRC among all groups. The incidence rate of colorectal cancer is more than 14 times higher in adults 50 years and older than in those younger than 50 years. Moreover, the mortality rates for CRC increases with age where 94 percent of deaths occur in individuals 50 years and older (70). CRC incidence and mortality rates are higher in men than in women. The reason behind this is not completely understood, but may can be partially explained by an inversely relation between oral contraceptive (OC) use and the risk of colorectal cancer (71;72).

CRC has been associated with certain ethnic groups; e.g., African people(73-75). Among African Americans, incidence rates are more than 20 percent higher and mortality rates are about 45 percent higher than those in whites. This could be partially attributed to racial differences in the trends in the prevalence of risk factors for colorectal cancer and/or greater access to and utilization of recommended screening tests by whites, resulting in detection and removal of precancerous polyps (73).

Incidence of CRC has been found to be higher in economically privileged countries (58;59;76-78). Furthermore, familial adenomatous polyposis, a family history of colon cancer (hereditary non-polyposis colorectal cancer or Lynch syndrome), a personal or family history of colorectal cancer and/or polyps, and being diagnosed with chronic inflammatory bowel disease, all predispose to colorectal cancer (79;80). On the other hand,

modifiable risk factors that have been positively associated with colorectal cancer included increased body mass index, increased caloric intake, diet rich in red or processed meat, insufficient intake of fruits and vegetables, sedentary lifestyle, prolonged cigarette smoking, and alcohol consumption (81-91).

2.4.4 Diagnosis and staging of Colorectal Cancer

Diagnosing CRC at an early stage has been associated with better survival rates compared to diagnosing the disease at a more advanced stage.

Initial examination includes complete history, family history and laboratory tests including advanced stool and blood based tests. Up until the present, colonoscopy remains the main method for the diagnosis of colorectal cancer. The procedure allows for visual examination, while biopsies or polyp removal could be done at the same time. This procedure is preceded by other diagnostic blood tests (92-94).

Another useful diagnostic method is the double contrast barium enema, being accurate in detecting more than 90 percent of colon cancer and polyps with a diameter of 6-10 mm. For the visual examination of the rectum and lower third of the colon, Flexible Sigmoidoscopy is also a widely used procedure (95). Moreover, Pan-body computed tomography (CT) is another important tool for diagnosing colorectal cancer (96;97).

Colon cancer staging is an estimate of the amount of penetration of a particular cancer. It is performed for diagnostic and treatment purposes. Moreover, the staging system allows determining the prognosis. The systems for staging colorectal cancers depend on the extent of local invasion, the degree of lymph node involvement and whether there is distant

metastasis. Definitive staging can only be done after surgery has been performed and pathology reports reviewed. An exception to this principle would be after a colonoscopy polypectomy of a malignant pedunculated polyp with minimal invasion. Preoperative staging of rectum cancers may be done with endoscopic ultrasound. Adjunct staging of metastasis include Abdominal Ultrasound, Computed Tomography (CT), Positron Emission Tomography (PET) Scanning and other imaging studies (96;97).

In 1932, Cuthbert Dukes introduced the first classification system (98). Dukes' staining system has been modified many times over the years to include additional prognostic factors beyond the depth of tumour invasion and extent of lymph node metastases (99). The American Joint Committee on Cancer (AJCC) has developed the Tumour, Node, Metastasis (TNM) staging. The TNM staging system provides greater precision in identification of prognostic subgroups. The stage of a cancer is usually quoted as a number I, II, III, IV derived from the TNM value and grouped by prognosis; a higher number indicates a more advanced cancer and likely a worse outcome (100). Table 1 clarifies stage classifications of colorectal cancer.

Table 1: Stage Classifications of Colon Cancer

Duke's Staging	TNM Staging
A – Limited to mucosa or sub mucosa. Not invading muscularis. No nodal involvement.	I, TI,T2, N0, M0
B – Invaded into muscularis and regional soft tissue. No nodal involvement.	II, T3, N0, M0
C – Local metastatic spread to lymph nodes	III, any T, N1, M0
D – Distant metastases	IV, any T, any N, M1

2.4.5 Screening of Colorectal Cancer

Risk assessment of CRC, and detecting the cancer at early stages are crucial in alleviating the mortality and morbidity associated with the disease. There are several screening

options available for the early detection of colorectal cancer. However, the recommended colon cancer-screening plan usually depends upon risk stage of the disease. The Gastrointestinal Consortium Panel has prepared a set of guidelines for screening average and high-risk individuals (93).

Screening options for average risk individuals embrace faecal occult blood testing (FOBT) every year, flexible sigmoidoscopy every 5 years, a combination of FOBT and sigmoidoscopy, colonoscopy every 10 years, and double contrast barium enema (DCBE) every five years (101).

Screening for colorectal cancer in high-risk individuals depends mainly on the associated risk factors. Individuals having a first-degree relative diagnosed with colon cancer or adenomatous polyps at age less than 60, or having two second-degree relatives diagnosed with colon cancer or adenomatous polyps at any age are recommended to have colonoscopy every five years starting at age 40 or 10 years younger than the earliest diagnosis in the family (102). In case adenomatous polyps are found, follow-up colonoscopy is to be done in the short term (102). If one or more of the polyps are malignant, or large and sessile, or if colonoscopy is not complete, if three or more polyps are found then follow- up colonoscopy is recommended in three years. If only one or two polyps with a diameter less than one centimetre is found, colonoscopy follow-up is recommended in five years. Individuals with Familial Adenomatous Polyposis (FAP) are advised to have genetic testing, in addition to flexible sigmoidoscopy starting at age 10-12. In case of Hereditary Nonpolyposis Colon Cancer (HNPCC), individuals are recommended to undergo genetic testing and colonoscopy every one to two years starting at age 20 to 25, or 10 years younger than the earliest case diagnosed in the family (103;104). Individuals

with a personal history of colorectal cancer should repeat colonoscopy in six months after resection if the colonoscopy was incomplete due to obstruction at time of diagnosis; otherwise, the colonoscopy is repeated in three years; and in case it was normal, repeated every five years. Moreover, individuals with inflammatory bowel disease are advised to have surveillance colonoscopy (93;94).

2.4.6 Treatment of Colorectal Cancer

Preoperative staging and treatment planning have evolved recently as crucial steps in CRC management (105). The disease is staged into: local disease, distant disease and synchronous colonic lesions.

When diagnosis is made at an early stage, endoscopic mucosal resection and endoscopic sub-mucosal resection are performed for superficial colorectal cancers (106), while colonoscopy polypectomy can be applied for cancer found within polyps. Moreover, colonoscopy can be used as part of a surveillance program to remove missed or new adenoma. For rectum cancer, options include per-anal excision besides the conventional colonoscopic polypectomy (94).

Until today, surgery continues to be the treatment of choice for CRC; five-year survival reaching 90 percent in Dukes A cancer and 75 percent in Dukes B (107). Exact surgical procedure is mainly determined by the preoperative staging (108). The aim of surgery is to adequately remove the cancerous lesion and ensure safe anastomosis, and at the same time, securing good vascularity and joining bowel ends under no tension (108). Rectum cancer survival, in particular, has improved immensely after the use of newly developed surgical

techniques, namely, total mesorectal excision (109). The use of laparoscopic procedures has shown less abdominal wall trauma and faster post-operative recovery than open surgical techniques (108). There is evidence from studies in the U.K., the U.S.A, and Europe that oncological outcomes in laparoscopic procedures are similar to those of open surgery (92).

Almost 20 percent of CRC patients would have developed liver metastases at time of primary diagnosis, and only 20 percent of these are candidates for surgical resection involving both the primary tumour and liver metastases in, generally followed by neoadjuvant treatment. Although it is a general rule to avoid surgery for cases with metastases, it is considered an effective palliation in case of highly symptomatic primary tumour. Moreover palliative surgery includes surgical bypass, loop colostomy or loop ileostomy and stent placement (110).

Adjuvant therapy such as chemotherapy or radiotherapy can be used along with surgical procedures in many cases (111). Chemotherapy is usually used to decrease the risk of disease relapse, cancer related death as well as for palliative purposes (112). The use of chemotherapy is still controversial in stage 2 (113). Drugs acting on novel targets or molecular markers are used in the treatment of advanced colon cancer, while cytotoxic agents, which are new innovations, are prescribed to patients with metastasis for improved results. Many drugs can be used for chemotherapy such as Fluorouracil, Capecitabine (Xeloda), Irinotecan (Camptosar), Oxaliplatin (Eloxatin), Cetuximab (Erbitux) and Evacizumab (Avastin) (112).

Preoperative adjuvant therapy such as combined modality therapy (i.e. chemotherapy and pelvic radiation) could help in the preservation of sphincter function (114). Radiotherapy in colon cancers may reflect postoperative adjuvant therapy in contrast to pre-operative treatment for rectum cancers. Furthermore, evidence indicated reduction of recurrence rate among rectum cancer cases after use of preoperative radiotherapy from 25 percent to 10 percent; resulting in more favourable survival rates (115).

2.4.7 Colorectal Cancer and Type 2 Diabetes Mellitus

Diabetes mellitus - type 2 (formerly known as noninsulin-dependent diabetes mellitus (NIDDM) or adult-onset diabetes) and CRC share similar risk factors, including physical inactivity and obesity. Various studies have found a positive association between diabetes and increased risk of colorectal cancer in both men and women (116-118). Although the relationship between diabetes mellitus type 2 and colorectal cancer is still sometimes controversial (108;119), a positive association between diabetes and colorectal cancer has been found in studies that accounted for physical activity, body mass index and waist circumference (118;120-123).

Extensive research published in 2012 showed additional shared modifiable risk factors for both colorectal cancer and type 2 diabetes mellitus. Out of 67 risk factors and risk factor clusters, only twelve were associated with colorectal cancer and/or diabetes mellitus. Of those twelve, seven were common to both colorectal cancer and type 2 diabetes mellitus; three were only associated with colorectal cancer and two only with type 2 diabetes mellitus (Table 2). Diet high in sugar-sweetened drinks was a newly reported risk factor for both diseases; diets low in milk, low in fibre and low in calcium were newly reported risk factors for colorectal cancer (124).

Table 2: Risk factors associated with CRC and type 2 DM

Item #	Modifiable risk factor	CRC	DM-2
1	Smoking and second-hand smoke	X	X
2	Alcohol – daily or binge	X	X
3	High Body Mass Index	X	X
4	Diet low in milk	X	
5	Diet high in red meat	X	X
6	Diet high in processed meats	X	X
7	Diet high in sugar-sweetened drinks	X	X
8	Diet low in fibre (all types: fruit, vegetable, grains, legumes, pulses)	X	
9	Diet low in calcium (incl. milk, yoghurt, cheese)	X	
10	Physical inactivity or low physical activity	X	X
11	High fasting plasma glucose		X
12	Diet low in whole grain		X

Source: Lim, S. *et al.*, *The Lancet*, 2012.

The study and the literature show associations between type 2 diabetes and colorectal cancer (albeit more strongly with colon cancer). These associations can be grouped by modifiable risk factor (Table 3).

Table 3: Modifiable risk factors affecting both diabetes and CRC

Risk factor	International characteristics	Jordanian statistics
Obese or overweight	High BMI ≥ 25 kg/m^2 Increased BMI	Overweight: Males 62.3 percent; females 66.0percent; Total 64.1percent (WHO 2008) Total 30.5percent (of n= 3 654 in 2007); (Al-Nsour *et al*. 2012) Obese: Males 24.0percent; females 36.4percent; Total 30.0percent (WHO 2008) Total 36.0percent (of n= 3 654 in 2007); (Al-Nsour *et al*. 2012)
Smoking	Smoker Prolonged cigarette smoking	Daily smoking: Males 48.8percent; females 4.1percent; Total 27.1percent (WHO 2008) Total 29.0percent (of n= 3 654 in 2007); (Al-Nsour *et al*. 2012)

Table 3: Modifiable risk factors affecting both diabetes and CRC

Risk factor	International characteristics	Jordanian statistics
Alcohol consumption	Excessive alcohol Alcohol consumption	No literature found for Jordan.
Unhealthy diet	Increased caloric intake, diet rich in red or processed meat, insufficient intake of fruits and vegetables	Number of fruit/vegetable servings daily: None = 5.3percent; 1-4 = 78.1percent; ≥ 5 = 16.7percent (of n= 3 654 in 2007); (Al-Nsour *et al.* 2012)
Physical inactivity	Sedentary lifestyle	No data (WHO 2008) Engages in moderate physical activity: Total 37.8percent (of n= 3 654 in 2007); (Al-Nsour *et al.* 2012)
Positive association between diabetes and colorectal cancer	Type 2 Diabetes Mellitus and colorectal cancer share similar risk factors when studies accounted for physical activity, BMI and waist circumference	Raised cholesterol: Males 46.3percent; females 46.4percent; Total 46.4percent (WHO 2008) Household survey 7.1percent (of n= 2 889 in 2007); Medical exam 9.1percent (n= 765 in 2007); (Al-Nsour *et al.* 2012) Raised blood glucose: Males 14.2percent; females 14.7percent; Total 14.4percent (WHO 2008) Impaired fasting glucose found on medical exam 23.9percent (n= 765 in 2007); (Al-Nsour *et al.* 2012) Raised blood pressure: Males 31.4percent; females 25.9percent; Total 28.8percent (WHO 2008) Household survey 16.4percent (of n= 2 889 in 2007); Medical exam 23.0percent (n= 765 in 2007); (Al-Nsour *et al.* 2012) Type 2 Diabetes: Household survey 9.4percent (of n= 2 889 in 2007); Medical exam 11.5percent (n= 765 in 2007); (Al-Nsour *et al.* 2012)
Other chronic conditions		Heart disease: Household survey 8.2percent (of n= 2 889 in 2007); Medical exam 7.5percent (n= 765 in 2007); (Al-Nsour *et al.* 2012) Asthma: Household survey 6.6percent (of n= 2 889 in 2007); Medical exam 7.7percent (n= 765 in 2007); (Al-Nsour *et al.* 2012)

The increase in the prevalence rates of diabetes mellitus in Jordan can be attributed to behavioural changes rather than genetic or family history factors. Developing countries adopting a Western lifestyle, characterized by decreased physical activity and overconsumption of energy-dense foods, have witnessed a substantial increase in the prevalence of obesity (3;4;125;126).

The Jordanian diet, like other countries in the Mediterranean Region, would not be expected to be low in fibre and calcium/milk; at the same time, like other growing Middle Income countries, the Jordanian diet would also not be likely to be low in sugar-sweetened drinks. Results of the latest (2007) National Jordan's Stepwise Surveillance survey conveyed the prevalence of a number of behavioural risk factors. E.g. smoking (33 percent) and obesity are high in Jordan; approximately one-third of participants of the medical evaluation were either overweight (30 percent) or obese (36 percent) (3). These factors coupled with a high rate of physical inactivity (only 34.1 percent engaged in moderate or severe physical activity) and low consumption of vegetables and fruits (only some 15.9 percent of survey respondents reported having consumed five or more cups of fruits and/or vegetables) increase the risk of NCDs and constitute a substantial challenge to the health of Jordanians (3;4;125).

The increased prevalence of rates of NCDs in Jordan have been linked to changes in lifestyle. Developing countries adopting a Western lifestyle characterized by decreased physical activity and overconsumption of energy-dense foods have witnessed substantial increased prevalence of obesity (4;127;128). Locally, the self-reported prevalence of type 2 diabetes among Jordanian adults aged 18 years or above increased from 6.2 percent in 2002, to 7.5 percent in 2004 and to 11 percent in 2007 (3;4;27;42;129) . However, in 2007,

19 percent of survey participants were diagnosed with diabetes according to laboratory testing or current use of insulin or an oral hypoglycaemic medication (3).

The increase in the prevalence of diabetes is closely linked to obesity with about 90 percent of acquired Type 2 diabetes being attributed to excess weight. Diabetic nephropathy accounted for over 29 percent of end-stage renal disease on haemodialysis in Jordan (130). The traditional diet in Jordan can be classified as a Mediterranean diet that is particularly rich in olive oil - monounsaturated oil). Such diet has been shown to offer protection against diabetes (131). People must be encouraged to return to their traditional diet and to increase their awareness of the role of such a diet in the prevention of diabetes.

Prevention of NCDs requires changing the lifestyle of the general population, which can only be achieved through community mobilization and high political commitment. As most of the needed interventions are outside the health sector, a multi-sectorial approach involving all governmental and nongovernmental stakeholders provides the basis for success. In 2010, The World Health Organization adopted the WHO action plan for the prevention and control of NCDS to guide countries in their efforts to curb the escalating epidemic of NCDs (34). The Global Status Report on NCD was developed as part of the implementation of the 2008–2013 Action Plan for the Global Strategy for the Prevention and Control of NCDs, which was endorsed by the World Health Assembly in 2008 (132).

Synopsis: Colorectal cancer is one of the most common cancers worldwide including Jordan. It is a disease when cancerous growths are found in the colon and/or rectum. The majority of colorectal cancers arise from an adenomatous polyp. As the second most common cancer in women and third in men, colorectal cancer ranks as the fourth most

common cause of death from cancers worldwide. In Jordan colorectal cancer ranks as the second most common among all cancers, (first rank in males and second in females). During the last decade, the Age specific incidence rate (ASIR) and Age standardized rate (ASR) for colorectal cancer in Jordan increased, with a tendency to being mostly diagnosed later in life. With symptoms depending on the stage of the tumour, colorectal cancer can present itself with no symptoms during its early stages, or with symptoms of conditions that are less serious. With an unidentified exact cause, colorectal cancer has been associated with various risk factors, including: age (less than 50 years), sex, ethnicity, family history, and modifiable risk factors such as dietary habits, inactivity, smoking and others.

Early diagnosis is important for improving colorectal survival. Furthermore, detecting colorectal cancer at an early stage affects its mortality and morbidity. Therefore, colon cancer-screening is recommended based on a set of guidelines that depends on risk stage of the disease with several screening options available for the early detection of colorectal cancer. With sigmoidoscopy as a commonly diagnostic procedure, prognosis of colorectal cancer is determined by staging the disease, which depends on the extent of local invasion, the degree of lymph node involvement and the presence of distant metastasis. Treatment regimen depends on the stage of the disease, which usually determines the surgical procedure and any adjunct radiotherapy or chemotherapy. Finally, the relationship between type 2 Diabetes Mellitus and colorectal cancer is widely reported in the literature with a reference to modifiable risk factors that are shared between these two diseases.

2.5 Colorectal Cancer Survival and its Correlates

This section presents available colorectal survival data in an attempt to describe the disease from a population perspective. The section discusses the effect of different factors on

colorectal cancer survival data including socio demographic factors, clinical characteristics, type of treatment, diabetes, health services and place of residence.

Survival statistics are means of quantifying the effectiveness of early detection strategies and treatment regimens at the population level. Nowadays the cancer registry role has developed beyond providing cancer counts and incidence. Cancer registry is playing a major role in monitoring and evaluation of screening programmes and follow-up of cancer patients to examine the quality of cancer services they receive (10;133-135). Information about the survival rates will help the healthcare community take further preventive and control measures in order to improve the quality of cancer care patients receive. Survival data is an important tool to evaluate the effectiveness and efficiency of cancer health services (10;11).

Understanding the different factors that influence the outcome of colorectal cancer is important for improving its relative survival. Accordingly, the literature identifies several aspects of health-care that could guide providers in the management of CRC. These include important prognostic factors that are related to patients as well as health-care providers. Although the literature widely addresses the association of colorectal survival outcome with patient and biological risk factors, few reports were found addressing providers' characteristics. For example, a review discussing the impact of patient and provider characteristics on the treatment and outcomes of CRC, reported hospital characteristics such as surgeon experience and high hospital volume to be consistently reported in the literature as factors affecting the outcomes of cancer care (136).

The literature presents health insurance status as a main factor that is associated with differences in survival among CRC patients. For example, excess mortality among rectum cancer patients without private insurance was reported by a national hospital-based study done in the United States. An interesting finding of this study was the cancer survival disparities observed by race and area of residence that might indirectly denote geographic and transportation barriers that are simply related to socioeconomic status (137). It is important to note that several nonmedical factors might influence patients' compliance to treatment, such as: patient preference, cost barriers, mistrust in the health-care system, and communication with the health-care provider, all of which are key structural elements of a health-care treatment site (136;137).

2.5.1 Socio-demographic characteristics and colorectal cancer survival

Different factors can influence colorectal cancer survival rates. Age, clinical characteristics of the tumour, type of treatment, comorbidity, socio-demographic characteristics, health services and residence-related factors have been shown to affect cancer survival. Investigating the relationship between the different factors and CRC survival deepens the understanding of disease progress and elevates the quality level of provided services. In this review the effect of each factor on CRC survival is discussed.

2.5.1.1 Age and colorectal cancer survival

The correlation between colorectal cancer survival and age is still uncertain. Although worse prognoses of the disease in young patients were reported by many researchers (138-143), analysing the data obtained from the Ontario (Canada) cancer registry, the relative odds of early death at 1-year increased by 85 percent in the age range of 65-69 years

compared with the age range of 40-49 years (144). Hazard ratios of death at 1-year for white and black patients registered in the national cancer data base increased by 37 percent and 38 percent, respectively, within the age range of 61-64 years compared with the age range of 18-49 years (145). On the other hand, the difference in survival rates among patients aged 40 years and younger and older patients aged more than 40 years was insignificant in a study conducted on 230 colorectal cancer patients of stage I-III and treated in a Beijing cancer hospital (140). An additional discrepancy was noticed in another study in which patients younger than 40 years old had poorer disease-free and cancer-specific survival rates with respect to patients older than 80 years old (146).

The tumour's clinical characteristics, co-morbidity, treatment and patients' demographics have been suggested as possible factors accounting for the higher survival in young patients despite the poor prognoses (147;148). Generally, advanced stage in diagnosis, poorly differentiated adenocarcinoma and presence of metastasis are characteristics of colorectal cancer tumours in young patients (141;146;147;149;150). Thus some researchers reported in their studies that poor survival in old patients is not related to the tumour characteristics (147). A study showed that survival for patients younger than 65 years of age improved over time compared with older patients. This improvement was attributed to an increase in the use of adjuvant treatment in younger patients as well as better tolerance to surgery (148). The effect of adjuvant therapy on improving cancer–related survival rate was also reported for patients younger than 50 years of age with rectum cancer. Furthermore, less co-morbidity and emergency operations, compared with older patients, were identified as possible factors (143). More investigation is needed to explore if the tumour characteristics contribute to survival differences with age.

2.5.1.2 Sex and colorectal cancer survival

The relationship between sex and colorectal cancer survival varies from one population to another and generally the investigation of this factor is not well established. Results of the CONCORD study showed that within most of the included regions, the survival rate of CRC patients was insignificantly affected by the patient's sex. Better survival was found among females, but did not exceed five percent in most of the registries. The same study found differences between the two sexes in a few regions. In Malta, the 5-year relative survival rates for female patients were better than those of male patients by a difference of 20 percent for colon cancer, 17.8 percent for rectum cancer and 19.8 percent for colorectal cancer. In the Navarre region, among the Spanish registries, the survival rate for females was higher by 15.4 percent for rectum cancer. Furthermore, better survival rates for male patients with rectum cancer were observed in the Ragusa, Italy registry and the Netherlands (South) registries where the differences were 12.5 percent and 12.9 percent, respectively (13).

The impact of sex on survival following surgery was assessed in Scotland for 3,200 patients who underwent resection surgery between 1 January 1991 and 31 December 1994. In this study, the 5-year overall survival for females (55.2 percent) was significantly higher than that of males (49.1 percent) ($p<0.001$) (151).

In another study, the effect of sex on survival rate was investigated for 52,822 patients with metastatic colorectal cancer from 1988-2004. Patients were registered in the Surveillance, Epidemiology and End results (SEER) programme. Young women less than 45 years of age had better overall survival rates than men of the same age by 20 percent at the

seventeenth month, whereas the rates became worse for women more than 55 years of age compared with men of the same age (152).

Rectum surgery is technically more difficult in men, so local spread and nodal clearance may be inadequate. Reasons of better survival rates in younger females when compared to men of the same age need further investigation. Many researchers have suggested that oestrogen inhibits CRC progression and thus better survival was observed in pre-menopause status (153-155). Studies indicated that a decline in oestrogen results in loss of oestrogen receptor beta that is associated with the survival differences between the two sexes. An accompanying research finding stated that the loss of oestrogen receptor beta is a mediator for oestrogen-dependent tumour progression (156), and it may cause an increase in proliferation and decrease differentiation of the colonic mucosa (157). Furthermore, selective loss of this receptor was detected in malignant tissues of colon cancer (158). Another supportive finding is the inverse correlation of contraceptives containing oestrogens with colorectal cancer risk (156-158).

2.5.1.3 Socio-economic status

Findings of many researchers showed that shorter CRC survival is associated with lower socioeconomic status after controlling for potential other risk factors (144;145;159-163). Many factors including stage at diagnosis, psychological support, differences in tumour biology, effect of treatment on the patient, quality of treatment, access to health care, access to diagnostic aids and/or burden of comorbid diseases, may partially contribute to the effect of socioeconomic status on survival (145;164;165).

Data on patients diagnosed with CRC between 1990 and 1997 and living in Ontario was analysed to investigate the effect of socioeconomic status on CRC survival. Probability of death within 30 days was 1.37 for the lowest socioeconomic status compared with the highest socioeconomic status (145). The five-year relative survival of colon cancer patients ranged, depending on socioeconomic status, from 40 percent to 46 percent for males and 45 percent to 55 percent for females diagnosed during 1994-2003 in Denmark (162).

2.5.1.4 Race and ethnicity

Race and ethnicity are important population characteristic that are widely used in epidemiologic and public health research. Understanding race and ethnicity and their influence on health is important for determining health outcomes. The literature debates the definition of race as a concept that has long been used as a marker to define the biological difference between population groups, hence giving it a biological context. Caution over using race as a biological concept has been criticized in the literature due to misuse, and a societal context for race has been increasingly adopted, bringing in the concept of ethnicity as a synonym for race (166).

Many researchers explored the influence of race on CRC survival in the U.S. Generally, results showed lower survival among blacks compared to whites for both sexes (13;73;167;168), and lower survival among Hispanic compared to non-Hispanic whites (169).

CRC survival variation was also detected in Denmark among Danish and immigrants (162), in Hawaii among Hawaiian and other ethnic groups including Japanese, Caucasian,

Chinese and Filipino (170), and among indigenous and non-indigenous people in New Zealand and Australia (77;171).

Disparities of survival from one race to another may be explained by cancer stage at diagnosis, access to health services, and quality of treatment, tumour biology, demographics or socioeconomic characteristics (161;167;168;172).

2.5.2 Clinical characteristics and colorectal cancer survival

2.5.2.1 Stage of tumour

Stage of tumour at diagnosis is the most important predictor of survival. Patients' survival from CRC was estimated for the different stages (i.e. Stage I through IV) of tumour at diagnosis (12;73;137;144;171;173-175). Findings indicated that survival rates became shorter as the cancer spread beyond the origin site. Thus, the highest survival rate was found for patients with localized tumour stage (Stage I) and the lowest for the distant tumour stage (Stage III). This result was found regardless of patient's race (73;137), quality of health care services (173), treatment type (174), and site of tumour (175). In a cohort study to examine the prognostic factors in CRC patients, the 5-year survival rates of CRC were 68 percent for Stage II, 44 percent for Stage III and 2 percent for Stage IV (176). Others found that the 5-year survival of CRC patients were 89 percent for Dukes' Stage A, 75 percent for Dukes' Stage B, 49 percent for Dukes' Stage C and 12 percent for Dukes' Stage D (177).

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2.5.2.2 Cancer grade and morphology

Cancer grade also plays an important role in predicting survival. Survival rate decreases with poorer cell differentiation (137;171). Hazard ratio for death at 5-years among non-elderly patients in the U.S. National Cancer Data Base ranged from 1 to 2.53, as the cancer grade became higher (137).

The different histological types of colorectal cancer tumours were investigated. It was reported that patients with rectum cancers rose from polyp or adenoma, and carcinoid had 5-year survival rates ranging from 85 percent to 90 percent--the highest rate among various histological types. In the same study, the poorest 5-year survival rates (i.e. less than 30 percent) were estimated for small cell and adenosquamous of colon cancer, whereas for rectum cancer, the poorest 5-year survival rates were for undifferentiated, small cell and melanoma histological types (178). Another study demonstrated that patients with: different papillary adenocarcinoma had the best survival; moderately differentiated and mucinous adenocarcinoma had moderate survival; and poorly differentiated adenocarcinoma had poor prognosis (179). In addition, mucinous tumours were found to have worse survival when compared with non-mucinous tumours; their 5-year survival rates were 51 percent and 69 percent, respectively, while signet ring tumours were worse (for both mucinous and non-mucinous tumours) with a 5-year survival rate of 27 percent (180).

2.5.2.3 Tumour site

Effect of tumour site varied among the different studies. One study estimated the survival rate of patients with colon and rectum cancer in different sub-sites (i.e. cecum, appendix,

ascending, hepatic flexure, transverse, splenic flexure, descending, sigmoid, overlapped and colon NOS) for colon cancer, as well as recto sigmoid and rectum for rectum cancer. Researchers found that five-year survival rates between sub-sites or between colon cancer and rectum cancer were insignificantly different (64.0 percent for colon cancer and 62.7 percent for rectum cancer), but the other two sub-sites (overlapping and NOS) had much poorer survival outcomes. Distinct difference was shown for patients with stage II colorectal cancer where the 5-year survival rate was 82.7 percent and 69.7 percent for colon and rectum cancers, respectively (178). In another study, the survival rate for colon cancer was significantly higher than rectum cancer (181). In a recent study in which the survival rates of colon and rectum cancers were investigated at different survival times, patients with colon cancer had the worse 1-year survival rate, while they had better 2-, 3-, 4- and 5-year survival rates compared with patients with rectum cancer (182).

A study in New Zealand reported that the hazard ratio was 1.11 for right-sided tumours compared with the left-sided, indicating better survival for patients with left-sided tumours (171). Similar results were reported by a study conducted in the Hospital of Larissa, Greece (175). Other research, though, suggested higher survival associated with right-sided tumours (0.3 and 0.4 hazard ratio for females and males, respectively) compared with left-sided tumours (0.45 and 1.08 hazard ratio for females and males, respectively) (183).

2.5.3 Type of treatment and colorectal cancer survival

Definitive surgery and adjuvant chemotherapy were found to contribute to variations in colon cancer survival of New Zealanders. Hazard ratio reduced significantly to 0.24 for patients who underwent definitive surgery and to 0.55 for patients who received adjuvant chemotherapy (171).

Three types of treatment were investigated in CRC in the state of Ohio, in the U.S. Palliative care, surgery plus chemotherapy treatment and surgery treatment only. Compared to palliative treatment, hazard ratio was 0.56 when surgery treatment was used alone and 0.76 when surgery combined with chemotherapy were used (184).

In a study done to evaluate laparoscopic surgery versus open colectomy in colorectal cancer patients, no significant differences were observed in the 5-year survival rates between the two methods. Depending on cancer stage, 5-year survival rates ranged from 0 to 100 percent for the laparoscopic method and 0 to 89.7 percent for the open surgical method (185). Other studies supported this finding, whereas no statistical difference was observed when the two methods were compared regarding their impact on survival (108;114).

In a randomized clinical trial done in Brussels to investigate the impact of combining chemotherapy with preoperative and/or postoperative radiotherapy on rectum cancer survival, found that adding Fluorouracil-based chemotherapy to radiotherapy preoperatively and/or postoperatively did not have any effect on survival (114).

A Swedish rectum cancer trial concluded that preoperative radiotherapy has beneficial effects on survival of rectum cancer patients undergoing surgery. The improvement in 13-years' survival rate was not significant for Stages 2 and 3 of rectum cancer. Risk of recurrence was found to be reduced after receiving preoperative radiotherapy, and this reduction could have contributed to the improvement of survival (174).

2.5.4 Comorbidity and colorectal cancer survival

The presence of concurrent illness is common in colorectal cancer patients and it significantly affects survival (161;162;171;172;186-191). Hazard ratio for death at 1- year for colorectal cancer patients in the U.S. National Cancer Data Base 2003-2005 was estimated according to the number of comorbid conditions. The hazard ratio increased with the number of comorbid conditions: by 12-48 percent in white patients having one or more comorbid conditions; whereas in black patients, hazard ratios increased significantly with three or more comorbid conditions (190).

The Charlson comorbidity index is used to predict the 10-year mortality for a patient with comorbidities; i.e. it is used as a measurement of the effects of the presence of comorbidities. A Charlson comorbidity index score of one or more was found to be associated with lower 5-year survival rates of male colon and rectum cancer patients in Denmark, whereas similar results were found for Danish females, with a score of two or higher (162).

In a retrospective cohort study done to assess the impact of comorbidity on colon cancer patient survival among New Zealand colon cancer patients, the number of comorbid conditions, as well as the Charlson comorbidity index scores, was found to be associated with the survival of patients. The hazard ratio increased by 32 percent and by 48 percent for Charlson score 1-2 and 3 or higher, respectively. Also, hazard ratio increased by 23 percent when two comorbidities were present, and by 33 percent when three or more comorbidities were present (191).

The impact of combinations of comorbidities on survival from colorectal cancer was difficult to predict. The effect of multiple comorbidity conditions had variable patterns depending on the type of the combined comorbidities (191;192).

Diabetes mellitus was identified as a prognostic factor as well as being comorbidity associated with colorectal survival rate. Inconsistency of results was noticed in the literature. Zhou Zhong-guo *et al*. investigated the effect of diabetes mellitus on the survival of colorectal cancer patients who underwent resection in Stages II and III. Researchers found that patients with diabetes mellitus experienced worse disease-free survival rates than those without diabetes mellitus. However, the overall survival rate was not affected by the presence of diabetes mellitus (193). The same result was found in research that aimed to investigate the impact of diabetes mellitus on colorectal cancer survival rates for patients who underwent resection in the First Affiliated Hospital of Sun Yat-sen University in China. The five-year survival rate was 34.2 percent for diabetic patients and 55.1 percent for non-diabetic patients (187-189;191;192). Another study conducted on colorectal cancer patients who underwent surgery at Korea Cancer Center Hospital showed that both the disease-free survival rate and the overall survival rate were not affected by the presence of diabetes mellitus, while both the five-year disease-free rate and overall survival rate significantly decreased in the presence of diabetes mellitus during a study on patients with Stage II and III colon cancer (194).

In a 2003 cohort study throughout the United States, 3 759 patients with high-risk stage II and stage III colon cancer were treated in a randomized adjuvant chemotherapy trial between 1988 and 1992. Within the cohort, 287 patients were identified as having diabetes

mellitus. "At 5 years, patients with diabetes mellitus, compared with patients without diabetes, experienced a significantly worse disease-free survival (DFS; 48 percent diabetics versus 59 percent non-diabetics; P < .0001), OS (57 percent versus 66 percent; p<0.0001). Median survival was 6.0 years and 11.3 years for diabetics and non-diabetics, respectively." (122). The decrease in 5-year overall survival rate with the presence of diabetes mellitus was also observed in patients who underwent curative resection at Levanger Hospital in Norway. In the same study, there were no differences observed in cancer-specific survival rates regardless of diabetes status (119). However, in a study of colon cancer survival in diabetic patients and segregated by stage of colon cancer, both overall survival rate and cancer-specific rate decreased in diabetic patients with Stage II colon cancer. I.e. patients with diabetes had worse CSS (HR = 1.24, P = 0.013) when compared to those without, but it was only significant for patients with stage II cancers. The impact of diabetes on CSS was attenuated in both early (Stage I) and advanced stages (III and IV) (120). The effect of diabetes mellitus on colorectal cancer outcomes is associated with hyperinsulinemia and insulin-like growth factor-1 (IGF-1) (121;193;195).

2.5.5 Health services and colorectal cancer survival

Quality of health services provided to patients is strongly related to cancer survival. Perhaps the best model to describe this notion is Donabedian's famous framework for assessing quality of care which is built on three concept elements: structure, process and outcome. This framework links the structure and process of care to patient outcome and suggests a direct relationship between the structure (organizational structure, material resources and human resources), process (organization and performance of clinical tasks and processes) and outcome of care (clinical results, their effect and patient satisfaction (196).

In a study of cancer survival in developing countries, survival in two groups of countries was analysed. One of the groups (Group A) included Turkey and Singapore where health services are well developed. The other group (Group B) included India, Philippines and Thailand where health services are less developed. The five-year relative survival rate in Group A countries versus Group B countries was 64.1 versus 49.8, 45.7 versus 32 and 8.6 versus 2.4 for local, regional and distant colorectal cancer, respectively. The higher survival in Group A countries reflects well established screening programs, accessibility to health facilities as well as developed treatment practices, after controlling for potential confounders e.g age, sex, stage and treatment (14).

Health insurance is one of the health services that affect colorectal cancer survival. For patients registered with the U.S. national cancer data base from 2003 to 2005, the hazard ratio for death at 1-year was increased for patients without private insurance (i.e. patients who have Medicare or Medicaid insurance in addition to uninsured patients) (137). The same result was found for the relationship between insurance status and survival among nonelderly rectum cancer patients registered by the U.S. national cancer data base from 1998 to 2002 (190). Comorbidity accounted partially for the increase of poorer survival of patients without private insurance, and it is expected that difference in the receipt of treatment may also lead to poorer survival (190). Many other studies showed variation in the relationship between colorectal cancer survival and insurance status (197-201).

Different type of surgeons (general, specialist, and trainee) as well as different treatment facility types (e.g. secondary public, teaching public and private hospitals) are other factors of disparities in colorectal cancer survival as shown in a study carried out in New Zealand

(171). Early death was not found to be associated with distance to clinic, though, as shown in a study conducted in Ontario, Canada (145).

2.5.6 Residence-related factors and colorectal cancer survival

<u>2.5.6.1 Country-related residential factors</u>

Wide variation is observed when colorectal cancer survival rates are compared among different countries. This fact is supported by the results of a global cancer survival study for 31 countries distributed across the five continents (CONCORD study). Researchers analysed the data for patients diagnosed with primary invasive malignant colorectal cancer during 1990 through 1994 in order to estimate the 5-year relative survival rate. The results showed that colorectal cancer's 5-year relative survival rate was generally greater than 55 percent for both sexes in Japan, France, U.S.A., Canada and Australia, reaching 61.1 percent for males in Japan and 61.5 percent for females in France. Colorectal cancer's 5-year relative survival rate was generally lower in Algeria (male 22.5 percent, female 22.6 percent) and Poland (male 28.6 percent, female 30.6 percent) (13).

In Europe, large gaps in colorectal cancer survival rates were observed across the different European countries (12;13). In general, survival was lower in Eastern European countries compared to the Western European countries. In the CONCORD study the range of 5-year relative survival rate among the European registries was 25.7-57.8 percent for males and 22.5-64.2 percent for females.

Variations in survival rates across the Western European countries were also observed. In England and Scotland, survival rates were found to be 42.3 percent and 44.6 percent,

respectively for males, and 44.7 percent and 47.7 percent respectively for females. Yet, the rate exceeded 50 percent for both sexes in France, Germany and Italy with France reaching 61.5 percent for females (13). Moreover, in France, a population-based study was conducted on data from patients who were diagnosed between 1989 and 1997. The results provided age standardized 5-year relative survival rates among males and females, which were 55 percent and 57 percent, respectively (202).

Another study which compared the survival differences between European and U.S. patients diagnosed between 1990 and 1991 showed that 3-year relative survival ranged from 67 percent in Modena, Italy to 44 percent in Thames, U.K. Comparing European with U.S. patients, 3-year relative survival was found to be 69 percent in the U.S. and 57 percent in Europe (12). The CONCORD study also showed higher survival rates in the U.S. compared with Europe (13).

In a report on cancer survival in developing countries, survival analysis was performed for patients diagnosed with disease from 1990 to 2001 (11). As in other studies, results demonstrated large discrepancies between the different regions. Furthermore, a five-year relative survival was reported to be greater than 50 percent in Singapore, Turkey and South Korea; ranging from 28 percent to 44 percent in India, Thailand, Philippines and China; whereas it didn't exceed 8 percent in Uganda and Gambia (14;17;173).

2.5.6.2 Community-related residential factors

Residents in rural areas were found to have lower colorectal cancer survival compared with those living in urban areas, as shown by the results obtained from studies conducted in

India, China, and New Zealand. Place of residence is associated with many factors such as life style, early detection, awareness and access to health services (13;171;173).

Other reports demonstrated that distance from treatment centres is associated with the survival rate of colorectal cancer. In Australia, a study conducted in Queensland found that mortality risk of patients with rectum cancer increased by 6 percent for each 100 km increment in distance from radiotherapy facility (203).

The association between colorectal cancer survival rate and access to healthcare was investigated in a study conducted in the U.S. state of Texas (159). Results showed a significant association between the spatial access to treatment and survival rate only in rural areas but not in urban areas; this was attributed to the greater concentration of oncologists in metropolitan areas.

Synopsis: Examining different factors that might influence survival of colorectal cancer is important for determining disease progress. Survival statistics presented in this section indicated that colorectal cancer survival differs with age with a tendency of older patients to have poorer survival. Although the literature seems to be inconsistent in defining the link between sex and colorectal cancer survival, the survival rate of colorectal cancer patients is remains mostly insignificantly affected by the patient's sex. Furthermore, there seems to be a consistent agreement in the literature for the association of lower socioeconomic status with a shorter colorectal cancer survival, as well as variations of survival by ethnicity or race. These variations may be explained by cancer stage at diagnosis, access to health services, quality of treatment, tumour biology, demographics or even risk factors such as obesity.

Evidence indicates that the stage of tumour at diagnosis is the most important predictor of survival with survival rates getting shorter with the spread beyond the site of origin. In addition, cancer grade also plays an important role in predicting colorectal cancer survival, where survival rate decreases with poorer cell differentiation. Alternatively, the literature provides controversial viewpoints on the effect of tumour site on colorectal cancer survival. Similarly, surgery and adjuvant chemotherapy were reported to contribute to variations in colorectal cancer survival with a tendency to have a lower survival among patients who underwent surgery compared to those who received adjuvant chemotherapy. Other important predictors conveyed through the literature include the presence of comorbidities in colorectal cancer patients which tend to significantly decrease survival. In this aspect, the literature emphasizes the effect of Diabetes Mellitus on colorectal survival with a tendency to support a decreased survival rate with the presence of Diabetes Mellitus.

The literature provides strong evidence to support the relationship between the quality of health services and cancer survival. In addition, the literature identifies the availability of health insurance as a predictor to a decreased cancer survival, which might be partially related to the presence of other comorbidities that tend to decrease survival of patients without insurance. In addressing variations in colorectal cancer survival between countries the literature identifies large discrepancies between different regions with survival rates being lower in developing countries. Other factors identified in the literature as being associated with survival of colorectal cancer include residential factors, where residents in rural areas were found to have lower colorectal cancer survival compared with those living in urban areas.

2.6 Summary of the Literature Review

There are demographic concerns for Jordan. Its population will nearly double by 2035; the majority of the population will be 40 years of age or more by then and also represent a greater risk of developing cancer. As non-communicable diseases play a greater role in the overall disease burden of countries experiencing economic improvement. It is likely that Jordan's future economic development positions the broadest segment of the population (i.e. those 40 years of age or more) to be especially at risk for developing cancer.

However, it could be said that Jordan's health care system is somewhat more robust than that of its neighbours as well as other wealthier countries. Jordan has a considerably greater number of physicians per 10,000 population than its close neighbours and slightly more than the wealthier countries of U.A.E. and Qatar. Jordan has made significant strides in provision of health care services to its population placing it on a par with the U.K. and Australia in terms of total health care expenditure as a percentage of GDP. Curative care takes up approximately 80 percent of health care expenditure while primary care remains less than 20 percent.

As the chapter discussed, on a global basis, there are differences in the epidemiology of colorectal cancer. While colorectal cancer globally is the third most common cancer in males, in Jordan it is the most common cancer among newly diagnosed male patients. Among females, colorectal cancer is the second most common cancer in Jordan, as well as globally. Throughout the world, as GDP increases, the incidence of colorectal cancer also climbs. The only country to witness a decline in incidence has been the U.S.

On a worldwide basis, colorectal cancer accounts for 9.4 percent of all cases. While Jordan's colorectal cancer rates of 9.8 percent for males and 9.0 percent for females are not dissimilar to worldwide rates, they are lower than the rates of most Arab countries (whose economic development have been slower than that of Jordan). This fact also suggests, though, the possibility that Jordan's population may experience a more rapid rise in new cases than countries outside the region that share similar levels of economic growth as Jordan.

The incidence rate in Jordan has been lower than that of other middle-income countries, but not unlike the (relatively) lower rates across the Eastern Mediterranean Region. Despite the differences in incidence rates, a common set of variant risk factors have been identified; these include being older than 45 to 50 years, being male versus female, having a specific ethnicity (or familial history), *et al*. Other modifiable risk factors exist (e.g. high blood pressure, high BMI, impaired fasting glucose, high cholesterol) that are also common in patients with diabetes mellitus. This section discussed, Jordan is already witnessing the impact on its population of increased experience of the modifiable risk factors. However, survival rates for colorectal cancer are possibly most affected by early presentation and localized staging. These types of differences form part of the framework for comparison of Jordan's colorectal survival rates with those of other countries.

Due to gaps in the literature, the question remains of whether: i) Jordan has better, or worse, survival than other countries; and ii) whether it can be explained by known risk factors. In order to address these gaps, six Study objectives have been designed (Section 1.4.2). Table 4a shows how the study objectives map against a summary of the known risk

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factors discussed in the literature review; Table 4b shows how Study objectives map against survival statistics found in the literature. The column headed "Impact of the risk factors on populations outside Jordan" highlights pertinent data describing other countries; the column headed Jordanian metrics shows reciprocal data for Jordan. The scarcity of Jordanian data provides more specific detail to describe the Literature gaps.

As the chapter showed, differences between countries may be a result of differences in known risk factors (e.g. later presentation, older populations, poorer treatment) or some other country-specific factors. While the literature gives some indications of how Jordan compares with other countries, gaps in the literature prevent definitive comparisons being made between survival rates in Jordan and other countries.

 In addition, variation of colorectal cancer survival across the different countries can be attributed to socioeconomic status (SES), the screening programmes and the quality of treatment practices (12;13;173;204). Cancer survival is also an indicator for the country's capability to control the disease (13;21;76;205). Apart from efforts to prevent cancers, improvements making early diagnosis and treatment more accessible could be major challenges in the developing countries.

Table 4a: Summary of literature review related to risk factors

General risk factors			
Primary risk factor	**Secondary risk factor**	**Impact of the risk factors on populations outside Jordan**	**Jordanian metrics**
Age		Being >45–50 yrs. old. Incidence rate is more than 14 times higher in adults 50 years and older than in those younger than 50 years. Mortality rates increase with age; 94percent of deaths occur in individuals 50 years and older	To be addressed via Study objective 3.
Clinical characteristics of the tumour*:	Stage of tumour	Stage at Dx is single most important predictor of survival. Result constant regardless of race, quality of health services, treatment type and tumour site. Survival highest for localized tumours, lowest for distant. Duke's Staging and TNM Staging both showed that least advanced cancers (Duke's Stage A and TNM Stage I) had highest survival rates	To be addressed via Study objective 4.
	Cancer grade/ morphology	Survival rates worsen as cells become less differentiated. Higher cancer grades increased Hazard Ratio in non-elderly. Highest 5-yr. survival rates for rectum cancers from polyp/adenoma and carcinoid; poorest rates for small cell & adenosquamous types of colon cancer and rectum cancer with undifferentiated, small cell & melanoma types. Mucinous vs. non-mucinous tumours had the lower survival and signet ring was worse for both rectum & colon.	To be addressed via Study objective 4.
	Tumour site	Effect of tumour site varies considerably among various studies.	To be addressed via Study objective.
Type of treatment*		Preoperative radiotherapy improved survival for rectum cancer patients, but otherwise little conclusive evidence of improved survival with surgery vs. chemotherapy. Some evidence of better 5-year survival for laparoscopy vs. open surgery.	To be addressed via Study objectives 4 and 5.

Table 4a: Summary of literature review related to risk factors

General risk factors			
Primary risk factor	**Secondary risk factor**	**Impact of the risk factors on populations outside Jordan**	**Jordanian metrics**
Comorbidity*		Concurrent illness is common in colorectal cancers and significantly affects survival. Multiple comorbidities had variable patterns depending on combination of types. Presence of Diabetes Mellitus was both a prognostic factor and comorbidity associated with survival rate. Disease-free survival rates were lower in patients with Stages II or III colorectal cancer than those without diabetes. The effect of diabetes mellitus on colorectal cancer outcomes is associated with hyperinsulinemia and IGF-1.	To be addressed via Study objectives 4 and 6.
Socio-demographic characteristics:	Race/ethnicity	Higher incidence rates among Ashkenazi Jews and African Americans. Lower survival rates among U.S. blacks vs. whites and among Hispanics vs. non-Hispanics. Lower number of comorbid conditions increased hazard ratios in white patients than in blacks. Variations in survival can be seen in local vs. immigrant populations in Denmark and Hawaii and between indigenous and non-indigenous population in Australia and N.Z..	Jordan has a multi-ethnic society. Additional aspects of race/ethnicity will be addressed via Study objective 3.
	Sex	Incidence and mortality rates are higher in men than in women. One large study of metastatic colorectal cancer patients found that women <45 years had better survival rates than men, yet women > 55 years had worse rates than similarly aged men.	To be addressed via Study objective 3.
	Socio-economic status	Many researchers found lower socio-economic status to be positively associated with shorter survival. Many other factors (e.g. stage at Dx, quality of treatment, comorbidities) may play a role.	Considerable inequalities in obesity by socio-economic status exist in Jordan. Additional impacts of socio-economic status will be addressed via Study objective.

Table 4a: Summary of literature review related to risk factors

General risk factors			
Primary risk factor	**Secondary risk factor**	**Impact of the risk factors on populations outside Jordan**	**Jordanian metrics**
Health services		Quality (i.e. degree of development) of health services is strongly related to survival. Adequate health insurance coverage also affects survival rate. Levels of surgeon's skills as well as various type of treatment hospital affect survival rates. Distance to clinics was not related to early death in Canada.	Health care expenditure in Jordan (8.4percent of GDP) is similar to rates found in the U.K. and Australia. Some 79 percent of Jordan's population is covered by insurance. Jordan was ranked world's fifth most popular medical tourism destination in 2008. Additional impacts of health services will be addressed via Study objectives 2, 3 and 5.
Residence-related factors:	Country of residence	Incidence rate is higher in wealthier countries. Survival rates vary greatly across countries, per CONCORD study. CONCORD showed differences between European countries (e.g. higher survival in France, lower survival in Poland, better in the U.K. but still lower than France and Italy) and between Europe and the U.S. (higher survival in the U.S. and lower survival in Europe); Asian countries showed generally lower rates but representative of general economic status. Variation across countries is attributed to success of screening programmes.	To be addressed via Study objectives 3 and 5.
	Community-related factors	Residents in rural areas have lower survival rates than patients living in urban areas.	To be addressed via Study objectives 3 and 5.
Other modifiable risk factors:			To be addressed via Study objectives 1, 2, 3 and 6.
Non-modifiable	Family/ personal history	Adenomatous polyposis; hereditary non-polyposis colorectal cancer or Lynch syndrome, history of colorectal cancer and/or polyps; being diagnosed with chronic inflammatory bowel disease.	No literature found for Jordan.

Table 4b: Summary of literature review related to CRC survival statistics

Survival statistics	CRC survival statistics and populations outside Jordan		CRC survival statistics related to Jordanians	
Independent of risk factors: survival statistics for CRC in Jordan	Not applicable.		Literature gap to be filled by Study objective 1 (Section 1.4.3).	
Independent of risk factors: survival statistics for CRC in countries outside of Jordan	*Country*	*Period/Year of the study: reference*	Literature gap to be filled by Study objective 2 (Section 1.4.3).	
	Worldwide incidence of new CRC cases = 1.2 million cases	2008	*Literature related to Jordan*	*Period/Year of the study: reference*
	8percent of all cancer deaths worldwide are from CRC		Estimate for Jordan: CRC ASR of: 15.3 for males; 11.9 for females	GLOBOCAN 2008
	West Asia CRC ASR of: 13.1 for males; 10.1 for females	GLOBOCAN 2008	Jordan 2008: 548 new cases CRC; 11.9percent of all new Jordanian cases; male-to-female ratio 1.5:1	
	Highest ASR for CRC: males: Czech Rep 59.1; NZ 49.3; For females: NZ 39.5; South Australia 34.1	Between 1998-2003		
	Lowest ASR for CRC: males: Mumbai, India 5.9; Quito, Ecuador 8.4; For females: Mumbai India	Between 1998-2003		

Table 4b: Summary of literature review related to CRC survival statistics

Survival statistics	CRC survival statistics and populations outside Jordan		CRC survival statistics related to Jordanians
	4.4; Quito Ecuador 8.9		
	ASIR of overall cancer in Jordan: 134.7 per 100 000 for males; 136.0 per 100 000 for females	2009	
	In region:		
	Highest ASR for CRC: Israeli non-Jews: males 34.0 & females 34.7	1998-2003	
	Lowest ASR for CRC: Oman males 3.7		

CHAPTER 3 – MATERIALS AND METHODS

3.1 Introduction

This chapter describes the general methodological issues and introduces the reader to the subjects and methods used to fulfil the study objectives and answer the research questions (concerning colorectal cancer survival statistics in Jordan for the 2003 through 2007 timeframe). The methodological approach included review of documents and other published materials. A study instrument was developed for capturing all pertinent data.

The chapter starts with a description of the methods used for conducting the literature review as well as the source of data that has been utilized. The study instrument (questionnaire) is described in detail. The data collection procedures are also explained in detail. Data quality control measures, data analysis and human research ethical approvals were discussed, as well. At the end of this chapter, the main terms and conditions that have been used in the study are addressed.

The main source of the study data was Jordan Cancer Registry. The vital status of patients was ascertained using the data of the Jordan National Civil Registration Bureau. The researcher completed the missing data and collected additional information from hospitals by reviewing medical records and laboratories from both governmental and non-governmental bodies.

The study was carried out at the national level: the Jordan Cancer Registry (JCR), hospitals, and laboratories from both governmental and non-governmental bodies were accessed.

3.2 Study methods

This is a descriptive study carried out to estimate the observed and relative colorectal cancer survival rates among the study population during the period 2003 (01 January) through 2007 (31 December). The survival rates were described in relation to many variables (such as age, sex, residency, extent of cancer, site, morphology, treatment and presence of diabetes mellitus type 2).

3.3 Data sources

The study was carried out at the national level: the Jordan Cancer Registry (JCR), hospitals, and laboratories from both governmental and non-governmental bodies were accessed. The vital status of patients was ascertained using the data of the Jordan National Civil Registration Bureau.

Data from JCR was collected and coded in accordance with the International Classification of Diseases for Oncology, 3rd edition (ICD-O3) (54), in addition to the International Classification of Diseases (ICD-10) (55). In addition to the use of routine JCR records, hospital records were reviewed and pathological laboratory reports at national level were used to complete any missing information. Field visits were conducted and data was collected from public health hospitals, King Hussein Cancer Center, military (i.e. Royal

Medical Services), teaching hospitals and hospitals in the private sector. In addition to these sites, data was also collected from pathology laboratories.

It should be mentioned that the Civil Registration Bureau (CRB) in Jordan is a centralized system. Overseen by the Ministry of Interior, the CRB is responsible for the civil registrations in the country. Its main role is to register all vital events experienced by Jordanian citizens, living in the country or abroad, as well as other nationalities resident in Jordan. The CRB provides certificates for vital events, registers Jordanian families, issues family books and provides national IDs for all Jordanian citizens.

3.4 Eligibility and inclusion criteria

Only Jordanian colorectal patients, aged 15 through 99 years of age, diagnosed with first invasive primary colorectal cancer during the period 01 January 2003 through 31 December 2007, verified by histopathology report and registered in Jordan Cancer Registry were included in the study. Non-Jordanian nationals, those Jordanians who were diagnosed before 01 January 2003 or after 31 December 2007 or any case with no histological report were all excluded from the study. The CRC cases were categorized according to ICD-10 site codes (C18-C20-9).

3.5 Study instrument

The study instrument (Annex 1) was developed for capturing information from JCR, medical records, the histopathology report as well as CRB. The study instrument was designed to gather information on socio-demographic characteristics, clinical and histopathology information, treatment, co-morbidities and information about the patients'

vital status. Sections 3.5.1 through 3.5.5 describe more fully each relevant section of the study instrument.

3.5.1 Socio-demographic information

This section of the study instrument collected data that identified the patient serial number, sex, age, date of birth, place of residency (i.e. governorate), occupation, level of education, and main source of medical services.

3.5.2 Clinical and pathological information

This section identified date of diagnosis, site of the tumour, morphology, staging and grade. Further information about tumour size and number of positive lymph nodes was partially extracted from pathology reports.

3.5.3 Treatment

Treatment information included the type of treatment, whether palliative or curative, information about surgery (type, date and procedure) and information about chemotherapy as well as radiotherapy (date and frequency) was collected.

3.5.4 Co-morbidity

This section focused on the major co-morbidities in Jordan: diabetes mellitus, hypertension, raised cholesterol and obesity.

3.5.5 Vital status

This section determined the vital status of the patient: whether alive, dead or unknown; time passed from date of diagnosis to date of death or to date of last visit, and the cause of death, if available.

3.6 Data collection

3.6.1 Preparatory Phase

The preparatory phase was comprised of literature review, preparation of study tools, finalization of administrative steps and conducting a pilot study.

3.6.1.1 Administrative steps

Preparatory administrative communication with key personnel was made to facilitate implementation of the study. Official letters were addressed to the Ministry of Health in order to get required information. As a result, written permissions from the JCR, the Ministry of Health, King Hussein Cancer Center, Royal Medical Services Hospitals, private hospitals and laboratories, and the Civil Registration Bureau – CRB (under jurisdiction of the Ministry of Interior) were obtained (Annex 2).

3.6.1.2 Pilot study

A pilot study was conducted to test the instrument and to check the validity of the data collection techniques. The pilot study was conducted in Al-Bashir Hospital (a Ministry of Health hospital), the King Hussein Cancer Center, one teaching hospital and one private hospital. For each site ten forms were filled out. The study instrument was modified

accordingly. The pilot study confirmed the feasibility of conducting the study and the commitment of the Jordan Cancer Registry and other sites to support the study. On the other hand, the results of the pilot study showed variation in the quality of medical records across different hospitals. The pilot study also showed that some of the patients received treatment at different sites during their treatment plan.

3.6.2 Implementation phase (Data collection and follow up)

3.6.2.1 Jordan Cancer Registry

Data from the JCR was obtained for patients diagnosed with the colorectal cancer during the 2003 through 2007 study period. A prerequisite step to this was to discuss and present the study protocol to the JCR and to the Jordan Ministry of Health before gaining their permissions. JCR provided CRC data on 2,093 records, according to the study eligibility and inclusion criteria. Data was supplied based on the anatomical location of colorectal cancer coded to the tenth revision of the International Classification of Diseases (ICD-10) or the third revision of the International Classification of Diseases for Oncology (ICD-O-3); colon (ICD-10 C18.0–C18.9), rectosigmoid junction (C19; ICDO-3 C19.9), and rectum (C20; ICD-O-3 C20.9) excluding anus and anal canal (ICD-10 C21). Data was collected for age, sex, date of presenting, residency, date of diagnosis, anatomical site, morphology, grade and stage at diagnosis. There was no available information about occupation, level of education and treatment.

3.6.2.2 Medical records

In addition to using the routine JCR data base, active strategies for collecting more clinical information on treatment, co-morbidity, the site of receipt of health care services were

followed by reviewing hospital records and pathological laboratory reports at the national level. Furthermore, the medical records and pathological laboratory reports were used to compensate for the missing clinical information such as the site, stage and grade of the cancer.

3.6.2.3 Vital status

The vital status of the patients was ascertained from CRB based on use of the unique National Identification (ID) number of the patients with follow-up to 31 December 2010. The outcome of interest was whether colorectal cancer cases were alive, dead or unknown. The survival duration of each case was determined as the time difference (in days) between the date of diagnosis (index date) and the date of death, date of loss to follow-up, or the closing date for follow-up (31 December 2010).

Data collection took place between February 2010 and December 2010 after getting official permissions to conduct the study.

3.7 Quality control

3.7.1 Data processing

As mentioned earlier, JCR provided CRC data on 2,093 subjects according to the study eligibility and inclusion criteria. After checking the data that was received, 46 duplicate records were excluded. Duplication of data was avoided by using the patient's unique national ID number and their full names (i.e. use of four elements: name of patient, father, grandfather and family name). Seven records indicating patients' age of less than 15 years and above 99 years were excluded as well as 47 records for non-Jordanian patients, 38

records with anal cancer (C 21) and two records with other types of cancer. Also excluded were the records of 20 patients whose tumours were benign (behaviour code 0), of uncertain or borderline malignancy (1), or metastatic (6) to the index organ from elsewhere (e.g. Lymphoma in large intestine: 9590, 9591, 9680 and 9731). Furthermore, another 37 patients were excluded because of the lack of availability of any kind of follow-up information as of 31 December 2007. No cases were found based on information from death certificate only (DCO). Records with invalid codes, impossible sequences of dates or improbable combinations of tumour site and morphology were revised and checked with the JRC. Corrected records were integrated in the study. As a result, there were 1,896 records included in the study. Figure 7 shows the corresponding data processing procedure.

Figure 7: Data processing of colorectal cancer records (2003-2007)
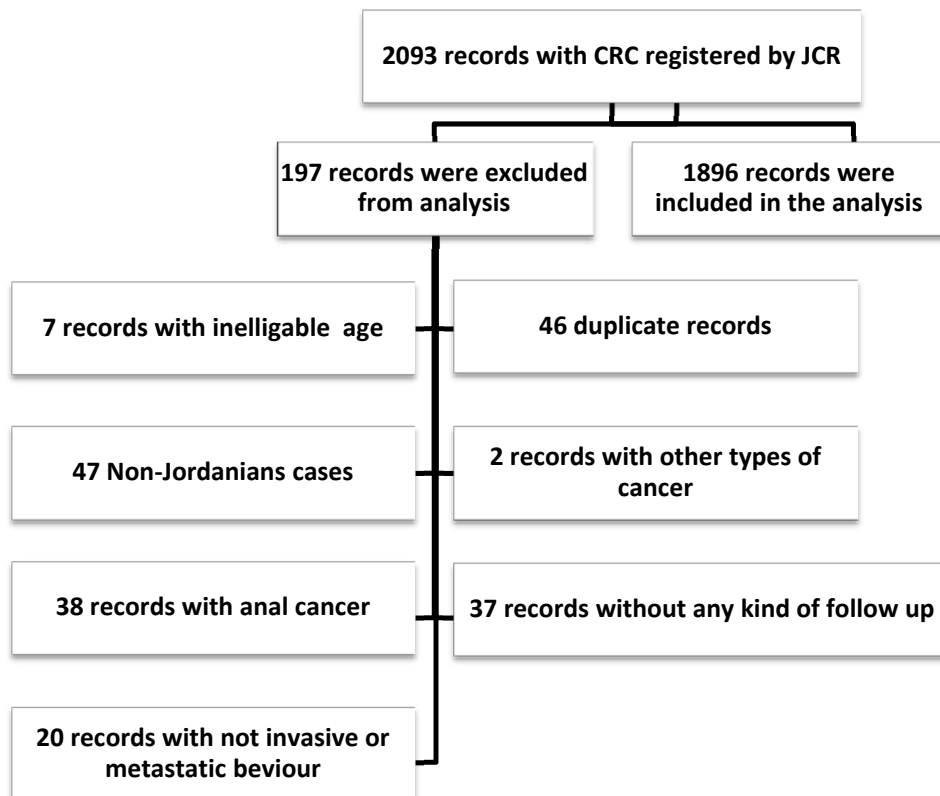
3.7.2 Vital Status and follow up time

Identifying the vital status of the included patients was ascertained from the CRB through the use of the unique National Identification numbers (IDs) of the patients. In case no ID was present, the vital status was identified through a search of full four-element names (patient, father, grandfather and family name) and of three–element names (patient, father and with the third name element being the family name) and then comparing the results to the data in the CRB. In both of the above scenarios, names were matched with age and sex. Another source of identifying vital status was discharge data from the hospital assuming the date of discharge to be the date of the last visit of the patients. As a result, the vital status was identified through National Identification Numbers (IDs) for 1,499 cases, through checking with four-element names for 241cases, and through checking with three-element names (the third name being the family name) for 20 cases. Medical records were used to follow up only 136 cases (from the date of diagnosis and the last day of the study (i.e. 31 December 2010). Figure 8 illustrates the procedure used for following up with vital status.

Figure 8: Vital status follow up for CRC cases
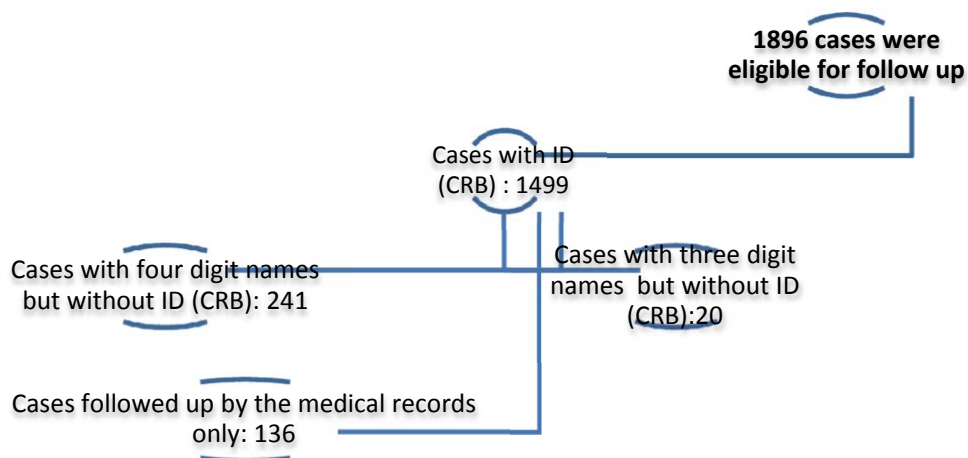
3.8 Statistical Analyses

3.8.1 Incidence of colorectal cancer

To better understand the CRC in Jordan, the crude and age–specific incidence rates (ASIR) per 100,000 population for each year were estimated for both males and females. The overall crude incidence rate was estimated using the total population in the period of the study corresponding to the sum of the populations for each year between 2003 and 2007. Standardization is necessary when comparing several populations that differ with respect to age because age has a powerful influence on the risk of cancer. The Age Standardized Rate (ASR) is a weighted mean of the age-specific rates; the weights are taken from the population distribution of the standard population. Similar to the crude incidence rate, the age-standardized incidence rate is expressed as the number of new cases per 100,000 persons in a given year. The most frequently used standard population is the World Standard Population that we used in this study. World Age Standardized Rates (ASR), using the Jordanian national population age-specific estimates, were calculated using the methods proposed by Segi and modified by Doll et al (78;206). To allow comparisons with different countries, the CRC age-specific incidence rates were aggregated by 5-year age groups (aged 15-74 years) as described by the International Agency for Research on Cancer (58).

3.8.2 Survival probability

The Kaplan-Meier method was used to determine the observed survival probability over time. Kaplan-Meier provides for calculating the proportion surviving to each point in time when death occurs. Thus it was used to measure the length of time people remain living after being diagnosed with colorectal cancer (207). An important advantage of the Kaplan–Meier method is that it can take into consideration types of censored data, particularly

right-censoring, which occurs if a patient withdraws from a study (i.e. is lost from the sample before the final outcome, death, is observed. The Kaplan-Meier method and life table method give identical results in the absence of withdrawals (207;208). Kaplan-Meier was used in a univariate analysis to identify the potentially important prognostic variables-effect of different predictors on survival rate (e.g. age at diagnosis, sex, stage, site, grade and type of treatment).

The logrank test was used to estimate if the difference between the groups is statistically significant (P <0.05). The logrank test matches estimates of the hazard functions of the two groups at each observed event time. It is created by computing the observed and expected number of events in one of the groups at each observed event time and then adding these together to obtain an overall summary across all time points in which an event occurs (209;210) .

In this study we used the complete approach of estimation of observed survival probability, implemented in the open-source program *Strs* with the statistical package Stata (version 10.1) (211). The complete approach includes all subjects who are diagnosed as incidents of colorectal cancer cases until the closing date of the follow up. Cases with complete follow up of five years as well as those who had incomplete follow up of less than five years were both included (173;212;213). This approach allows for inclusion of all patients in the study period (2003-2007).

Expected survival was estimated from the general population of Jordan, which was extracted from the National life tables (Department of Statistics/DOS estimation) of death rates by sex, single year of age and calendar year 2000. In this study, expected survival

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probabilities were estimated according to the Ederer II method (173;212-214). The advantage of the Ederer II method is that calculations of the expected survival rates for patients under observation at each point of follow-up are made so that the matched individuals are considered to be at risk until the corresponding cancer patient dies or is censored (173;212;213;214).

Relative survival is the standard approach for population-based cancer survival. It is interpreted as observed survival adjusted for other cases of background mortality (expected survival) (173;213).

To compare the results with other countries, age-standardized relative survival was calculated using the International Cancer Survival Standards (ICSS) to correspond to the age distribution of cancer patients (215). These categories were derived from discriminant analysis to find the smallest number of sets of standard age weights that enable adequate standardization of survival. Each standard provides age-standardized survival estimates that are not too different from the unstandardized estimates.

Observed and relative survival estimates at 1-, 3- and 5-years were estimated separately for each of the age groups 15–44, 45–54, 55–64, 65–74, and 75–99 years for both sexes.

Cox proportional hazard regression was used to assess the net effect of each variable after simultaneously controlling the effects of potential confounders. This model, which takes into account the effect of censored observations, was chosen because it is recommended when the time of an event has particular interest (216;217). Since the Cox proportional

hazards model relies on the hazards to be proportional, i.e. that the effect of a given covariate does not change over time, it was very important to verify that the covariates satisfy the assumption of Proportionality (216-218). In our study the assumption of Proportionality was tested by assumption of Proportionality and including Time Dependent Covariates in the Cox Model techniques.

Multivariable analyses were used to examine the adjusted odds of death within 30 days of surgery. The adjusted odds ratios for CRC thirty-day postoperative mortality for sex, age, place of residence, extent of disease, topography, operation type, and treatment site were calculated using the logistic regression modelling procedure.

In addition to the Kaplan-Meier and Cox approaches, multivariate analysis was made by analysing Poisson Regression of relative survival. Both approaches yielded similar results. However, it was decided to present Kaplan-Meier and Cox approaches since the Cox Proportional Hazards Model is the most commonly applied model in medical time-to-event studies. Moreover, researchers from Jordan and the region are more familiar with the Kaplan-Meier/Cox approach rather than Poisson regression and thus the methods presented are more likely to be reproduced. The Poisson method is potentially more statistically powerful as it is a parametric approach; however, it assumes that the baseline hazards are constant over time. The Cox approach does not make this assumption and as a non-parametric method is potentially weaker. However, baseline hazards do vary over time in colorectal cancer patients and it was felt that the Cox approach was the better one. In practice, however, both approaches yield extremely similar results.

3.9 Human research ethical approvals

Data was handled in compliance with the principles of the Data Protection Act 1988. In particular, only data that is required to answer the research questions was obtained; data was only used for the intended purposes. Secure encrypted electronic storage media was used to handle data, which was made anonymous prior to analysis by removing all sensitive data such as names and address and replacing them with computer-generated numbers. Using the data was approved by the national health ethical review board (ERB), Jordan ministry of health as well as by the institutional review board (IRB) of King Hussein Cancer Center. Furthermore, the study protocol was approved by the ethics committees of Glasgow University as well as the International Agency for Research on Cancer (IARC). As patients were not directly contacted or involved, the principal ethical consideration in this study was to avoid disclosure of personally identifiable information. After completing the data analysis according to the Study objectives, the data was provided to the JCR. Study approvals are annexed (Annex 2).

3.10 Terms and definitions

3.10.1 Colorectal cancer

Colorectal cancer was classified according to international classification of oncology (ICD-O third edition, in addition to the International Classification of Diseases, ICD-10) as (C18.0-C20.9) which include cancers of the colon (i.e. appendix C18.0, cecum C18.1, ascending colon C18.2, hepatic flexure of colon C18.3, transverse colon C18.4, splenic flexure of colon C18.5, descending colon C18.6, sigmoid colon C18.7, overlapping lesion of colon C18.8, colon, NOS C18.9), recto-sigmoid junction C19.9, rectum (rectum, NOS C 20.9) (54;55).

3.10.2 Differentiation and grading

According to ICD-O third edition, colorectal cancer grades were divided into four categories: well differentiated, moderately differentiated, poorly differentiated, undifferentiated anaplastic, and grade and differentiation not unknown (54).

3.10.3 Stage definition

In Jordan, the JCR uses Surveillance Epidemiology and End Results (SEER) Staging. However, a number of staging conventions had been used by treating doctors, as documented in the records of patients in this project, including Tumour, Nodes and Metastasis (TNM) scores, American Joint Committee on Cancer (AJCC) Staging Scores (I – IV) and Dukes (A-D) Scores (100). To compensate for the missing data by JCR, with assistance of Jordan cancer tumour registrar (CTR) in the JCR, scores of AJCC, TNM and Dukes scoring systems were converted into SEER scores, namely localized disease, regional spread and distant metastasis based on Summary Stage Book 2000 of colorectal cancer as shown in the reference table in AJCC for TNM staging system (100). Coding conventions used to derive a SEER score from the actual TNM, AJCC and Dukes scores were developed using commonly accepted cut points.

3.10.4 Morphology type

The type of histopathology includes adenocarcinoma (M8140), mucinous adenocarcinoma (M8480), carcinoma, and (M8010) other morphology according to the international classification of oncology ICD-O third edition (54).

3.10.5 Comorbidities

For this study comorbidity, namely diabetes mellitus, hypertension, hypercholesterolemia and obesity were included in the study instrument. Information about these comorbidities was ascertained from the medical records of each patient. Due to the poor quality of medical records, poor comorbidities documentation, unavailability of electronic hospital discharge records and the fact that diabetes mellitus poses a high burden on the Jordanian population, justify investigating diabetes mellitus as the only factor in relation to colorectal cancer survival in this study.

3.11 Summary

This is a descriptive study carried out to estimate the observed and relative colorectal cancer survival rates among the study population during the period 2003 (01 January) through 2007 (31 December). The survival rates were described in relation to many variables (such as age, sex, residency, extent of disease (stage of cancer), site, morphology, treatment and presence of diabetes mellitus type 2). Only Jordanian colorectal patients, aged 15 through 99 years of age, diagnosed with first invasive primary colorectal cancer during the study period, verified by histopathology report and registered in Jordan Cancer Registry were included in the study. Colorectal cancer was classified according to international classification of oncology (ICD-O third edition in addition to the International Classification of Diseases, ICD-10) as C18.0-C20.9.

The study was carried out at the national level: the Jordan Cancer Registry (JCR), hospitals, and laboratories from both governmental and non-governmental bodies were

accessed. In addition to the use of routine JCR records, hospital records were reviewed and pathological laboratory reports at the national level were used to complete any missing information. The study instrument was designed to gather information on socio-demographic characteristics (e.g. sex, age, date of birth, place of residency), clinical and histopathology information (e.g. site of the tumour, morphology, staging and grade), treatment (e.g. type of treatment, information about surgery, chemotherapy and radiology), co-morbidities (e.g. diabetes mellitus) and information about the patients' vital status. Field visits were conducted and data was collected from various hospitals. In addition to these sites, data was also collected from pathology laboratories. A pilot study was conducted to test the instrument and to check the validity of the data collection techniques.

The vital status of the patients was ascertained from CRB based on use of the unique National Identification number (ID) of the patients with follow-up to 31 December 2010. The outcome of interest was whether colorectal cancer cases were alive, dead or unknown. The survival duration of each case was determined as the time difference (in days) between the date of incidence (index date) and the date of death, date of loss to follow-up or the closing date for follow-up (31 December 2010).

The data was checked and revised. Data with invalid codes, impossible sequences of dates or improbable combinations of tumour site and morphology was revised and checked with the Jordan Cancer Registry. Corrected records were integrated in the study. As a result, there were 1 896 records included in the study.

The Kaplan-Meier method was used to determine the observed survival probability over time. The logrank test was used to estimate if the difference between the groups was

statistically significant. The complete approach of estimation of observed survival probability was used. Cox proportional hazard regression was used to assess the net effect of each variable after simultaneously controlling the effects of potential confounders. The crude and World Standardized incidence rates (ASR) were also calculated.

Use of the data was approved by the national health ethical review board (ERB) and the Jordan Ministry of Health as well as by the institutional review board (IRB) of King Hussein Cancer Center. Furthermore, the study protocol was approved by the ethics committees of Glasgow University as well as the International Agency for Research on Cancer (IARC). Data was only used for the intended purposes. Secure encrypted electronic storage media was used to handle data, which was anonymised before analysis by removing all sensitive data such as names and address and replacing them with computer-generated numbers.

CHAPTER 4 – SAMPLE DESCRIPTION

4.1 Introduction

This chapter describes the sample in terms of its socio-demographic characteristics (age, sex, place of residence, and year of diagnosis), clinical characteristics (extent of disease, morphology, and topography), and treatment characteristics (type of treatment, type of surgery, chemotherapy and radiotherapy). The chapter also examines cancer site by socio-demographic, clinical characteristics, and treatment characteristics.

4.2 Socio-demographic characteristics

The study population consisted of 1,896 patients, with socio-demographic characteristics as seen in Table 5. Over half of the patients were men (55.5 percent). About one third of the patients were in the age group 45-59 (32.3 percent) and only 10 percent in the age group of 75 years or older. Three-quarters of the patients lived in the central region of Jordan compared with only 3.5 percent who lived in the south (Table 5).

With one-fourth of the patients diagnosed during 2007, one-fifth was diagnosed in 2006 and around 18 percent in each year from 2003 through 2005. Additional information showed that among all included cases, 1,132 (59.7 percent) patients were alive and 764 (40.3 percent) patients had died on the closing day of the study. There were more deaths among male patients, where 442 (57.9 percent) of deaths being males and 322 (42.1 percent) females. More than half of the deaths (54.2 percent) were patients aged 60 years and above, with the majority (41.2 percent) being in the age group of 60 to 74 years old (information not shown in the table).

Table 5: Percent distribution for socio-demographic characteristics of patients diagnosed with colorectal cancer during 2003-2007, Jordan

Variable	Number	Percent
Sex:		
Male	1053	55.5
Female	843	44.5
Age group:		
15-44	327	17.3
45-59	613	32.3
60-74	764	40.3
>=75	192	10.1
Region:		
North	390	20.6
Middle	1430	75.4
South	67	3.5
Unknown	9	0.5
Year of diagnosis:		
2003	350	18.5
2004	339	17.9
2005	338	17.8
2006	392	20.7
2007	477	25.2

4.3 Clinical characteristics

With regard to colorectal site for cancer, 1,204 (63.5 percent) of patients had colon cancer and 36.5 percent (692 cases) had rectum cancer. Table 6 shows that more than half of the patients (58.9 percent) had regional metastasis, 22.8 percent had distant metastasis, and 11.2 percent had localized CRC at diagnosis. Only 7.1 percent of the cases were found with an unknown extent of the disease.

Table 6: Percent distribution for clinical characteristics of patients diagnosed with colorectal cancer during 2003-2007, Jordan

Variable	Number	Percent
Colorectal site		
Colon (C18)	1,204	63.5
Rectum(C19-20)	692	36.5
Sum stage		
Localized	212	11.2
Regional	1,118	58.9
Distant	432	22.8
Unknown	134	7.1
Morphology		
Adenocarcinoma	1,598	84.4
Mucinous	148	7.8
Carcinoma, NOS	82	4.3
Others	55	2.9
Missing	11	0.6
Grade		
Well	125	6.6
Moderate	1,189	62.7
Poor/anaplastic	282	14.9
Unknown	300	15.8

Adenocarcinoma was the most common form of CRC as it was found in 84.4 percent of cases, followed by mucinous tumours that were found in 7.8 percent of the patients; and neoplasms and NOS were found in 4.3 percent of the patients. Other types of morphology were found in 2.9 percent of the patients, while unknown morphology was only found in less than one percent of the patients. In terms of grade, only 6.6 percent were classified as well, while more than half (62.7 percent) were classified as moderate, 14.9 percent as poor and 15.8 percent as unknown (Table 6).

To better understand the relationship between mucinous adenocarcinoma and other variables, this study explored this morphological variable by selected potential factors.

Table 7 shows that mucinous adenocarcinoma was equally present among male and female patients. With three quarters of the mucinous adenocarcinomas occurring in the colon, 61.5 percent of them were present among those who were 50 years of age or older. Moreover, the majority of the mucinous cancers were of a moderate grade (61.6 percent) and with a regional extent (64.86 percent).

Table 7: Percent distribution of mucinous cases by selected variable

Variable	Patients (n)	Percent
Sex		
Male	75	50.7
Female	73	49.3
Age at diagnosis		
<=50	57	38.5
>50	91	61.5
Grade of tumour		
Well	10	8.9
Moderate	69	61.6
Poor/anaplastic	33	29.5
Extent of disease		
Localized	9	6.1
Regional	96	64.9
Distant	37	25.0
Site of tumour		
Colon	111	75.0
Rectum	37	25.0

Table 8 illustrates the topography of CRC in Jordanian patients. For colon cancer (C18); 20.2 percent were located in the sigmoid (C18.7), 12.9 percent were located in the colon (i.e. colon, NOS), 7.2 percent and 6.1 percent were respectively located in the ascending (C18.2) and descending (C18.6) colons, 6 percent were located in the cecum (C18.1)and 3.9 percent were located in the transverse colon (C18.4).

Almost similar percentages (2.4 percent) were located in the splenic flexure (C18.5), the overlapping (C18.8) (2.3 percent) and the hepatic flexure (C18.3) (2.1 percent), while only 0.5 percent was located in the appendix (C18.0). While for rectum cancer (C19-20); 11.3 percent were located in the recto-sigmoid (C19.9), and 25.1 percent were located in the rectum (C20.9).

Table 8: Topography of colorectal cancer in Jordan (2003-2007)

Topography*	Frequency	Percent
Colon (C18)		**63.6**
Ascending (right) colon (C18.2)	136	7.2
Descending (left) colon (C18.6)	116	6.1
Colon, NOS (C18.9)	245	12.9
Overlapping (C18.8)	43	2.3
Sigmoid (C18.7)	383	20.2
Appendix (C18.1)	10	0.5
Cecum (C18.0)	114	6.0
Hepatic flexure (C18.3)	40	2.1
Splenic flexure (C18.5)	46	2.4
Transverse colon (C18.4)	74	3.9
Rectum (C19-20)		**36.4**
Rectosigmoid (C19.9)	214	11.3
Rectum (C20.9)	475	25.1

* Shown with ICD-0-3 topography codes

4.4 Cancer site by selected characteristics

Cancer site (colon and rectum) was examined by selected socio-demographic (age, sex, place of residence, and year of diagnosis,) clinical characteristics (distance of disease, grade, and morphology) and treatment characteristics that included type of treatment, type of surgery, and intent of treatment.

Differences in the percentages of cancer site within the categories of each of the selected characteristics were examined for their significance by checking chi-square values and their pertinent p-value. Differences were considered statistically significant if a chi square p-value was lower than 0.05.

4.4.1 Cancer site and socio-demographic characteristics

Table 9 displays the percent distribution of colon and rectum cancers and by socio-demographic characteristics (age, sex, place of residence, and year of diagnosis). Differences in the percentage of cancer site by these socio-demographic characteristics were examined for statistical significance.

Results showed a statistically significant difference in the percentage distribution of age categories between rectum and colon cancer patients (p-value <0.001). The percentages of rectum cancer patients aged (15-44 and 45-59) were higher (20.8 percent and 35.6 percent respectively) than the percentages of colon cancer patients in these age categories (15.2 percent and 30.5 percent respectively). Contrary, the percentages of colon cancer patients for the older age groups (60-74, and ≥75) were higher (42.6 percent and 11.7 percent respectively) than those for rectum cancer patients (36.3 percent and 7.4 percent respectively).

No significant differences were found between the colon and rectum cancer patients in terms of their distribution by sex, place of residence, and year of diagnosis.

Table 9: Percent distribution of colon and rectum cancers by selected socio-demographic variables, Jordan (2003-2007)

Variable	Colon		Rectum		P-value
	No.	(percent)	No.	(percent)	
Sex					0.305
Male	658	54.7	395	57.1	
Female	546	45.3	297	42.9	
Age					< 0.001
15-44	183	15.2	144	20.8	
45-59	367	30.5	246	35.6	
60-74	513	42.6	251	36.3	
>=75	141	11.7	51	7.4	
Place of residence					0.128
North	234	19.4	156	22.5	
Middle	920	76.4	510	73.7	
South	42	3.5	25	3.6	
Unknown	8	0.7	1	0.1	
Year of diagnosis					0.189
2003	236	19.6	114	16.5	
2004	207	17.2	132	19.1	
2005	204	16.9	134	19.4	
2006	243	20.2	149	21.5	
2007	314	26.1	163	23.6	

4.4.2 Cancer site and clinical characteristics

Table 10 illustrates the percent distribution of colon and rectum cancer patients by their clinical characteristics (distance of disease, grade, and morphology). Differences in the percentage distribution of cancer site by these clinical characteristics were examined for their significance.

Results showed a statistically significant difference in the percentage distribution of the grade of cancer between colon and rectum cancer patients (p-value=0.005). The percentages of rectum cancer patients with moderate and poor/anaplastic types of cancer were higher (65.2 percent and 16.8 percent respectively) than colon cancer patients with the same type of disease grade (61.3 percent and 13.8 percent respectively). Alternatively, the percentage of well differentiated grade of cancer was higher among colon cancer (7.3 percent) than rectum cancer patients (5.4 percent).

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No significant differences were found between the colon and rectum cancer patients in terms of their extent of disease and morphology distribution.

Table 10: Percent distribution of colon and rectum cancers by selected clinical characteristics, Jordan (2003-2007)					
Variable	Colon		Rectum		P-value
	No.	(percent)	No.	(percent)	
Extent of disease					0.125
Localized	133	11.1	79	11.4	
Regional	689	57.2	429	62.0	
Distant metastasis	290	24.1	142	20.5	
Unknown	92	7.6	42	6.1	
Grade					0.005
Well	88	7.3	37	5.4	
Moderate	738	61.3	451	65.2	
Poor/ anaplastic	166	13.8	116	16.8	
Unknown	212	17.6	88	12.7	
Morphology					0.138
Adenocarcinoma	1,013	84.3	585	84.5	
Mucinous	111	9.2	37	5.3	
Carcinoma, NOS	61	5.1	21	3.0	
Others	30	2.5	25	3.6	
Unknown	8	0.7	3	0.4	

4.4.3 Cancer site and treatment characteristics

Table 11 presents the percent distribution of colon and rectum cancers by treatment characteristics (surgery, chemotherapy, radiotherapy, type of surgery, and intent of treatment). Differences in the percentage of cancer site by treatment characteristics were examined for statistical significance.

As shown in Table 11, the intent of treatment among CRC cancer patients was mainly curative (76.5 percent) and to a lesser degree palliative (23.5 percent). The majority of CRC (77.9 percent) patients underwent surgery, the majority of which (82.0 percent) underwent elective surgery with only 18.0 percent undergoing emergency surgery. Alternatively, 49.3 percent of CRC cancer patients received chemotherapy; while only 17.6 percent of CRC cases received radiotherapy treatment.

Results showed that the percentage of rectum cancer patients (60.7 percent) who had chemotherapy treatment to be significantly higher than that for colon cancer (42.8 percent) (p-value <0.001). Conversely, the percentage of rectum cancer patients who received radiotherapy treatment (42.2 percent) was significantly higher than that of colon cancer patients (3.5percent) (P-value=<0.001). Similarly, the percentage of rectum cancer patients who underwent elective surgery (87.7 percent) was found to be significantly higher than that of colon cancer patients (78.7 percent) (P-value <0.001).

Table 11: Percent distribution of colon and rectum cancers by selected treatment characteristics, Jordan (2003-2007)							
Variable	**Colon**		**Rectum**		**Colorectal**		**P-value**
	No.	**(percent)**	**No.**	**(percent)**	**No.**	**(percent)**	
Surgery							0.091
Yes	924	76.7	552	79.8	1,476	77.9	
No	53	4.4	36	5.2	89	4.7	
Unknown	227	18.9	104	15.0	331	17.5	
Chemotherapy							<0.001
Yes	515	42.8	420	60.7	935	49.3	
No	192	16.0	85	12.3	277	14.6	
Unknown	497	41.3	187	27.0	684	36.1	
Radiotherapy							<0.001
Yes	42	3.5	292	42.2	334	17.6	
No	1,162	96.5	400	57.8	1,562	82.4	
Type of surgery*							<0.001
Elective	726	78.7	485	87.7	1,211	82.0	
Emergency	197	21.3	68	12.3	265	18.0	
Intent of treatment							0.086
Curative	906	75.3	544	78.7	1,450	76.5	
Palliative	298	24.8	147	21.3	445	23.5	

* Among those who underwent surgery

No significant difference was found between in the percentage distribution of surgery treatment and intent of treatment between colon and rectum patients.

4.5 Type of surgery

Table 12 shows the type of surgical procedure carried out for CRC patients. Among those who underwent surgery (1,476), information about type of surgical procedure was

available for 1,099 patients (74 percent). The most common surgical procedures were left hemicolectomy (22.4 percent) and right hemicolectomy (21.2 percent) followed by lower interior resection (LAR) (17.6 percent) and abdomino-perineal resection (APR) (13.2 percent). Sigmoidectomy was done for 6.3 percent of cases while patients underwent partial colectomies, subtotal colectomies/hemicolectomies and total colectomies were carried out at a similar rate of 3 percent for each.

Table 12: Percent distribution for type of surgery procedure among colorectal cancer patients in Jordan, (2003-2007)

Surgery procedure	Freq.	Percent
Left Hemicolectomy	246	22.38
Right Hemicolectomy	233	21.2
Lower Interior Resection	193	17.56
Abdimino-Perineal Resection	145	13.19
Sigmoidectomy	69	6.28
Partial Colectomy, NOS	35	3.18
Subtotal colectomy/ hemicolectomy	34	3.09
Total Colectomy	34	3.09
Surgery, NOS	29	2.64
Excisional Biopsy	26	2.37
Hartman Operation	22	2
Colectomy, NOS	18	1.64
Others	15	1.36
Total	**1099**	**100**

Surgery and excisional biopsy were done in 2.6 percent and 2.4 percent of cases, respectively. Hartman operation accounted for 2 percent of the surgical procedures undergone in CRC cases, while colectomy accounted for just 1.6 percent. Other types of surgical procedures were reportedly carried out in 1 percent of cases.

4.5.1 Thirty-days postoperative mortality after colorectal cancer surgery

Among one thousand and four hundred and seventy four (1,476) individuals who were diagnosed with colorectal cancer and who subsequently underwent surgery for tumour

resection, information about the date of surgery was available for one thousand and three

hundred and fifty six of them (91.9 percent). Of those (1,356), 4.8 percent died within 30-

days of resection.

Table 13 shows characteristics of the study population of 30-days postoperative mortality.

Thirty-day postoperative mortality (the percentage of patients dead within 30 days of

surgery among those who underwent surgery with an available date of surgery) was

calculated for sex (male, female), age group in years (≤ 65, > 65), place of residence

(north, middle, south), topography (colon, rectum), extent of the disease (local, regional,

distant), operation type (elective, emergency), and treatment site (public & teaching, and

private, KHCC and other hospitals). The statistical significance for any differences in

postoperative mortality among groups was assessed using the chi-square test χ^2 (Table 13).

Results showed that postoperative mortality within 30 days of surgery was significantly

lower among patients aged ≤ 65 years (2.9 percent) than among those over 65 years (7.1

percent) (p-value < 0.001). Patients with colon cancer had significantly higher

postoperative mortality (5.3 percent) than those with rectal cancer (2.7 percent) (P-value =

0.020). Moreover, postoperative mortality was noted to be higher among patients with

more advanced tumours (1.3percent localized; 2.8 percent for localized and regional,

compared to 9.3 percent for distant tumours) (p-value<0.001). Thirty-days postoperative

mortality was significantly higher among those who underwent emergency operations (8.0

percent) compared to those who underwent elective surgery (3.6 percent) (p-value=0.015).

Table 13: Characteristics of study population of thirty- day postoperative mortality

Variables	Total	Died within 30 days of surgery		P-Value
		Number	Percent	
Sex				0.216
Male	758	37	4.8	
Female	598	21	3.5	
Age				<0.001
<=65	917	27	2.9	
>65	439	31	7.1	
Place of residence				0.158
Middle	1,016	39	3.8	
North & South	337	19	5.6	
Topography				0.020
Colon	831	44	5.3	
Rectum	525	14	2.7	
Extent of disease				<0.001
Localized & regional	1,067	30	2.8	
Distant	279	26	9.3	
Operation type				0.015
Elective	1094	39	3.6	
Emergency	259	18	8.0	
Treatment site				0.070
Public/teaching	755	39	5.2	
Private/KHCC & others	601	19	3.2	

Note: Among (1,476) individuals who were diagnosed with colorectal cancer and who subsequently underwent surgery, information about the date of surgery was available for 1,356 of them (91.9 percent). Of those (1,356), 4.8 percent died within 30-days of resection.

In addition, Thirty-days postoperative mortality was significantly higher among those who received treatment in public or teaching hospitals (5.2 percent) compared to those who received treatment in private, KHCC, or other hospitals (3.2 percent) (p-value=0.070). As expected, postoperative mortality within 30 days of surgery did not differ by sex or by place of residence.

4.6 Colorectal cancer and treatment sites

In order to detect differences of colorectal cancer survival estimates across treatment sites in Jordan and explain the variation, the study population was divided into five categories

based on the type of treatment site (public, teaching, KHCC, private, and other). Table 14 displays the percent distribution for the treatment site location (hospital) which represented the main source of medical services sought by the patient during the course of cancer treatment. Almost one third (32.4 percent) of the cases were treated at public hospital facilities; 23.4 percent at King Hussein Cancer Center (KHCC); 18.4 percent at teaching hospitals; and 16.8 percent at private health facilities. Only nine percent were treated at other sites, which would mainly indicate charitable, non-governmental or out-of-country hospitals.

Table 14: Percent distribution for treatment site of colorectal cancer patients in Jordan (2003-2007)

Site of treatment	Frequency	Percent
Public hospitals	614	32.38
Teaching hospitals	348	18.35
KHCC	444	23.42
Private hospitals	319	16.82
Others	171	9.02
Total	**1896**	**100**

Table 15 describes the percent distribution of treatment sites (public, teaching, KHCC, private and other hospitals) and the sample characteristics in terms of their socio-demographic (age, sex, place of residence), clinical characteristics (extent of disease, topography, grade and morphology), and treatment modalities.

Table 15: Percent distribution of treatment sites by selected variables, Jordan (2003-2007)

Type of Hospital / Variable	Public hospitals No. (percent)	Teaching hospitals No. (percent)	KHCC No. (percent)	Private hospitals No. (percent)	Others No. (percent)
Sex					
Male	323(52.6)	214(61.5)	248(55.9)	164(51.4)	104(60.8)
Female	291(47.4)	134(38.5)	196(44.1)	155(48.6)	67(39.2)
Age					
< 65y	413(67.3)	210(60.3)	333(75.0)	192(60.2)	99(57.9)
>= 65 y	201(32.7)	138(39.7)	111(25.0)	127(39.8)	72(42.1)
Place of residence					
Middle	455(74.4)	162(46.6)	385(86.7)	297(93.9)	131(78.4)
North	130(21.2)	177(50.9)	50(11.3)	9(2.9)	24(14.4)
South	27(4.4)	9(2.6)	9(2.0)	10(3.2)	12(7.2)
Extent of disease					
Localized	63(10.2)	27 (7.8)	43 (9.7)	62(19.4)	17(9.9)
Regional	388 (63.1)	223(64.1)	267(60.1)	159(49.8)	81(47.4)
Distant metastasis	133(21.7)	91(26.2)	116(26.1)	60(18.8)	32(18.7)
Topography					
Colon	353(57.5)	252(72.4)	238(53.6)	234(73.4)	127(74.3)
Rectum	261(42.5)	96(27.6)	206(46.4)	85(26.6)	44(25.7)
Grade					
Well	50(8.1)	25(7.2)	15(3.4)	23(7.2)	12(7.0)
Moderate	406(66.1)	204(58.6)	333(75.0)	167(52.4)	79(46.2)
Poor/ anaplastic	81(13.2)	72(20.7)	49(11.1)	51(16.0)	29(16.9)
Morphology					
Adenocarcinoma	511(83.4)	287(82.5)	389(87.8)	270(84.6)	141(82.5)
Mucinous	52(8.5)	29(8.3)	35(7.9)	18(5.6)	14(8.2)
Carcinoma, NOS	24(3.9)	24(6.9)	5(1.1)	16(5.0)	13(7.6)
Others	25(4.1)	3(0.86)	13(2.9)	12(3.8)	2(1.2)
Surgery					
Yes	516(84.0)	289(83.1)	363(81.8)	224(70.2)	84(49.1)
No	27(4.4)	17(4.9)	35(7.9)	6(1.9)	4(2.3)
Chemotherapy					
Yes	405(65.9)	148(42.5)	280(63.1)	69(21.63)	33(19.3)
No	86(14.0)	47(13.5)	75(16.9)	53(16.61)	16(9.4)
Radiotherapy					
Yes	182(29.6)	18(5.2)	115(25.9)	13(4.1)	6(3.5)
No	432(70.4)	330(94.8)	329(74.1)	306(95.9)	165(96.4)
Type of surgery					
Elective	394(75.9)	231(79.9)	335(91.8)	178(80.9)	73(90.1)
Emergency	125(24.1)	58(20.1)	30(8.2)	44(19.8)	8(9.9)

Among all four treatment sites, over half of the patients were men, and almost two third of the sample were aged less than 65 years. Less than ten percent of the patients lived in the south compared to three-quarters living in the central region of Jordan for public, KHCC and private treatment sites. However, fifty percent of the patients receiving treatment at

teaching hospitals lived in the northern part of the country. For all sites, at least fifty percent of the patients had regional metastasis compared to one quarter or less who had CRC distant metastasis at diagnosis. Across all sites, more than half of the patients had colon cancer, with the same percent being classified as moderate grade. Adenocarcinoma was the most common form of CRC for all treatment sites as it was found approximately in eighty percent of cases, followed by mucinous tumours.

More than two third of the patients at all sites underwent surgery with three quarter of them undergoing an elective type of surgery. In addition, about two thirds of patients received chemotherapy at public or HKCC hospitals, compared to forty percent at teaching hospitals; and reaching only four percent at the private hospitals. Receiving radiotherapy was most commonly provided at public hospitals (30 percent) and KHCC (26 percent) with less than five percent at all other treatment sites.

4.7 Summary

This chapter described the sample's socio-demographic, clinical and treatment characteristics of the sample. Males (55.5 percent), age group 60 years and above (50.4 percent) and central residency (75.4 percent) were prevailing socio-demographic characteristics of the total 1,896 study participants. With more cases being diagnosed in both 2006 and 2007, the event of death was accounted for by 40.3 percent of all cases with more deaths recorded among males (57.9 percent) and those over 60 years of age (54.2 percent).

Topographic data indicated that 63.5 percent (1,204 patients) had colon cancer and 36.5 percent (692 cases) had rectum cancer. Examination of the clinical characteristics of the sample indicated that more than half of the patients (58.9 percent) had regional metastasis, 22.8 percent had distant metastasis, and 11.2 percent had localized CRC at diagnosis. While adenocarcinoma was most commonly found tumours (84.4 percent), mucinous tumours were found in 7.8 percent of the patients. In terms of grade, only 6.6 percent was classified as well differentiated, while more than half (62.7 percent) were classified as moderate and 14.9 percent as poor.

There were significant differences in the percentage distribution of age categories between rectum and colon cancer patients, where the percentages of colon cancer patients for the older age groups (60-74, and ≥75) were higher (42.6 percent and 11.7 percent respectively) than those for rectum cancer patients (36.3 percent and 7.4 percent respectively). In addition, the percentages of rectum cancer patients with moderate and poor/anaplastic types of cancer were higher than in colon cancer patients.

With the majority of CRC patients (77.9 percent) undergoing surgery, these surgeries were found to be mostly elective (82.0 percent). Curative treatment was found to be a more common form of treatment for CRC patients (76.5 percent) than palliative (23.5 percent). Elective surgery was significantly higher among rectum cancer (87.7 percent) that colon cancer patients (78.7 percent). The most common surgical procedures were left hemicolectomy (22.4 percent) and right hemicolectomy (21.2 percent) followed by lower interior resection (LAR) (17.6 percent) and abdomino-perineal resection (APR) (13.2 percent). Of those undergoing surgery, 4.8 percent has died within 30-days of resection. Moreover, patients aged ≤ 65 years had significantly lower 30 days postoperative mortality

(2.9 percent) than those over 65 years (7.1 percent). Thirty days postoperative mortality was significantly higher among colon cancer patients (5.3 percent), patients with more advanced tumours and those who underwent emergency operations.

Rectum cancer patients were more commonly treated with chemotherapy (60.7 percent) than colon cancer patients (42.8 percent). Conversely, rectum cancer patients were found to receive radiotherapy treatment (42.2 percent) more than colon cancer patients (3.5percent).

In examining the percentage distribution of treatment site, almost one third (32.4 percent) were treated at public hospital facilities, 23.4 percent at KHCC, 18.4 percent at teaching hospitals; and 16.8 percent at private health facilities. Among all four treatment sites, over half of the patients were men, and almost two third were aged less than 65 years. Less than ten percent of the patients lived in the south compared to three-quarters living in the central region of Jordan for those treated in the public, KHCC and private treatment sites. Across all sites, more than half of the patients had colon cancer, with the same percent being classified as moderate grade.

CHAPTER 5 – INCIDENCE AND SURVIVAL PATTERNS OF COLORECTAL CANCER

5.1 Introduction

This chapter aims at describing the incidence of CRC in the Jordanian population over the study period, and to explore age, sex and temporal patterns to allow comparison with other populations. The chapter also looks at the observed and relative survival estimates as well as survival probability using a variety of approaches and timeframes. In addition, this chapter examines the relationship between patients' socio-demographic characteristics (i.e. sex, age, place of residency and year of diagnosis) and the observed and relative colorectal survival estimates. This chapter concludes with a summary and discussion of the main results.

5.2 Incidence of colorectal cancer by age and sex

To better understand the CRC in Jordan, the crude and age–specific incidence rates (ASIR) for each year were estimated for both males and females. The overall crude incidence rate was estimated using Jordan's total population in the period of the study corresponding to the sum of the populations for each year between 2003 and 2007. World Standardized incidence rates (ASR) were used to compare Jordan's incidence rates to other populations. Incidence rate were calculated and analysis undertaken for those patients aged 15-74 who were diagnosed with a primary CRC (C18-C20.9) cancer during the study period (2003-2007). This resulted in a population of interest of 1,704 CRC patients when doing the incidence rates.

5.2.1 Crude and adjusted colorectal incidence rates by sex

Within the group of interest (1,704), 924 of the patients were males (54.2 percent) and 780 patients were females (45.8 percent). Overall, 1063 (62.4 percent) of cases were colon cancer and 641 (37.6 percent) were rectum cancer. Among male cases, 562 (60.8 percent) were registered as colon cancer and 362 (39.2 percent) as rectum cancer; while among females, 501 (64.2 percent) of cases were registered as colon cancer and 279 (35.8 percent) as rectum cancer, [$\chi 2$=2.1, P=0.148].

The study reported an annual average of 341 newly diagnosed CRC patients aged from 15 years through 74 years of age. During the 5-year study period, the overall crude colorectal cancer incidence rate for males was 5.6 per 100,000 population and 5.1 per 100,000 population in females. For colon cancer, the crude incidence rate was 5.4 per 100,000 population in males and 4.1 per 100,000 population in females. Crude incidence rate for rectum cancer was 3.0 per 100,000 population for males and 2.4 per 100,000 population for females.

The overall colorectal ASR was 15.5 per 100,000 male population and 12.5 per 100,000 female populations with a male/female ratio of 1.2:1. While ASR for colon cancer was 11.1 and 8.4 per 100,000 for males and females respectively, for rectum cancer, the ASR was 6.1 per 100,000 males and 4.9 per 100,000 females respectively (Table 16).

Table 16: Number of new cases, Crude Incidence Rates, and Age-standardized incidence rates per 100,000 population of CRC among Jordanian population, 2003-2007

Year	Cancer	Male			Female		
		No. Cases	Crude Incidence	*ASR	No. Cases	Crude Incidence	*ASR
2003	Colon	120	5.1	8.3	96	4.1	6.6
	Rectum	63	2.9	4.8	43	2.2	3.5
2004	Colon	110	4.7	9.3	87	4.2	7.6
	Rectum	70	2.6	4.4	60	2.2	3.6
2005	Colon	101	4.5	8.9	90	4.6	8.0
	Rectum	72	2.9	5.3	52	2.3	4.0
2006	Colon	142	5.5	11.0	98	4.7	8.4
	Rectum	87	3.1	5.7	58	2.5	4.4
2007	Colon	170	6.4	13.0	130	5.8	11.4
	rectum	98	3.5	6.7	66	2.8	5.0

*ASR: World Health Organization Age-standardized incidence

5.2.2 Colorectal incidence rates by age and sex

To allow comparisons with different countries, CRC incidence rates were aggregated into 5-year age groups (aged 15-74 years). The age-standardized incidence rates and crude incidence rates were calculated and examined by sex, age and temporal patterns.

The age specific incidence rates were found to increase with age (Figure 9). Rates were slightly higher in females than in males, but this difference was limited to those 55 years or younger. In later life, rates in men became more predominant compared to those in females. All in all, the results showed a high percentage (13.8 percent) of CRC among the young age groups (i.e. less than 40 years of age). Also, almost one third of colorectal cancers (31.0 percent) occurred among patients less than 50 years of age; whereas more than half (60.3 percent) of the cases were less than 60 years of age.

Figure 9: Age-specific incidence rates of colorectal cancers by sex, Jordan (2003-2007)
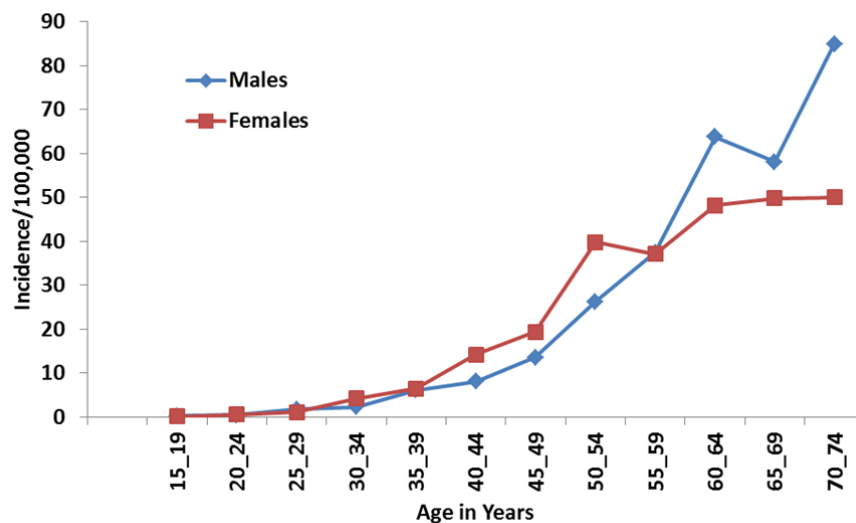
The study examined colon and rectum cancers as grouped in Volume IX of CI5, to show the different incidence rates of CRC among the different countries in the Eastern Mediterranean and other regions. The CRC incidence data in CI5 monograph are categorized according to ICD-10 site codes (C18-C20-9), which include cancers of the colon and rectum. In Jordan, colon and rectum cancers in both sexes are among the highest rates in the region, while it ranked low when compared to European countries (Table 17).

Table 17: Age-Standardized Rates (ASR) per 100,000 population of CRC in different countries in the Eastern Mediterranean and other Regions

Country	Colon Cancer (C18)		Rectum Cancer (C19-C20)		Colorectal Cancer (C18-C20)	
	Male	Female	Male	Female	Male	Female
Jordan	11.1	8.4	5.4	4.1	15.5	12.5
Algeria, Setif	4.9	5.2	3.2	3.5	8.1	8.7
Egypt, Gharbiah	3.6	3.4	2.1	1.9	5.6	5.3
Tunisia, North	6.3	5.5	4.2	3.7	10.5	9.2
Libya, Benghazi	8.8	9	5	3.3	13.7	12.3
Bahrain: Bahraini	8.8	7.8	5.7	3.2	14.5	11
Qatar: Qatari	13.6	9.1	6.6	7.5	20.2	16.7
Saudi Arabia	6.9	6.3	5.3	4	12.3	10.3
Kuwait: Kuwaitis	11.2	9.2	5	4.5	16.2	13.7
Turkey, Izmir	12.5	7.9	8.8	4.8	21.3	12.7
Israel: Non-Jews	17.1	16.5	10.9	7.1	28	23.6
India, Mumbai	3.4	2.3	2.9	2	6.3	4.4
Korea	21.2	12.4	19.5	10.2	40.6	22.7
China, Beijing city	10.5	9	8.9	6.5	19.4	15.5
Brazil, Goiania	18.9	15.7	11.9	10.6	30.8	26.3
Ecuador, Quito	7.3	7.8	4	2.9	11.2	10.6
Canada	25.8	19.6	15.9	8.3	41.7	27.9
USA, Virginia	23.6	18.8	10.7	6.7	34.3	25.5
Austria	23.3	14.3	15.3	7.6	38.6	21.9
Czech Republic	31.1	17.2	25.9	11.3	57	28.5
France, Bas-Rhin	25.4	15.2	17.1	8.4	42.5	23.6
Italy, Latina	22.1	14.8	13	7.6	35.1	22.4
Ireland	25.8	18.4	17.5	8.8	43.3	27.3
UK, Scotland	24.9	17.6	16	8.2	40.9	25.8
South Australia	29.2	22.3	18.3	10.1	47.4	32.4
New Zealand	27.6	25.7	18.2	10.4	45.7	36

* Source: Cancer Incidence in Five Continents, Vol. X (electronic version) Lyon, IARC. http://ci5.iarc.fr last accessed on 2/2/2014.

Table 18 includes the ASR of CRC in Jordan and Nordic countries. Differences between age specific rates of patients in Nordic countries and Jordanian patients were observed in Jordanian males and females < 65. These differences were more pronounced for females compared to females in Nordic countries in the same age group. Age specific rates among

patients in Nordic countries became much larger and more pronounced for individuals aged 65 years or older compared to Jordanian patients.

Table 18: A comparison between the colorectal cancer age-specific rates per 100,000 by sex in Jordan and Nordic countries*

Age group	Males		Females	
	Jordan	Nordic Countries	Jordan	Nordic Countries
15_19	0.2	0.3	0.1	0.6
20_24	0.4	1.0	0.5	1.2
25_29	1.7	1.3	1.0	1.6
30_34	2.2	3.6	4.2	3.3
35_39	6.1	6.3	6.4	6.2
40_44	8.0	10.8	14.2	12.5
45_49	13.5	22.5	19.3	23.4
50_54	26.2	45.0	39.8	42.7
55_59	37.4	77.5	37.1	65.9
60_64	63.7	137.0	48.1	106.8
65_69	58.0	217.7	49.8	156.5
70_74	84.9	313.3	50.0	213.6

*Source: Engholm G, Ferlay J, Christensen N, Johannesen TB, Khan S., Køtlum JE, Milter MC, Ólafsdóttir E, Pukkala E, Storm HH. NORDCAN: Cancer Incidence, Mortality, Prevalence and Survival in the Nordic Countries, Version 6.0 (04.12.2013). Association of the Nordic Cancer Registries. Danish Cancer Society. Available from http://www.ancr.nu, accessed on 24/03/2014.

5.2.3 Summary and Discussion

During the 5-year study period, the overall crude colorectal cancer incidence rate for males was 5.6 per 100,000 population and 5.1 per 100,000 population in females. This identifies Jordan as a low-risk country for CRC compared to developed countries. However, it ranks high when compared to neighboring countries for both males and females. In line with other studies, this study revealed that the incidence of CRC in the Jordanian population to be low compared to developed countries (7;13;58;219). However, this low incidence rate is relatively higher than some countries in the region (58;65;220;221). Results from this study also revealed, that the CRC incidence rate in Jordan was higher than most Eastern

Mediterranean countries (including Algeria, Egypt, Bahrain, Tunisia, and Saudi Arabia), and almost similar to rates that were reported in, Qatar, Libya and Kuwait. At the same time, the study found colorectal ASR to be lower than those for European countries (including UK, Scotland, France, Australia, and New Zealand).

The difference in rates between developing and developed countries can be partially attributed to life-style and dietary habits (222;223). Genetics may also play a role in explaining the differences in incidence rates between developed and developing countries (224;225). In addition, this study found no significant difference between males and females CRC patients. These results are consistent with other international studies (7;58).

The study reported a high percentage of CRC patients (13.8percent) among the younger age groups (<40 year). This concurs with other studies from the region, which reported that 15-35 percent of colorectal cases in the Eastern Mediterranean countries occur among young people (226;227). Alternatively, in the developed countries, only 2-8 percent of the colorectal cancers occur in young people (228;229). The high proportions of CRC cases seen in Jordan among the young population, as other countries from the region, might be due to the young age-structure where 80 percent of the Jordanian population are below 50 years of age (1;22) . On the other hand, comparison of age specific rates of CRC patients in Nordic countries (as an example from the European countries) with those of Jordanian individuals, showed a higher rates in females Jordanian population who are 54 years of age or younger. This difference could be attributed to CRC aetiology in the Eastern Mediterranean Region, which may be different from other countries with genetic factors playing a role in the development of CRC in young population (230).

Another explanation that could explain this difference is the relatively low rates of CRC among elderly age groups in Jordan. Moreover, this could also be due to lower recording of cases among the elderly. Being 'affected at an early age' is a significant group characteristic and is an important result that should be taken into account when implementing CRC prevention and control strategies. Therefore, further analytical studies are needed to better explore these differences, if they truly exist.

According to Jordanian Ministry of Health, the burden of colorectal cancer cases is growing; the latest JCR report (2009) has shown the ASR for colorectal cancers among males to be 18.2 and for females 16.5 per 100,000 (51). In summary, the increasing in life expectancy together with the lifestyle changes in Jordan lead to hypothesize that the burden of CRC will continue escalating in the forthcoming years.

5.3 Observed and relative survival estimates

Kaplan-Meier survival analysis was used to determine the observed survival probability of CRC patients. Kaplan-Meier survival analysis allows for measuring the cumulative proportion of patients surviving over a period of time and the length of time people remain living after being diagnosed with CRC. Kaplan-Meier was used in a univariate analysis to identify the potentially important prognostic variables-effect of different predictors on the survival rate (e.g. age at diagnosis, sex, stage, site, grade and type of treatment). The logrank test was used to compare estimates of the hazard functions of the two groups at each observed event time. The logrank test is constructed by computing the observed and expected number of events in one of the groups at each observed event time and then adding these to obtain an overall summary across all time points where there is an event.

Using the Kaplan-Meier technique and logrank tests, the observed 5-year survival probability rates were examined for CRC by site, year of diagnosis and socio-demographics characteristics (e.g. sex, age, place of residence) for Jordanian patients diagnosed with CRC between 2003 and 2007. Expected survival was estimated from the general population of Jordan, which was extracted from the National life tables of death rates by sex, single year of age and calendar year 2000 (22). Relative survival used in this study is interpreted as observed survival adjusted for other cases of background mortality (expected survival). The relative survival allows for the account of dying from causes other than the disease in question (CRC in this study).

Tables A.1, A.2 and A.3 in Appendix A, show the observed and relative survival estimates for colorectal, colon and rectum cancers, respectively; as well as the overall survival estimates during 2003 through 2007 for male and female patients. To better understand the survival pattern, Year 1 was divided into 10 intervals; Year 2 and Year 3 into two intervals; Year 4 and Year 5 into one interval each.

Kaplan-Meier survival analysis by cancer site and selected socio-demographic variables (i.e. sex, age, region or residence and year of diagnosis) are seen in Figures 12a, 12b, 12c, 13a, 13b, 13c, 14a, 14b, 14c, 15a, 15b and 15c. The effect of these four socio-demographic variables on colorectal cancer, colon cancer and rectum cancer are presented in the following sections.

5.3.1 Observed and relative colorectal survival probability by cancer site

Using the Kaplan-Meier technique, the 5-year survival probabilities for CRC patients was found to be slightly higher than 50 percent (Figure 10a).

Figure 10a: Observed survival probability for 1,896 Cases of Colorectal Cancer in Jordan, (2003-2007)
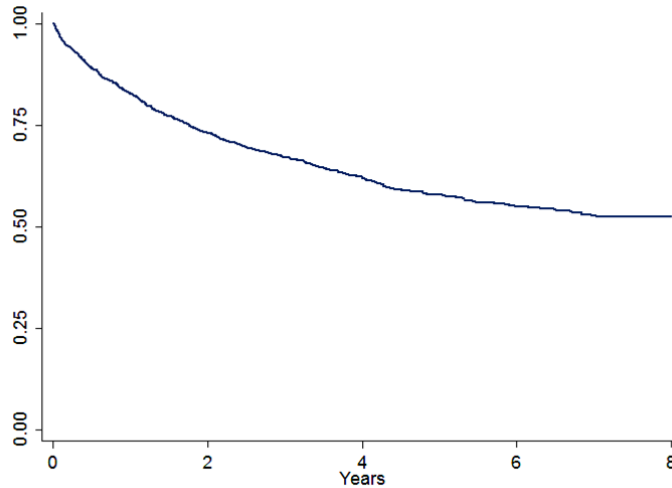
When comparing the observed survival probability for rectum cancer and colon cancer, a slightly higher probability was found for rectum cancer in the first two years of the disease. However, later on gradually the colon cancer became higher than rectum (Figure 10b). These differences did not reach significance level (Log-rank test p-value = 0.1474).

Figure 10b: Observed survival probability for 1,204 Cases of Colon Cancer and 692 Cases of Rectum Cancer in Jordan, (2003-2007)
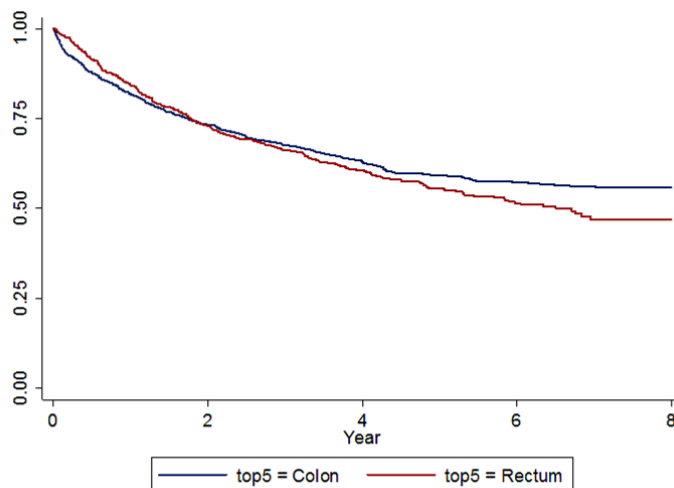
Log-rank test p-value= 0.1474

Figures 11a, 11b and 11c depict the relative survival statistics at 1-, 3- and 5 -years from diagnosis for colorectal cancer (Figure 11a) and by cancer site: colon (Figure 11b) and rectum (Figure 11c).

Figure 11a: Five-year relative survival from colorectal cancer for 1,896 Cases, Jordan
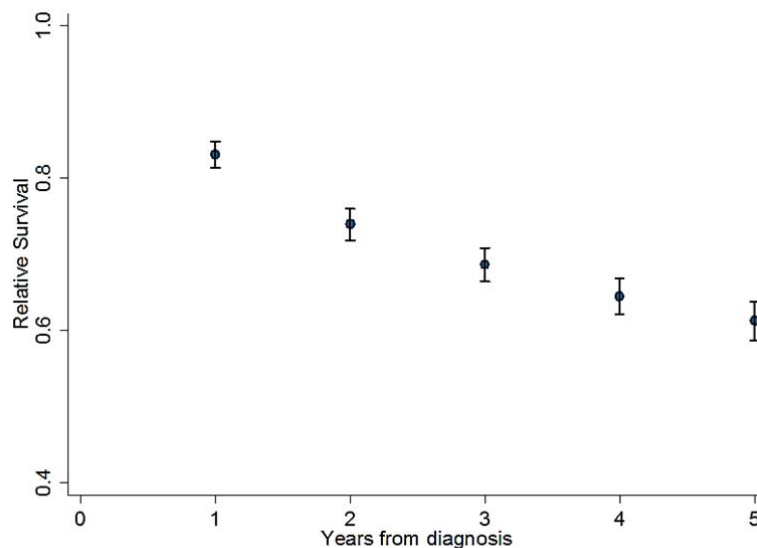
Figure 11b: Five-year relative survival from colon cancer for 1,204 Cases, Jordan
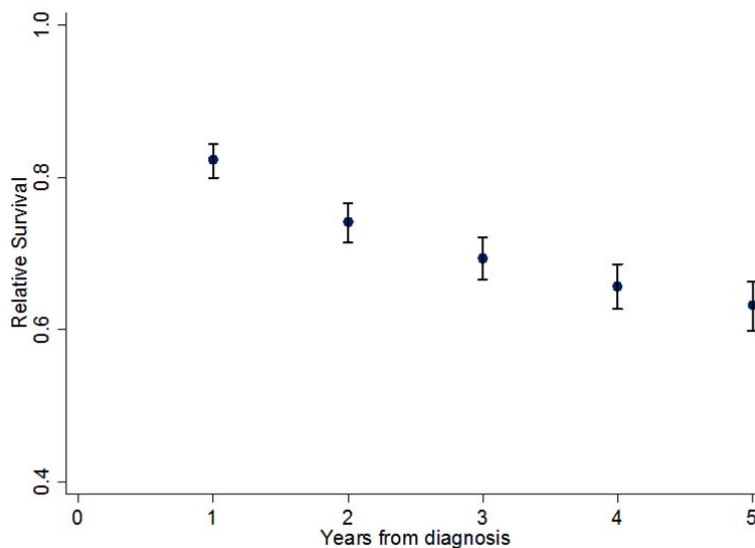
Figure 11c: Five- year relative survival from rectum cancer for 692 Cases, Jordan
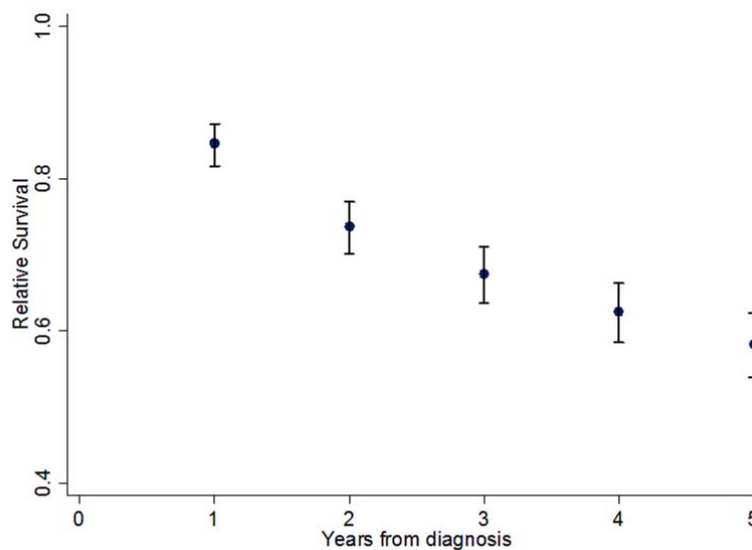
Using the Cox analyses to examine the observed survival at 1-, 3- and 5-years from diagnosis for all colorectal cancer, and by cancer site: colon or rectum, data demonstrated no temporal trend toward improving or worsening survival over the study period. The observed survival rates for the overall cases of colorectal cancer were 82.7 percent at year 1, 67.2 percent at year 3 and 57.7 percent at year 5 of diagnosis. Corresponding relative

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survival rates were 83.1 percent at year 1, 68.6 percent at year 3 and 61.3 percent at year 5

of diagnosis (shown in Table 19).

Table 19: Observed and relative cancer survival estimates by type of colorectal cancer, Jordan (2003-2007)

Variable	Observed survival (percent)			Relative survival (percent)		
	1 year	3 years	5 years	1 year	3 years	5 years
Colorectal	82.7	67.2	57.7	83.1	68.6	61.3
Colon	81.9	67.8	59.1	82.3	69.4	63.2
Rectum	84.3	66.3	55.4	84.7	67.5	58.3

Patients with rectum cancer showed slightly better observed and relative survival rates at

year 1 of diagnosis than colon cancer, and vice versa at 3- and 5-years of diagnosis. The

observed survival rates for colon and rectum cancers at year 1 of diagnosis were 81.9

percent and 84.3 percent, respectively, the corresponding relative survival rates were 82.3

percent and 84.7 percent, respectively. At 3 years of diagnosis, the observed colon and

rectum cancer survival rates were 67.8 percent and 66.3 percent, respectively, while at 5

years of diagnosis these rates were 59.1 percent and 58.3 percent, respectively. The

corresponding relative survival rates at 3 years of diagnosis were 69.4 percent and 67.5

percent, while at 5 years of diagnosis they were 63.2 percent and 58.3 percent, for colon

and rectum cancer respectively (Table 19).

5.3.2 Observed and relative colorectal survival probability by sex

Figures 12a, 12b and 12c show that males and females have almost similar 5-year survival

probability for the first two years, which gradually change to slightly higher survival rates

among females towards the end of the study period in colon cancer and vice versa in

rectum cancer. This observed pattern was found insignificant in colorectal cancer (log-rank test p-value=0.1698), colon cancer (Log-rank test p-value=0.0919) and rectum cancer (Log-rank test p-value=0.8992).

Figure 12a: Observed survival probability by sex for 1,896 cases of colorectal cancer in Jordan
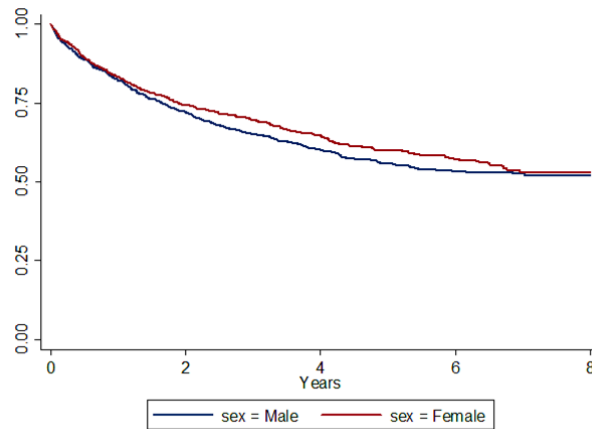
Log-rank test p-value = 0.1698

Figure 12b: Observed survival probability by sex for 1,204cases of colon cancer in Jordan
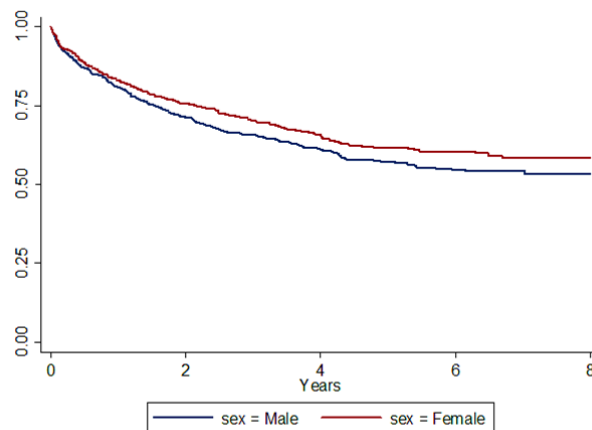
Log-rank test p-value = 0.0919
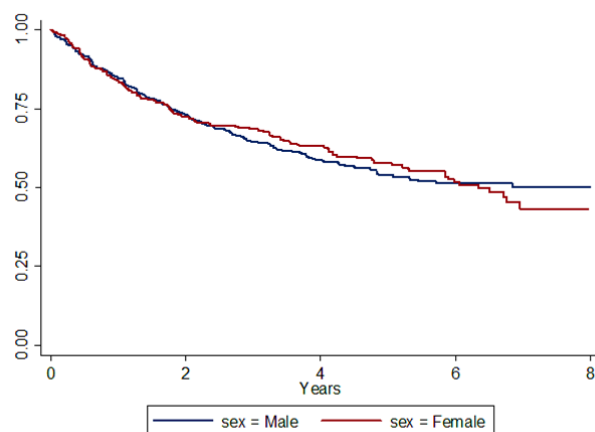
Log-rank test p-value = 0.8992

No substantial differences were observed in colon and rectum cancer survival estimates in the first year intervals for both sexes. Although observed and relative survival estimates were higher for females in the three scenarios (i.e. colorectal, colon and rectum), these differences were not significant when examined by sex.

Observed and relative survival rates for males and females by site of cancer displayed in Table 20, show that females had a slightly better observed survival rates for overall CRC at year 1 of diagnosis (83.4 percent) than males (82.2 percent). Similarly, the observed survival rates for CRC at year 3 of diagnosis was higher among females (69.7 percent) than among males (65.2 percent); with a similar higher rate at year 5 of diagnosis among females (59.9 percent) than males (55.9 percent).

Reported relative survival rates were also better in females; for year 1 of diagnosis: 83.6 percent and 82.7 percent, for females and males respectively; for year 3 of diagnosis: 70.7 percent and 67.1 percent, for females and males respectively; and for year 5 of diagnosis: 62.4 percent and 60.5 percent, for females and males respectively. The same pattern was

observed for colon cancer where observed and relative survival rates were higher in females at year 1, year 3 and year 5 of diagnosis (OS 83.1 percent, 70 percent and 61.1 percent), (RS 83.4 percent, 71.4 percent and 64.2 percent) compared to males (OS 80.1 percent, 65.7 percent and 57.1 percent), (RS 81.4 percent, 67.7 percent, 62.3 percent), as illustrated in Table 20.

Table 20: Observed and relative cancer survival estimates by type of colorectal cancer and sex, Jordan (2003-2007)

Variable	Observed survival (percent)			Relative survival (percent)		
	1 year	3 years	5 years	1 year	3 years	5 years
Colorectal						
Male	82.2	65.2	55.9	82.7	67.1	60.5
Female	83.4	69.7	59.9	83.6	70.7	62.4
Colon						
Male	80.1	65.7	57.1	81.4	67.7	62.3
Female	83.1	70.0	61.1	83.4	71.4	64.2
Rectum						
Male	84.6	64.5	54.1	84.9	66.0	57.6
Female	83.9	68.7	57.3	84.1	69.5	59.2

Alternatively, rectum cancer male patients have shown slightly higher observed and relative survival rates at year 1 of diagnosis (OS 84.6 percent, RS 84.9 percent) compared to females (OS 83.9 percent, RS 84.1 percent). However, rectum cancer female patients displayed higher observed and relative survival rate at year 3 (OS 68.7 percent, RS 69.5 percent) and year 5 (OS 57.3 percent, RS 59.2 percent) of diagnosis, compared to males (OS 64.5 percent, RS 66 percent), and (OS 54.1 percent, RS 57.6 percent) (Table 20).

5.3.3 Observed colorectal survival probability by age

The observed survival rates noticeably declined for the age group of 75 years of age or older (Figures 13a, 13b and 13c) for overall colorectal, colon and rectum cancer scenarios. The other age groups were nearly comparable. The observed survival rate mostly decreased through all age groups. Early deaths were observed for patients above 75 years of age during the first two years. The survival rate for patients among the age group of 15 through 44 years old and the age group of 60 through 74 years old were quite similar during the first three years, after which slightly higher rates were estimated for those aged 15 through 44 years old. Patients aged 45 through 59 years old had the highest survival estimates among all studied age groups.

Figure 13a: Observed survival probability by age for 1,896 cases of colorectal cancer in Jordan
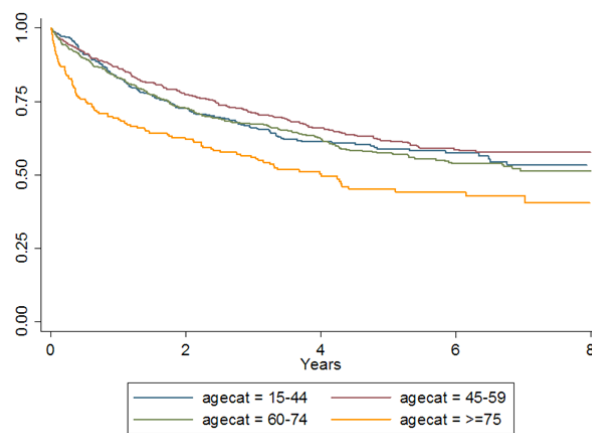
Log-rank test p-value < 0.0001

Figure 13b: Observed survival probability by age for 1,204 cases of colon cancer in Jordan
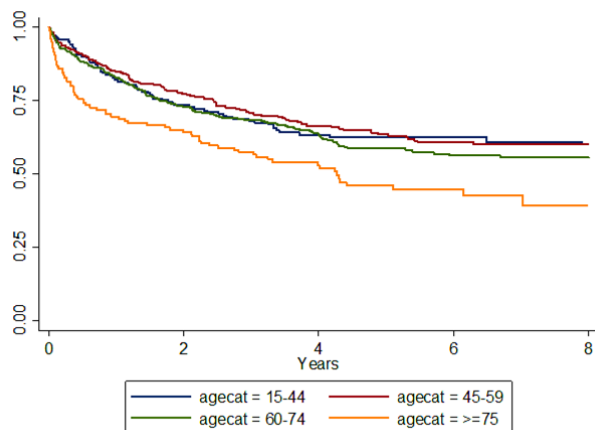
Log-rank test p-value = 0.0008

Figure 13c: Observed survival probability by age for 692 cases of rectum cancer in Jordan
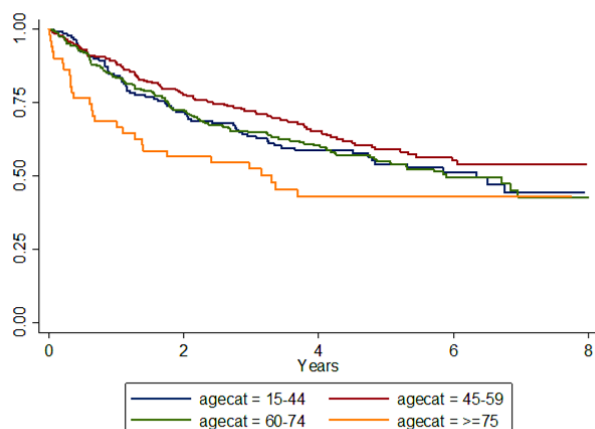
Log-rank test p-value = 0.0400

Examination of the observed and relative survival rates showed a noticeable decline in the age group of 75 years and older (Table 21). In general, younger age groups between 15 and 44 years of age had lower observed and relative survival rates at all years of diagnosis for colon and rectum cancer compared to patients' age groups 45 through 59. The 5-year observed and relative survival rates of colorectal cancer were highest in age group 45-59 years and lowest the 75 years of age and older group.

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The 5-year observed and relative survival rates for colon cancer were approximately similar in age groups 15 through 44 years (OS 58.9 percent, RS 59.4 percent) and 60 through 74 years (OS 57.1 percent, RS 61.5 percent). The poorest survival rates (OS 45.4 percent, RS 59.1 percent) were for patients 75 years of age and older.

In cases of rectum cancer, the highest 5-year observed and relative survival rates were for the age group 45 through 59 years (58.9 percent and 60.2 percent, respectively), while the poorest observed survival (42.9 percent) was for patients 75 years of age and older. However, the poorest relative survival rate (55 percent) was for patients aged 15-44.

Table 21: Observed and relative cancer survival estimates by type of colorectal cancer and age, Jordan (2003-2007)

Variable	Observed survival (percent)			Relative survival (percent)		
	1 year	3 years	5 years	1 year	3 years	5 years
Colorectal						
15-44	83.2	66.1	58.9	83.2	66.4	59.4
45-59	86.4	71.2	61.8	86.6	71.8	63.2
60-74	83.1	67.3	57.1	83.5	69.1	61.5
>=75	69.1	55.8	44.7	70.4	61.1	58.8
Colon						
15-44	83.2	66.2	58.9	82. 3	66.4	60.1
45-59	86.4	71.3	65.1	86.6	71.8	63.2
60-74	83.1	67.4	57.1	83.5	69.1	61.5
>=75	69.3	57.2	45.4	70.7	62.6	59.1
Rectum						
15-44	84.4	63.6	54.6	85.5	63.9	55.0
45-59	88.4	72.0	58.9	88.6	72.6	60.2
60-74	83.6	65.1	55.1	84.0	66.7	59.1
>=75	68.3	52.2	42.9	69.5	57.1	55.4

5.3.4 Observed colorectal survival probability by place of residence

This study estimated the survival rates for colorectal cancer patients living in three different areas of Jordan: middle, north and south. Figures 14a, 14b and 14c show significant differences of survival rates in relation to place of residency. While the poorest survival was in the south, the highest survival estimates were obtained for patients living in the middle part of the country followed by the north, (Log-rank test p-value= 0.0001).

Figure 14a: Observed survival probability by residency for 1,896 cases of colorectal cancer in Jordan
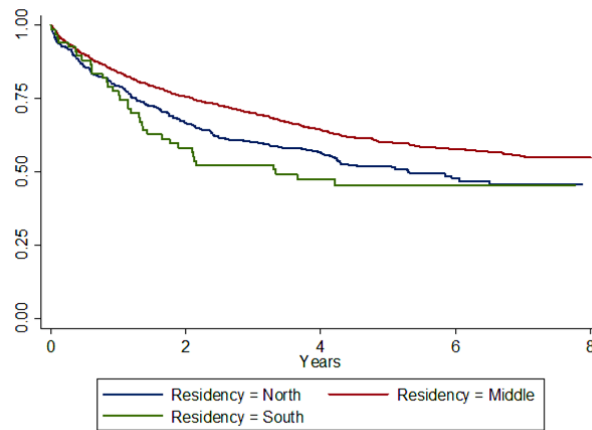
Log-rank test p-value = 0.0001

Figure 14b: Observed survival probability by residency for 1,204 cases of colon cancer in Jordan
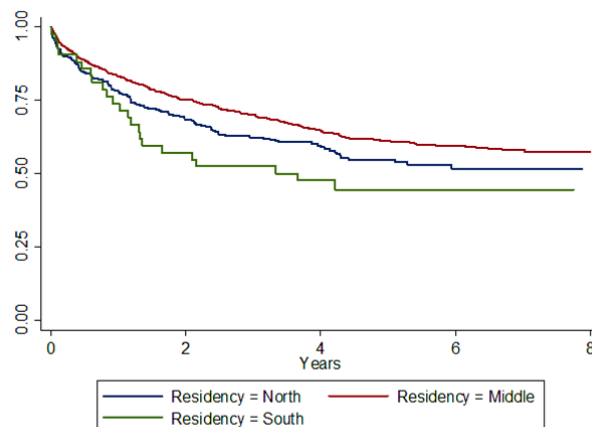
Log-rank test p-value = 0.0138

Figure 14c: Observed survival probability by Residency for 692 Cases of Rectum Cancer in Jordan
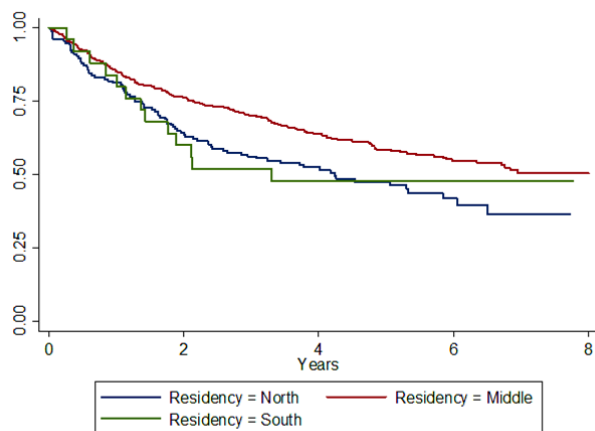
Log-rank test p-value = 0.0045

Table 22 displays the observed and relative survival rates for colorectal, colon and rectum cancers by place of residency. The 5-year observed survival rates of colorectal, colon and rectum cancers for patients living in the central part of Jordan were 60.1 percent, 61.0 percent and 58.5 percent, respectively. Their corresponding relative survival rates were 63.9 percent, 65.5 percent and 61.6 percent, respectively. The 5-year observed survival rates for colorectal, colon and rectum cancers for patients living in the north of Jordan were 51.5 percent, 54.1 percent and 47.3 percent, respectively. Their corresponding relative survival rates were 54.4 percent, 57.7 percent and 49.4 percent, respectively. The 5-year observed survival rates of colorectal, colon and rectum cancers for patients living in the south of the country were 44.7 percent, 44.1 percent and 46.8 percent, respectively. Their corresponding relative survival rates were 46.6 percent, 44.2 percent and 48.3 percent, respectively.

Table 22: Observed and relative cancer survival estimates by type of colorectal cancer and place of residence, Jordan (2003-2007)

Variable	Observed survival (percent)			Relative survival (percent)		
	1 year	3 years	5 years	1 year	3 years	5 years
Colorectal						
North	79.4	59.9	51.5	79.8	61.2	54.4
Middle	83.8	70.0	60.1	84.3	71.5	63.9
South	77.6	52.2	44.7	77.9	53.0	46.6
Colon						
North	78.2	62.4	54.1	78.6	63.8	57.7
Middle	83.1	69.9	61.0	83.5	71.6	65.5
South	73.8	52.4	44.1	74.2	53.3	44.2
Rectum						
North	81.3	56.2	47.3	81.7	57.1	49.4
Middle	85.3	70.1	58.5	85.6	71.5	61.6
South	84.0	52.0	46.8	84.3	52.6	48.3

5.3.5 Observed colorectal survival probability by year of diagnosis

Figures 15a, 15b and 15c show colorectal survival rates in relation to the year of diagnosis from 2003 through 2007. The figures show no temporal trend toward improving or worsening survival over the study period. However, results show that the best 5-year survival estimate was found for patients diagnosed in 2004, for all patients and separately for both colon and rectum. Alternatively, the poorest result was for patients diagnosed in 2006, also for combined and separately for both colon and rectum.

Figure 15a: Observed survival probability by year of diagnosis for 1,896 colorectal cancer cases in Jordan
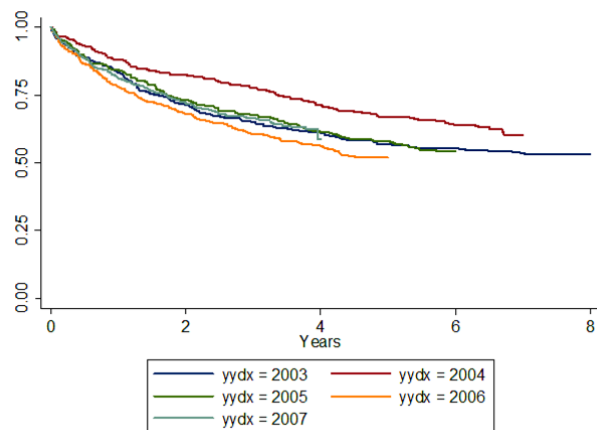
Log-rank test p-value = 0.0012

Figure 15b: Observed survival probability by year of diagnosis for 1,204 cases of colon cancer in Jordan
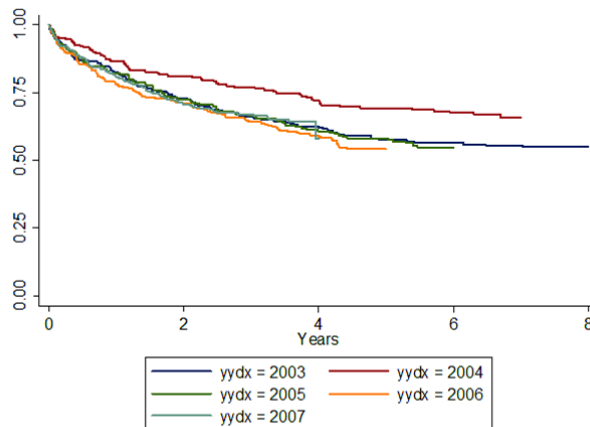
Log-rank test p-value = 0.0270

Figure 15c: Observed survival probability by year of diagnosis for 692 cases of rectum cancer in Jordan
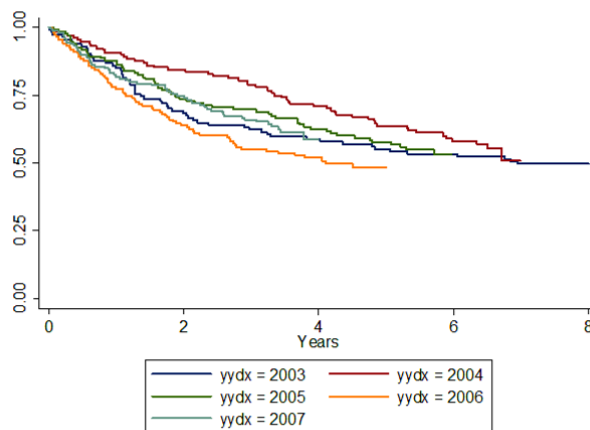
Log-rank test p-value = 0.0506

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Overall the observed and relative survival estimates were consistently highest during Year 1 and lowest during Year 5 (Tables A.1, A.2 and A.3 in Appendix A). Table 23 shows the observed and relative survival rates for colorectal, colon and rectum cancers by year of diagnosis. For colorectal cancer, the 5-year observed and relative survival rates ranged from 56.7 percent and 60.7 percent, respectively, for patients diagnosed in 2003, to 61.7 percent, and 64.3 percent for patients diagnosed at 2007, respectively. The highest observed and relative colorectal survival rates (67.1 percent and 70.8 percent respectively) were reported in patients diagnosed in 2004.

Table 23: Observed and relative cancer survival estimates by type of colorectal cancer and year of diagnosis, Jordan (2003-2007)

Variable	Observed survival (percent)			Relative survival (percent)		
	1 year	3 years	5 years	1 year	3 years	5 years
Colorectal						
2003	83.3	64.9	56.7	83.7	66.4	60.7
2004	88.1	77.7	67.1	88.5	79.2	70.8
2005	84.3	61.4	57.9	84.8	69.2	61.9
2006	77.8	60.7	50.0	78.2	61.8	52.7
2007	81.3	66.5	61.7	81.7	68.2	64.3
Colon						
2003	82.9	66.7	58.1	83.4	68.3	62.1
2004	87.3	77.0	68.2	87.7	78.5	72.2
2005	82.7	66.3	57.1	83.2	67.9	61.3
2006	77.1	63.2	52.5	77.3	64.4	55.4
2007	81.3	66.7	62.9	81.7	68.4	65.8
Rectum						
2003	84.3	59.1	52.8	84.7	60.3	56.3
2004	90.7	80.1	63.7	91.1	81.3	66.7
2005	89.2	71.7	60.2	89.5	73.1	63.6
2006	80.1	53.9	43.1	80.4	54.8	45.2
2007	81.5	66.2	58.3	81.8	67.5	60.2

Colon cancer patients diagnosed in 2004 had 5-year observed survival rate of 68.2 percent and 5-year relative survival rate of 72.2 percent, whereas those diagnosed in 2007 had 5-year observed survival of 62.9 percent and 5-year relative survival of 65.8 percent. Similarly, rectum cancer patients diagnosed in 2004 had the highest 5-year observed survival of 63.7 percent and 5-year relative survival of 66.7 percent, whereas those diagnosed in 2007 had 5-year observed survival rate of 58.3 percent and 5-year relative survival of 60.2 percent. The lowest 5-year observed and relative survival rates for rectum cancer were reported among patients diagnosed in 2006 (43.1 percent and 45.2 percent respectively).

5.3.6 Observed and Relative survival (%), age standardized to the ICSS weights

Table 24 shows the survival estimates age-standardised to the ICSS weights. The overall age standardized relative survival rate for colorectal cancer at 1 year, 3 years and 5 years from diagnosis were 75.9 percent, 63.2 percent and 57.7 percent, respectively.

Table 24: Observed and Relative survival (%), age standardized to the ICSS weights for patients (aged 15–99 years) diagnosed with colon and rectum cancers during 2003-2007 and followed up to Dec 31, 2010, Jordan

Cancer site	Number	Observed survival (percent)			Relative survival (percent)		
		1 year	3 years	5 years	1 year	3 years	5 years
Colorectal	1 896	75.1	60.3	50.2	75.9	63.2	57.7
Colon	1204	74.2	60.5	50.1	75.0	63.5	57.4
Rectum	692	78.2	59.3	50.5	78.9	62.4	58.6

The age standardized observed survival rate for rectum cancer at year 1 of diagnosis was 78.2 percent compared to 74.2 percent for colon cancer. Observed survival rates for colon and rectum cancer at 3 years were close; 60.5 percent and 59.3 percent, respectively.

Similarly, the observed survival rates for colon and rectum cancer at 5 years were almost the same: 50.1 percent and 50.5 percent, respectively.

The age standardized relative survival rate for rectum cancer was higher than the colon survival rate at 1 year: 78.9 percent and 75.0 percent, respectively. Similarly, the age standardized relative survival rate for rectum cancer was also higher than the colon survival rate at 5 years of diagnosis: 58.6 percent and 57.4 percent, respectively. Alternatively, the age standardized relative survival rate for colon cancer at 3 years diagnosis was slightly higher than for rectum cancer: 63.5 percent and 62.4 percent, respectively.

5.3.7 Summary and Discussion

This section presented the observed and relative survival estimates and probabilities using a variety of approaches and timeframes. The observed and relative colorectal survival probabilities were examined in relation to site of cancer, year of diagnosis and patients' socio-demographic characteristics (i.e. sex, age, place of residency). Relative survival rates were estimated to infer cancer-specific death rates.

The study revealed that 5-year relative survival rates for colorectal, colon and rectum cancer patients to be 61.3 percent and 63.2 and 58.3 percent, respectively. Males and females had almost similar 5-year survival probability for the first two years of diagnosis, which gradually changed to slightly higher survival rates among females. In the first year after diagnosis, females had better observed survival rates for overall colorectal cancer than males (Tables in the Appendix).

As expected, the observed survival rates mostly decreased through all age groups, with a noticeable decline for the age group of 75 years and older. Both the observed and relative survival rates declined noticeably for the age group 75 years and above. While the highest survival estimates were found among patients living in the central parts of Jordan, the poorest was significantly noted in the south. No temporal trend was observed through the study period (2003-2007).

The overall observed and relative survival estimates were highest during Year 1 and lowest in Year 5, with no significant differences between colon and rectum cancer survival in the first year for both sexes. Patients with rectum cancer showed slightly better observed and relative survival rates at year 1 of diagnosis than those with colon cancer, with a reverse relationship at 3- and 5-years of diagnosis. Results also showed that survival probabilities were highest in the central part of Jordan and significantly lower in the south of the country.

Colorectal survival rate in Jordan

The relative 5-year survival rate for colorectal cancer in Jordan found in this study (61 percent) is comparable with that of other developed countries. The study also revealed that the age standardized relative survival rate for the overall cases of colorectal cancer at 5 years of diagnosis to be 58.1 percent. This rate was slightly higher for rectum cancer (59.2 percent) when compared to colon cancer (57.8 percent).

This study showed a significance variation in survival from colorectal cancer in Jordan from other developed and less developed countries (13;18;202;231-235).

The CONCORD study (1990-1994) reported that CRC 5-year RS was higher than 55 percent in Japan, France, U.S., Canada and Australia, reaching 61.1 percent for males in Japan and 61.5 percent for females in France, while it was generally reported to be lower in Algeria (22.6 percent) and Poland (male 29.6 percent). In England and Scotland, survival rates were found to be 42.3 percent and 44.6 percent, respectively for males, and 44.7 percent and 47.7 percent, respectively for females (Figure 16) (13).

Figure 16: Five year relative survival (percent), age standardized to the ICSS weight with 95 percent CI for adults (aged 15-99 years) diagnosed with colorectal cancer during the period 1990-1999
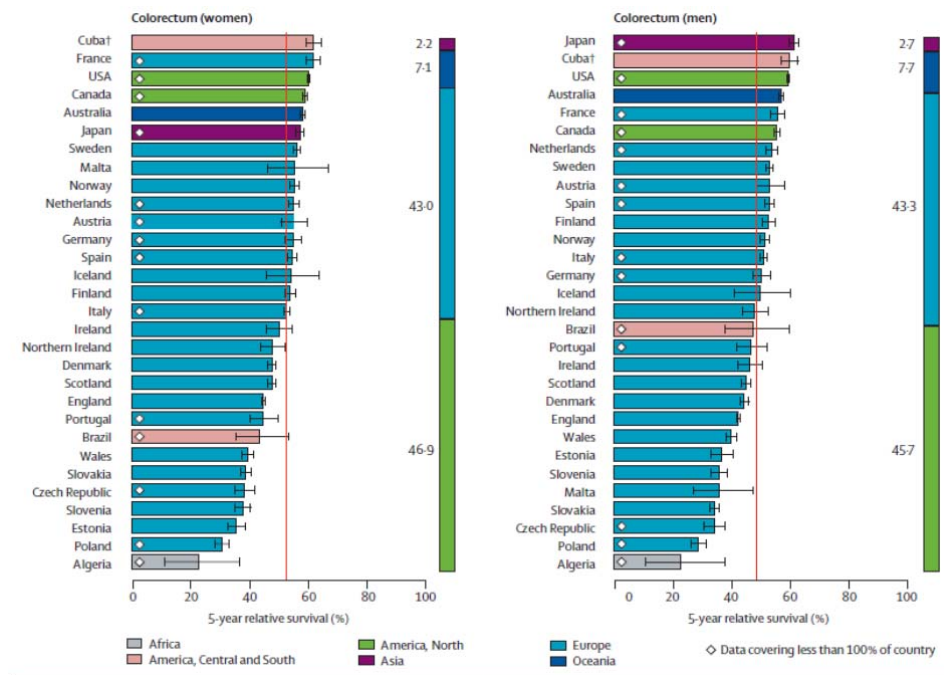
Table 25 displays information from developing countries (1990 to 2001), where the five-year RS was reported to be higher than 50 percent in Singapore, Turkey and South Korea;

and ranged from 28 percent to 44 percent in India, Thailand, Philippines and China; whereas it did not exceed 8 percent in Uganda and Gambia (14).

Table 25: 5-year age standardized (0-74 years) colorectal cancer relative survival by country according to Cancer survival in Africa, Asia, and Central America: a population-based study (1990 to 2001)

Country	5-year age standardized RS (percent)
China	44 percent (36 percent-63 percent)
India	28 percent (6 percent-31 percent)
Philippines	40 percent
Singapore	52 percent
South Korea	60 percent (57 percent-64 percent)
Thailand	35 percent (31 percent-44 percent)
Turkey	52 percent
The Gambia	4 percent
Uganda	8 percent

In conclusion, the study revealed that the age-standardized relative survival rate for the overall colorectal cancer cases at 5 years of diagnosis to be 58.1 percent. It was slightly better for rectum, 59.2 percent, compared to 57.8 percent for colon. These observations may be associated to differences in clinical characteristics or treatment, which will be examined and explored systematically in the next chapter. These results showed good survival estimates of CRC compared to developed countries as well as the most developed countries in the region and across the Asian continent. Jordan has one of the most modern health care infrastructures in the Middle East, a relatively good health expenditure, and high percent (79 percent) of health insurance coverage for the Jordanian population. In addition, some costly diseases are also insured against according to special regulations determined by the Health Insurance bylaw; this includes cancer and its side effects (46;47;236). Recently, independent reports and international organizations have begun to recognize Jordan's high level of health care services; the World Bank ranked Jordan as the number one health care services provider in the region and among the top five destinations

for medical tourism in the world, as well as being the top medical tourism destination in the Middle East and North Africa (25;26). Additionally, the King Hussein Cancer Center has also been recognized as the only specialized cancer treatment facility in the Middle East, and as one of the top cancer treatment facilities in the world (237;238).

Other possible factors could have attributed to the good CRC survival estimates in Jordan include early detection programs (102;104), accessibility to hospital care (164;239), affordability of health insurance (137;199), availability and affordability of suitable treatment and surgical techniques (136;179;240). Estimate of patient survival using the complete approach as well as other factors such as death certificate registration could have influenced survival estimates in this study. These factors are addressed in Chapter 9.

CHAPTER 6 – COLORECTAL CANCER SURVIVAL AND CLINICAL MANIFESTATION

6.1 Introduction

In the previous chapter (5) we established that there are significant demographic and other variations in the survival probability of colorectal cancer, and knowing from the evidence of the literature review that clinical factors are important determinants in survival, this chapter explores the effects of the clinical manifestations (e.g. site, grade, histopathology, stage, etc.) and treatment of colorectal cancer on survival estimates. The chapter presents and describes the results of colorectal survival analysis in relation to the clinical manifestations (grade, morphology or histopathology and extent or of disease or stage) and treatment of the tumour (surgery, chemotherapy and radiotherapy). Survival estimates by topography or site of cancer were presented and discussed in the previous chapter, and the topography variable was selected as a major variable for stratifying results. Furthermore, the chapter discusses the results obtained from running Kaplan-Meier technique and logrank tests to estimate colorectal survival probabilities in relation to the identified clinical and treatment modalities.

Using the life table method, relative survival estimates were computed to account for dying from causes other than colorectal cancer during the time of the study. These relative survival measures were used to adjust the observed survival rates for selected variables that might have an effect on the expected survival. This chapter provides a comparison of observed and relative survival proportions surviving at an end of specific time period (1-, 2- and 5-years).

Finally, the chapter discusses the results obtained from running the Cox logistic regression model procedure for colorectal survival rates in relation to the socio-demographic (age, sex, place of residence), clinical manifestations (topography or site, grade, morphology or histopathology and extent of disease or stage) and treatment type of the tumour (surgery, chemotherapy and radiotherapy).

6.2 Colorectal cancer and clinical characteristics

The clinical characteristics examined in this study included grade, morphology and extent of disease. G*rade* was classified into four categories: well differentiated, moderately differentiated, poorly differentiated, and undifferentiated anaplastic. M*orphology* included dividing the cancer type into adenocarcinoma, mucinous adenocarcinoma, carcinoma, and other morphology; and *extent of disease* included categorization into three main categories, namely: localized, regional and distant metastasis.

6.2.1 Observed and relative colorectal survival probability by grade of tumour

When survival rates were compared for the different grades of cancer (as shown in Figures 17a, 17b and 17c), a decrease in survival probability was seen for all grades and all cancer categories, with one exception. The exception was that while survival probability decreased over time for all grades of rectal cancer, for colon cancer cases of 'Well' grade the decreased survival probability appeared to level off from year 2 onwards. Moderate and well-differentiated colorectal tumours are similar up to 2 years but then diverge with better survival for the later. For rectum cancer, survival from moderate was found to be better than well-differentiated (for which there are very small numbers by the looks of it).

Figure 17a: Observed survival probability by grade of disease for 1,896 of colorectal cancer cases in Jordan
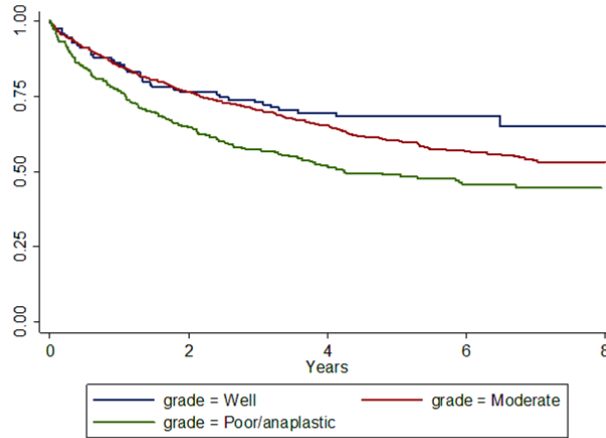
P-value of Log Rank test <0.0001

Figure 17b: Observed survival probability of colon cancer by Grade of disease (2003-2007), Jordan
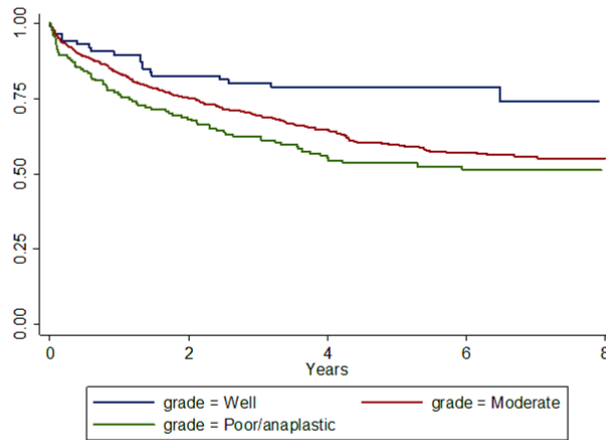
P-value of Log Rank test = 0.0017

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Figure 17c: Survival probability of rectum cancer cases cases by Grade (2003-2007), Jordan
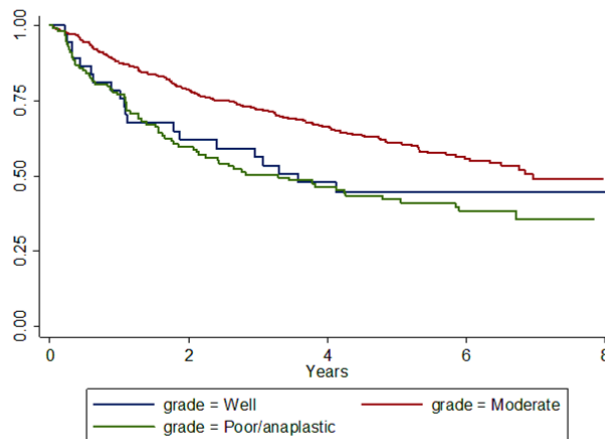
P-value of Log Rank test <0.0001

Findings shown in Table 26 indicate that 5-year survival rates for colorectal cancer varied by cell differentiation. The colorectal cancer patients showed 5-year observed survival rates of 68.1 percent for well-differentiated grade, decreasing to 48.4 percent for poor differentiated grade. Whereas, relative survival rate was 72.9 percent for well-differentiated grade decreasing to 51.2 percent for poor differentiated grade. The 5-year observed and relative survival rates for colon cancer were 78.9 percent and 84.8 percent respectively for well grade, followed by 59.4 percent and 63.7 percent respectively for moderate grade, and 53.5 percent and 56.2 percent respectively for poor grade.

Table 26: Observed (OS) and relative (RS) colorectal cancer survival by grade of tumour, Jordan (2003-2007)

Extent of Disease	Number	Observed survival (percent)			Relative survival (percent)		
		1yr	3yr	5yr	1yr	3yr	5yr
Colorectal							
Well	125	86.3	73.1	68.1	86.8	75.1	72.9
Moderate	1,189	85.0	70.5	60.0	85.4	71.9	63.7
Poor/ anaplastic	282	76.8	57.6	48.8	77.2	58.6	51.2
Colon							
Well	88	89.7	80.3	78.9	90.3	82.5	84.8
Moderate	738	83.4	69.4	59.4	83.9	71.1	63.7
Poor/ anaplastic	166	76.6	62.5	53.5	76.9	63.7	56.2
Rectum							
Well	24	78.4	56.3	44.1	78.9	57.7	46.8
Moderate	302	87.5	72.2	60.9	87.9	73.5	63.9
Poor/ anaplastic	82	77.2	50.5	42.2	77.5	51.3	44.2

The 5-year observed and relative survival for rectum cancer were 60.9 percent and 63.9 percent, respectively, for moderate grade, followed by 44.1 percent and 46.8 percent, respectively, for well grade and 42.2 percent and 44.2 percent, respectively for poor grade. Survival for well-differentiated colon cancer at 3-years and 5-years of diagnosis was higher than that of moderate differentiation grade. In contrast, rectum cancer illustrated different observations; survival from rectum cancer was the poorest for well differentiated. The observed survival for well-differentiated rectum cancer was 56.3 percent at year 3 and 44.1 percent at year 5; meanwhile, it was 80.3 percent at year 3 and 82.5 percent at year 5 for colon cancer. The relative survival rates for well-differentiated rectum cancer were 56.3 percent at year 3 and 44.1 percent at year 5, while they were 57.7 percent at year 3 and 46.8 percent at year 5 for colon cancer.

6.2.2 Observed and relative survival probability of colorectal cancer by disease morphology

Figures 18a show that the effect of cancer morphology on the survival rates of colorectal patients was observed to be poorest with mucinous tumours, where half of the patients died after less than 4 years from diagnosis. When this association was examined by site of cancer, Figure 18b shows that survival of colon cancer patients with mucinous carcinoma to be significantly lower than that of patients with other morphology types (P-value of log rank test = 0.0370), however this relationship was on the borderline of the level of significance for rectum cancer(P-value of log rank test = 0.0561) .

Comparatively, survival data analysis showed that adenocarcinoma and NOS carcinoma types have almost the same probabilities of survival. Although this association was found unchanged when looking at colon cancer (Figure 18b), rectal cancer patients with NOS carcinoma type exhibited significantly higher survival probability than patients with adenocarcinoma which could be attributed to the small number of cases (Figure 18c).

Figure18a: Observed survival probability of colorectal cancer cases by morphology (2003-2007), Jordan
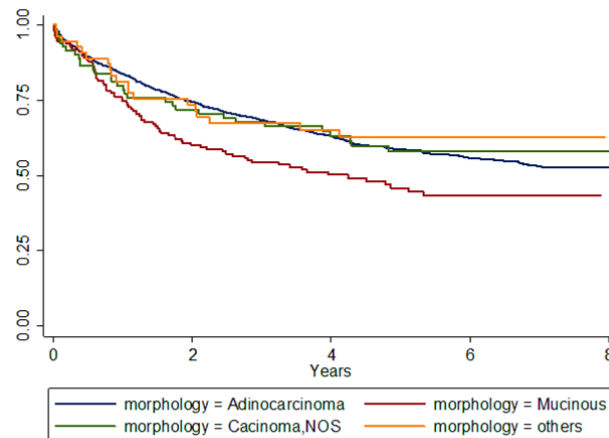
P-value of Log Rank test = 0.0125

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Figure 18b: Observed survival probability of colon cancer cases by morphology (2003-2007), Jordan
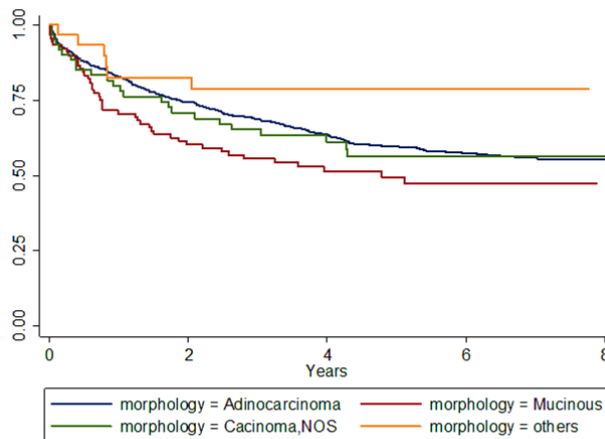
P-value of Log Rank test = 0.0370

Figure 18c: Observed survival probability of rectum cancer cases by morphology (2003-2007), Jordan
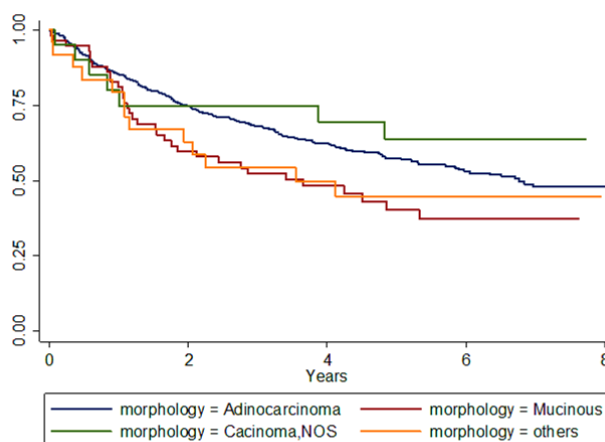
P-value of Log Rank test = 0.0561

Mucinous and serous tumours showed the poorest survival rates among the colorectal cancer histological classifications (Table 27). At year 1 of diagnosis, observed and relative survival for colorectal cancer were 83.7 percent and 84.2 percent, respectively, for adenocarcinoma; and observed and relative survival of 74.8 percent and 75.1 percent, respectively, for both mucinous and serous tumours.

At year 3, the observed and relative rates were 68.5 percent and 69.9 percent, respectively, for adenocarcinoma; 68.3 percent and 70.2 percent, respectively, for NOS and neoplasm; and 54.5 percent and 55.4 percent, respectively, for mucinous and serous tumours. With regard to 5-year survival, the observed and relative survival rates were 57.9 percent and 62.6 percent, respectively, for 'other' morphologies; and 46.4 percent and 48.4 percent, respectively, for mucinous and serous tumours. Considering the patients with colon cancer, the 1-year observed and relative survival rates were 82.8 percent and 83.1 percent, respectively, for 'other' morphologies; 82.9 percent and 83.3 percent, respectively, for adenocarcinoma; and 70.8 percent and 71.1 percent, respectively, for mucinous and serous tumours. At year 3 from diagnosis, the observed and relative survival rates for colon cancer were 79 percent and 80.4 percent, respectively, for 'other' morphologies; 55.8 percent and 56.7 percent, respectively, for mucinous and serous tumours; and 68.7 percent and 70.4 percent, respectively, for adenocarcinoma.

The results of survival analysis by morphology for rectum cancer illustrated that the 1-year observed and relative survival rates were the highest for adenocarcinoma: 85.3 percent and 85.6 percent, respectively; the lowest were for 'other' morphologies: 79.6 percent and 79.9 percent, respectively. Mucinous and serous reported the poorest survival rates at 3-years (52.6 percent and 53.3 percent, respectively) and 5-years from diagnosis (41.4 percent and 42.8 percent, respectively). At 3- and 5-years from diagnosis, neoplasm and NOS had the highest observed survival rates: 74.7 percent and 77.1 percent, respectively, and 63.4 percent and 70.1 percent, respectively.

Morphology	Number	Observed survival (percent)			Relative survival (percent)		
		1yr	3yr	5yr	1yr	3yr	5yr
Colorectal							
Adenocarcinoma	1,598	83.7	68.5	58.6	84.2	69.9	62.4
Mucinous and serous	148	74.8	54.5	46.4	75.1	55.4	48.4
Neoplasm, NOS	82	80.65	68.34	60.39	81.07	70.2	65.41
Others	55	79.6	67.5	57.9	80.0	69.3	62.6
Colon							
Adenocarcinoma	1,013	82.9	68.7	59.4	83.3	70.4	63.7
Mucinous and serous	90	70.8	55.8	49.9	71.1	56.7	52.4
Neoplasm, NOS	61	79.5	65.1	56.1	79.9	66.7	60.1
Others	38	82.8	79.0	78.5	83.1	80.4	83.2
Rectum							
Adenocarcinoma	403	85.3	68.1	57.4	85.6	69.3	60.3
Mucinous and serous	33	81.0	52.6	41.4	81.3	53.3	42.8
Neoplasm, NOS	11	80.0	74.7	63.4	80.5	77.1	70.1
Others	19	79.6	54.5	44.1	79.9	55.1	45.8

Note: types of morphology do not round up to 100% because of missing information.

6.2.3 Observed and relative colorectal survival probability by extent of disease

Analysis showed that the survival rates of colorectal cancer patients to be significantly associated with the extent of disease (Figures 19a, 19b and 19c). Poor survival rate was found for patients with the distant type tumours which seemed to hold plausible when examining the association for colon and rectum cancer individually. Although the condition was much better when examining the survival rates by localized and regional type of tumours, colorectal patients with regional tumours illustrated poorer survival rates when compared with the localized the type (P-value < 0.0001). Further examination of

colon and rectum cancer survival rates showed that rectal cancer patients with local or

regional tumours had worse survival rates than patients with colon cancer of such types.

Figure 19a: Observed survival probability of colorectal cancer cases by extent of disease (2003-2007), Jordan
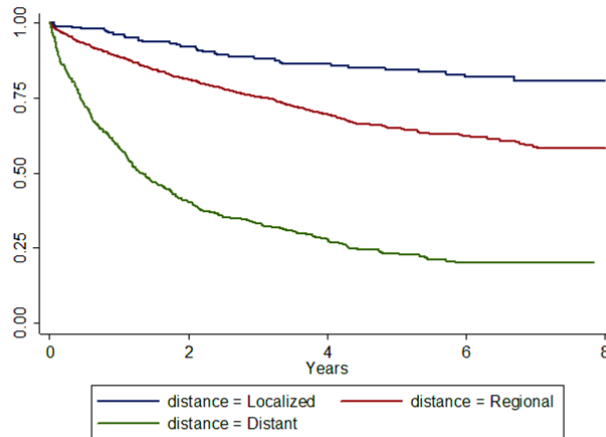
P-value < 0.0001

Figure 19b: Observed survival probability of colon cancer cases by extent of disease (2003-2007), Jordan
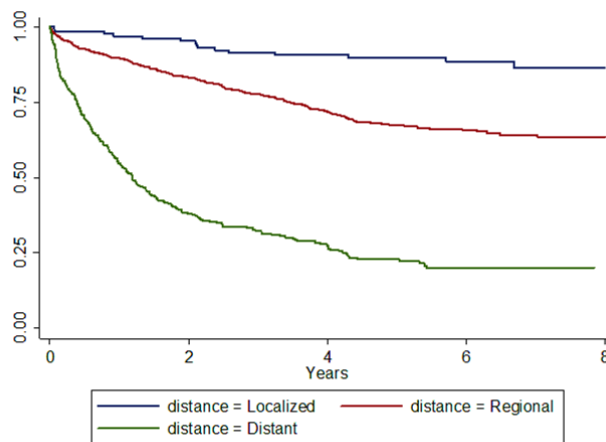
P-value < 0.0001

Figure 19c: Observed survival probability of rectum cancer cases by extent of disease (2003-2007), Jordan
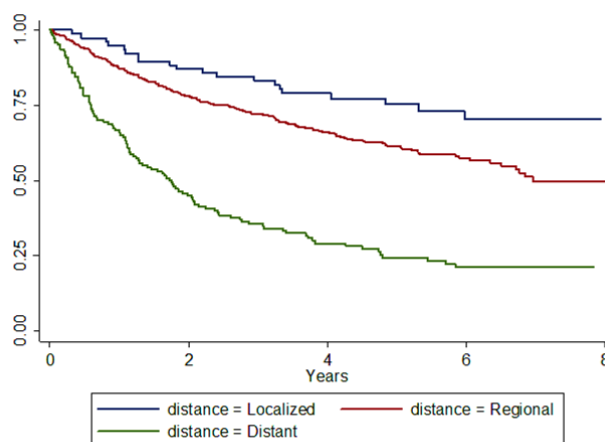
P-value < 0.0001

At year 5, observed survival rates of colorectal cancer cases were 84.3 percent in cases of localized stage, decreasing to 64.9 percent in cases of regional stage and reaching 23.3 percent in cases of distant stage. The corresponding relative survival rates were 86.2 percent, 68.6 percent and 24.8 percent, respectively (Table 28).

Table 28: Observed (OS) and relative (RS) for colorectal cancer survival by extent of disease, Jordan (2003-2007)

Extent of Disease	Number	Observed survival (percent)			Relative survival (percent)		
		1yr	3yr	5yr	1yr	3yr	5yr
Colorectal							
Localized	212	96.2	88.4	84.3	96.8	90.5	86.2
Regional	1,118	88.7	75.4	64.9	89.1	76.9	68.6
Distant	432	58.6	33.4	23.3	58.9	34.2	24.8
Colon							
Localized	133	96.5	91.5	89.6	97.3	94.3	91.3
Regional	689	89.7	77.7	67.3	90.2	79.4	71.7
Distant	290	54.7	32.5	22.7	55.0	33.1	23.9
Rectum							
Localized	68	94.9	83.2	74.9	95.3	85.0	79.4
Regional	272	87.1	71.9	61.2	87.4	73.2	63.8
Distant	88	66.7	35.6	24.7	67.0	36.4	26.7

Survival from localized and regional colon cancer was better than survival from rectum cancer in the same stages at 1-, 3- and 5-years of diagnosis. Cases of localized tumours in colon cancer showed 5-years observed survival rate of 89.6 percent and relative survival rate of 97.3 percent, and regionally spread tumours 67.3 percent and 71.7 percent, respectively. The corresponding values of localized and regional rectum cancers were 74.9 percent and 61.2 percent respectively for the observed survivals, 79.4 percent and 63.8 percent respectively for the relative survivals. The situation differed with regard to the distant tumours: the rectum cancer data produced better survival rates than that of colon cancer throughout the first five years after diagnosis. The observed and relative survival rates of distant tumours for rectum cancer were 35.6 percent and 36.4 percent, respectively, at 3-years of diagnosis; and 24.7 percent and 26.7 percent respectively at 5-years of diagnosis. The reciprocal observed and relative survival rates for distant colon cancer at 3-years were 32.5 percent and 33.1 percent, respectively; and observed and relative survival rates for distant colon cancer at 5-years were 22.7 percent, and 23.9 percent, respectively.

6.2.4 Observed and relative colorectal survival probability by extent of disease stratified by age and sex

Table 29 illustrates the colorectal cancer 5-year survival rate by extent of disease stratified by age and sex. Results indicated that observed survival became poorer with increasing age for both localized and regional tumours. This observation was applicable for both males and females.

When combining both sexes across all age groups, the observed 5-year survival rate ranged from 84.3 percent to 63.8 percent for localized tumour, and 68.9 percent to 44.3 percent for regional tumour. Results of distant tumour for males and females showed highest 5-year

observed survival rate for patients in the age group of 45 through 64 years, while observed survival of the age group 15 through 44 years was slightly higher than that of the age group of 65 years of age or more. For both sexes, the observed 5-year survival rate was 26.1 percent in the age group 45 through 65 years and decreased to 20.2 percent in age group 65 years of age or older.

Table 29: Fiver year relative survival rates of colorectal cancer patients by extent of disease, age, sex, and calendar year of diagnosis Jordan (2003–2007)

Extent of disease	Age	Both sexes		Males		Females	
		OS percent	RS percent	OS percent	RS percent	OS percent	RS percent
Localized	15-44	84.31	85.02	82.79	83.6	85.0	85.60
	45-59	81.02	82.79	78.96	81.01	83.33	84.75
	60-74	80.35	86.74	78.75	85.90	82.93	88.09
	≥75	63.75	81.10	59.40	78.83	67.73	82.61
	All ages	**79.04**	**84.51**	**77.04**	**83.26**	**81.61**	**86.10**
Regional	15-44	68.61	69.11	71.38	72.05	66.61	67.00
	45-59	68.90	70.39	62.17	63.85	75.50	76.79
	60-74	65.28	70.25	65.71	71.68	64.59	68.09
	≥75	44.33	56.39	42.61	56.02	47.70	57.26
	All ages	**65.43**	**69.02**	**63.24**	**67.86**	**68.02**	**70.41**
Distant	15-44	19.08	19.25	19.40	19.62	19.05	19.16
	45-59	30.46	31.19	34.89	35.92	26.29	26.71
	60-74	17.70	19.14	19.72	21.60	14.47	15.27
	≥75	21.87	28.95	22.72	31.04	18.18	21.19
	All ages	**22.49**	**23.98**	**24.12**	**26.17**	**20.17**	**20.86**
All	15-44	57.64	58.08	55.46	55.90	57.17	57.61
	45-59	60.55	61.88	59.39	60.71	60.24	61.56
	60-74	56.79	61.18	55.26	59.59	55.38	59.61
	≥75	40.89	52.35	38.38	49.49	41.21	52.56

6.3 Colorectal survival estimates and treatment

The treatment characteristics examined in this study included intent of treatment, surgery, chemotherapy and radiotherapy. Colorectal cancer survival probabilities for the treatment-

related variables (surgery, chemotherapy, and radiotherapy) were computed using Kaplan-Meier technique and logrank tests. These probabilities were examined in relation to tumour site.

6.3.1 Surgery treatment

6.3.1.1 Thirty-days postoperative mortality after colorectal cancer surgery

Table 30 displays the results of multivariable analyses done to examine the adjusted odds of death within 30 days of surgery. The adjusted odds ratios for CRC thirty-day postoperative mortality for sex, age, place of residence, extent of disease, topography, operation type, and treatment site were calculated using the logistic regression modelling procedure. Irrespective to the level of significance of the sex variable, we entered it into the multivariable model to confirm that it remain non-significant determinant of thirty-days postoperative mortality after adjustment for other confounding factors. For other variables, significant predictors (p-value ≤ 0.2) were included in the adjusted model.

The odds of dying were significantly higher among colorectal cancer patients older than 65 years who underwent surgery (OR 2.3, 95percent CI: 1.3-4.1). In addition, CRC patients with distant tumors who underwent surgery had higher odds of dying than those with local/regional tumors (OR 3.6, 95 percent CI: 2.0-6.2); and those operated upon as an emergency had higher odds compared with those operated upon electively (OR 2.3, 95percent CI: 1.2-4.1). Sex, place of residence, topography, and treatment site were insignificant predictors.

Table 30: Multivariable analyses for odds of dying within 30 days of surgery for colorectal cancer patients

Variables	multivariable analyses		
	OR	(95percent CI)	P-value
Sex			0.482
Male	1	-	
Female	.81	0.45-1.4	
Age			0.003
<=65	1	-	
>65	2.3	1.3-4.1	
Place of residence			0.400
Middle	1		
North & South	1.3	0.70-2.4	
Topography			0.141
Colon	1	-	
Rectum	.62	0.33-1.2	
Extent			<0.001
Localized / regional	1	-	
Distant	3.6	2.0-6.2	
Operation type			0.008
Elective	1	-	
Emergency	2.3	1.2-4.1	
Treatment site			0.257
Public/teaching	1	-	
Private/KHCC & others	.70	0.38-1.3	

6.3.1.2 Survival probability of colorectal cancer by surgery

Figure 20a shows that the observed survival probability was significantly higher for colorectal cancer patients who underwent surgery than for those patients who did not undergo surgery. This scenario was similarly observed for both colon and rectum (p-value < 0.001; Figures 20b and 20c, respectively).

Figure 20a: Observed survival probability of colorectal cancer cases by undergoing surgery (2003-2007), Jordan
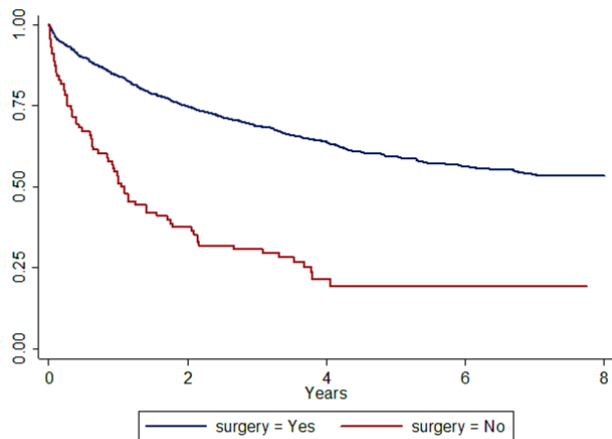
P-value< 0.0001

Figure20b: Observed survival probability of colon cancer cases by undergoing surgery (2003-2007), Jordan
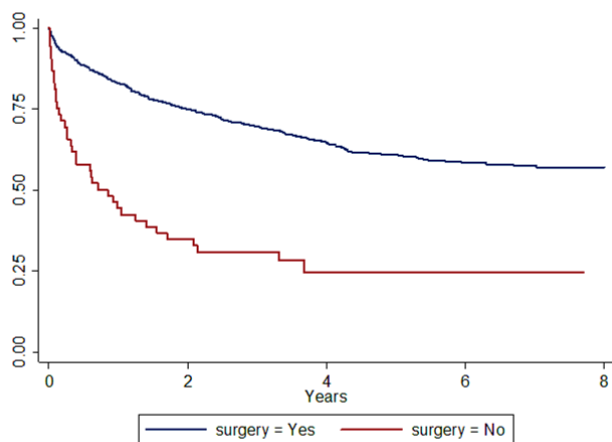
P-value < 0.0001

Figure 20c: Observed survival probability of rectal cancer cases by undergoing surgery (2003-2007), Jordan
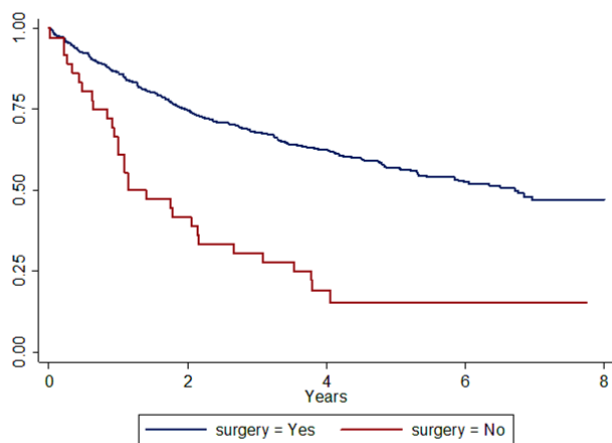
P-value < 0.0001

6.3.1.3 Relative survival rates of colorectal cancer undergoing surgery

Table 31 illustrates relative survival (RS) for patients of colorectal, colon and rectum cancer in terms of undergoing surgery. For this effect three models were constructed, one for each type of cancer. To better understand changes in RS between the first and fifth year the period between zero timing and the end of the first year was divided into ten intervals. The periods between the start of the second year and the end of the second year as well as the start of the third year and the end of the third year were divided into two intervals for each. The periods between the start of the fourth year and the end of the fourth year, as well as the start of the fifth year and the end of the fifth year, were divided into single intervals for each (as seen in Table 31).

The colorectal model showed that RS declined all the way from 96.2 percent to 62.6 percent for patients who underwent surgery and from 86.5 percent to 23.5 percent for patients who did not undergo surgery; the difference between the two groups was observed clearly during all time periods. The colon cancer model showed that RS declined from 95.4 percent to 64.7 percent for patients who underwent surgery; at the same time RS dropped from 81.3 percent to 24.1 percent for patients who did not undergo surgery. The difference between both groups in this model was clearly observed over all time periods as well.

The rectal cancer model illustrated that RS declined from 98.4 percent to 56.8 percent for patients who underwent surgery and from 96.7 percent to 21.0 percent for patients who did not undergo surgery. The difference between both groups was minimal until the end of the eighth time period of the first year; later the RS for patients who underwent surgery was clearly higher compared to those patients who did not undergo surgery. RS for those

patients who underwent surgery was always higher than those for patients who did not

undergo surgery (Table 31).

Table 31: Five year relative survival rates for colorectal, colon and rectum cancer patients by surgery, 2003–2007

Time		Colorectal		Colon		Rectum	
		Surgery	No surgery	Surgery	No surgery	Surgery	No surgery
Start	End	RS percent	RS percent	RS percent	RS percent	RS percent	RS percent
0	0.1	96.2	86.5	95.3	81.2	98.4	96.7
0.1	0.2	94.7	82	93.5	74.3	97.9	96.8
0.2	0.3	93.3	75.2	92.2	67.5	96.3	90.1
0.3	0.4	91.6	69.5	90.7	58.8	94.2	90.2
0.4	0.5	90.1	67.5	89.2	57.1	92.6	86.9
0.5	0.6	88.8	67.3	88.2	55.4	91.9	87.0
0.6	0.7	87.9	66.2	87.4	50.3	89.5	83.7
0.7	0.8	86.9	61.7	86.3	48.6	88.7	83.7
0.8	0.9	85.4	60.5	85.1	46.9	86.6	80.4
0.9	1	84.6	58.3	84.3	43.4	85.5	67.1
1	1.5	79.6	51.5	79.6	38.3	79.1	50.6
1.5	2	75.6	42.5	76.3	33.2	73.6	47.4
2	2.5	72.5	38.1	73.3	29.9	70.3	37.5
2.5	3	70.3	32.5	71.5	30.1	67.1	34.4
3	4	66.1	31.6	67.4	23.4	62.1	24.2
4	5	62.6	23.5	64.6	24.1	56.8	20.9

6.3.1.4 Survival probability of colorectal cancer by type of surgery

Figures 21a, 21b and 21c show the overall colorectal survival probability as well as

individually for colon and rectum cancers by surgery type. The figures show that no

significant pattern among patients who had elective surgery compared to those who

underwent emergency surgery for both colon and rectum.

Figure 21a: Observed survival probability of colorectal cancer cases by surgery type (2003-2007), Jordan
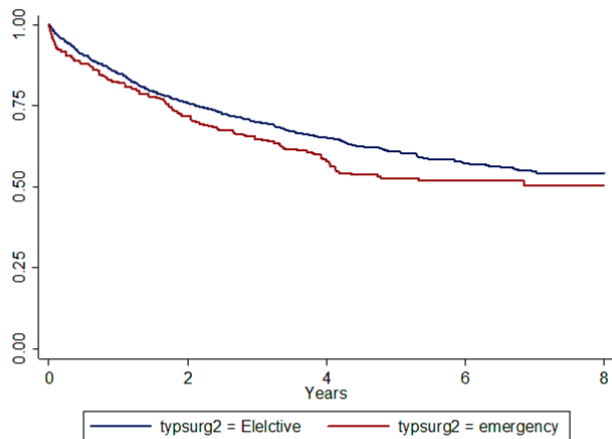
P-value 0.0601

Figure 21b: Observed survival probability of colon cancer cases by surgery type (2003-2007), Jordan
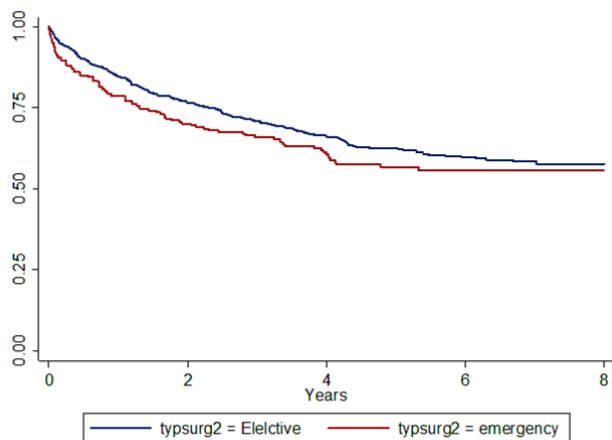
P-value 0.1738

Figure 21c: Observed survival probability of rectum cancer cases by surgery type (2003-2007), Jordan

P-value 0.0830

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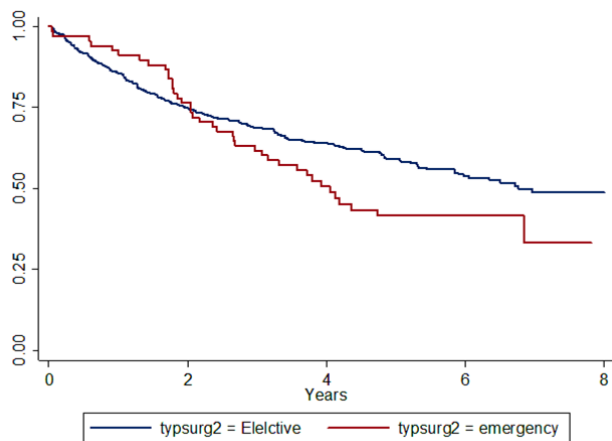
6.3.2 Survival probability of colorectal cancer by chemotherapy

Figures 22a, 22b and 22c show the survival probabilities of colorectal cancer by chemotherapy treatment during 2003 through 2007 in Jordan. The figures show that patients who received chemotherapy treatment had better survival for almost the first four years; later, though, patients who didn't receive chemotherapy treatment had better survival. However, this relationship did not reach significant levels either for colon or for rectum cancer. Moreover, the shapes of these Kaplan–Meier curves were found dissimilar; the non-chemo have a steep initial death rates which plateaus but the chemo group deaths are more constant over time. This could be because patients who died within the first few months were not offered or given chemotherapy.

Figure 22a: Observed survival probability of colorectal cancer cases by chemotherapy treatment (2003-2007), Jordan
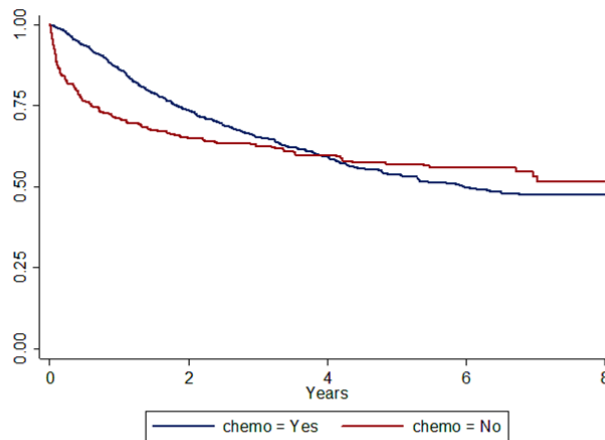
P-value 0.7981

Figure 22b: Observed survival probability of colon cancer cases by chemotherapy treatment (2003-2007), Jordan
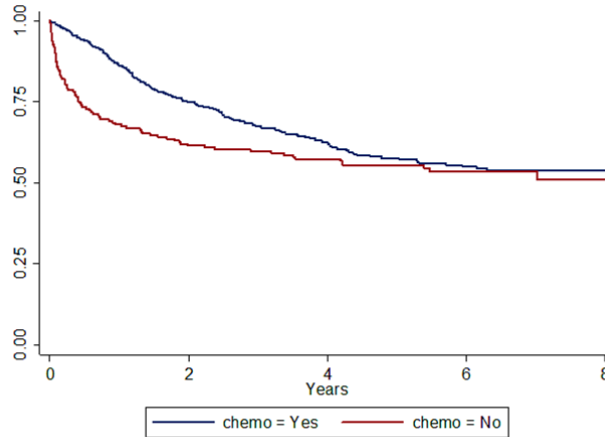
P-value 0.0595

Figure 22c: Observed survival probability of rectum cancer cases by chemotherapy treatment (2003-2007), Jordan
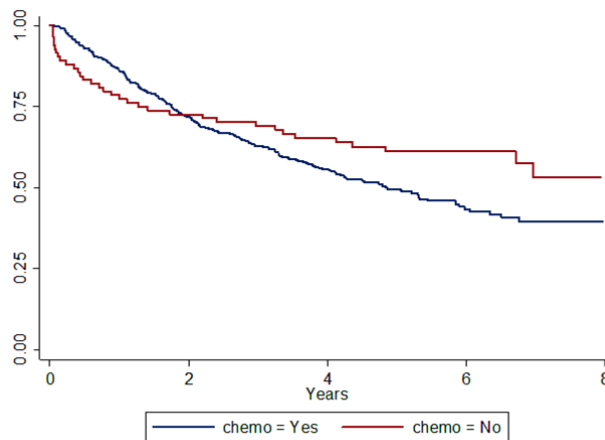
P-value 0.0650

6.3.3 Survival probability of colorectal cancer by Radiotherapy

Figures 23a, 23b and 23c show the survival probabilities of colorectal cancer by chemotherapy treatment during 2003 through 2007 in Jordan. Figures show that patients who received radiotherapy treatment had better survival for almost the first year; later, patients who did not receive radiotherapy treatment had better survival. This relationship reached significant levels for rectum cancer but not for colon cancer.

Figure 23a: Observed survival probability of colorectal cancer cases by radiotherapy treatment (2003-2007), Jordan
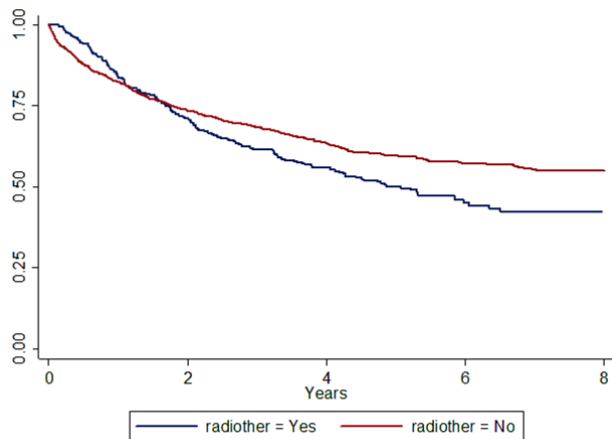
P-value 0.0041

Figure 23b: Observed survival probability of colon cancer cases by radiotherapy treatment (2003-2007), Jordan
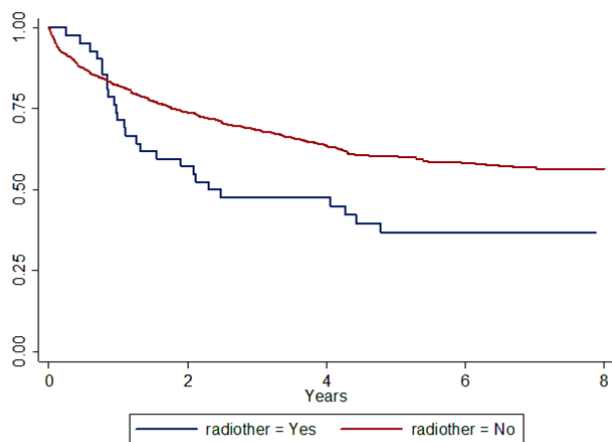
P-value 0.0074

Figure 23c: Observed survival probability of rectum cancer cases by radiotherapy treatment (2003-2007), Jordan
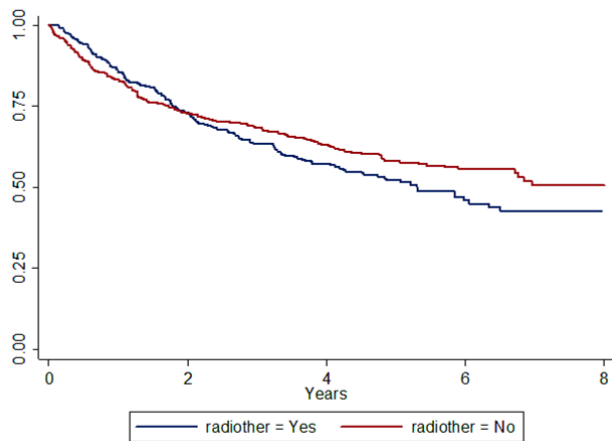
P-value 0.1232

6.4 General Predictive Model for Colorectal Cancer

Table 32 shows the hazard ratios for CRC calculated using the Cox logistic regression model. Three predictive survival models were examined and presented based on topography (overall CRC, colon, and rectum). Using the Cox logistic regression model procedure, hazard ratios for CRC survival were first estimated as crude, and then adjusted for sex, age, place of residence, year of diagnosis, extent of disease, grade, morphology, and topography. Irrespective to the level of significance of sex and age in univariate models, we entered them into the multivariable model. For other variables, only significant predictors (P-value ≤ 0.2) were included in each adjusted model.

Age was found to be a significant predictor for survival of colon cancer; colon cancer patients aged 75 years and above had 2.2 times higher risk of death than those aged 44 years or less (HR=2.2, 95% CI: 1.5-3.1). Residing in the central region of the country was a significant predictor for survival of rectum cancer, where patients residing in the central region had a 27 percent lower risk of death compared with those residing in the North (HR=0.73, 95% CI: 0.56-0.95).

Extent of disease was found to be a significant survival predictor for both colon and rectum cancers. Colon and rectum cancer patients with regional metastasis had three times and one and the half times higher risk of death than those with localized disease respectively (Colon: HR=3.3, 95% CI: 2.0-5.6); (Rectum: HR=1.6, 95% CI: 1.1-2.5). Moreover, colon patients with distant metastasis had fourteen times higher risk of death and rectum cancer patients portrayed four and the half times higher risk of death than those with localized disease (Colon: HR=14.0, 95% CI: 8.0-23.8); (Rectum: HR=1.6, 95% CI: 2.8-7.5). Colon patients with poor or anaplastic grade had almost twice the risk of death than those with

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well grade (HR=1.9, 95% CI: 1.1-3.2). On the other hand, patients diagnosed with mucinous rectum cancer had 1.4 times higher risk of death than those with adenocarcinoma (HR=1.4, 95% CI: 1.1-2.1). Sex and year of diagnosis were not significant survival predictors across the three models (CRC, colon and rectum). The HR CRC adjusted model showed no statistically significant survival difference between colon and rectum.

In summary, this study revealed that age, place of residency, extent of disease, topography and morphology to be significant predictors for colorectal cancer survival estimates. However, sex, grade and year of diagnosis were insignificant predictors.

Table 32: Cox hazard proportions for colorectal, colon and rectum cancers, Jordan (2003-2007)

Variable	Colorectal cancer		Colon cancer		Rectum cancer	
	Unadjusted HR (95percent CI)	Adjusted HR (95percent CI)	Unadjusted HR (95percent CI)	Adjusted HR (95percent CI)	Unadjusted HR (95percent CI)	Adjusted HR (95percent CI)
Sex						
Male	1	1	1	1	1	1
Female	0.90 (0.78-1.1)	1.0 (.90-1.2)	0.85 (0.71-1.1)	1.0 (0.86- 1.3)	0.98 (0.78-1.2)	1.1 (0.89-1.4)
Age						
15-44	1	1	1	1	1	1
45-59	0.88 (0.71-1.10)	0.89 (0.71-1.1)	0.95 (0.71-1.2)	0.95 (0.70-1.3)	0.81 (0.59-1.1)	0.83 (0.60- 1.2)
60-74	1.03 (0.84-1.27)	1.2 (0.94-1.4)	1.1 (0.83-1.5)	1.2 (0.93-1.6)	0.99 (0.73-1.3)	1.1 (0.80-1.5)
≥75	1.6 (1.2-2.03) *	1.8 (1.4-2.3)*	1.7 (1.2-2.4)*	2.2 (1.5-3.1)*	1.5 (0.95- 2.3)	1.3 (0.85-2.1)
Place of residence						
North	1	1	1	1	1	1
Middle	0.81 (0.63-0.88)*	0.77 (0.65-0.92)*	0.80(0.64-0.99)*	0.82 (0.65-1.1)	0.67 (0.52-0.86)*	0.73 (0.56-0.95)*
South	1.2 (0.83-1.7)	1.1 (0.65-1.5)	1.3 (0.83-2.1)	1.1 (0.66-1.7)	1.0 (0.57-1.8)	0.98 (0.54-1.8)
Year of diagnosis	1.1 (0.98-1.3)	1.0 (0.98-1.1)	1.0 (0.98-1.1)	0.99 (.93-1.1)	1.1 (0.98-1.2)	1.1 (0.98-1.2)
Extent of disease						
Localized	1	1	1	1	1	1
Regional	2.4 (1.7-3.4) *	2.4 (1.7-3.4)*	3.2 (1.9-5.5)*	3.3 (2.0-5.6)*	1.8 (1.1-2.8)*	1.6 (1.1-2.5)*
Distant metastasis	8.8 (6.2-12.5) *	8.6 (6.1-12.4)*	13.5 (8.0-22.9)*	14.0 (8.2-23.8)*	5.0 (3.1-8.1)*	4.6 (2.8-7.5)*
Grade						
Well	1	1	1	1	1	1
Moderate	1.3 (0.93-1.8)	1.1 (0.78-1.5)	1.9 (1.2-3.1)*	1.5 (0.92-2.4)	0.64 (0.40-1.1)	0.65 (0.40-1.1)
Poor/ anaplastic	1.9 (1.3-2.6)*	1.3 (0.90-1.9)	2.4 (1.4-4.0)*	1.9 (1.1-3.2)*	1.1 (0.69-1.9)	1.0 (0.60-1.7)
Morphology						
Adenocarcinoma	1	1	1	1	1	1
Mucinous	1.5 (1.2-1.9)*	1.3 (1.1-1.7)*	1.4 (1.1-1.9)*	1.2 (0.89-1.7)	1.5 (1.2-2.2)*	1.4 (1.1-2.1)*
Carcinoma, NOS	0.97 (0.68-1.4)	0.70 (0.48-1.1)	1.1 (0.71-1.6)	0.82 (0 .52-1.3)	0.76 (0.35-1.6)	0.51 (0.23-1.1)
Others	0.89 (0.56-1.4)	0.98 (0.61-1.6)	0.49 (0.22- 1.1)	0.65 (0.28-1.5)	1.4 (0.82-2.5)	1.3 (0.72-2.3)
Topography						
Colon	1	1				
Rectum	1.1 (0.96-1.3)	1.1 (0.98-1.3)				

* Statistically significant

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6.5 Summary and Discussion

This chapter examined and discussed colorectal survival probabilities and their relationship to clinical characteristics (i.e. morphology, extent of disease, topography and grade) and treatment characteristics (surgery, chemotherapy, and radiotherapy). In addition, these probabilities were explored in relation to patients' socio-demographic characteristics. Moreover, this chapter also examined and discussed 30-days postoperative mortality.

Using the Cox logistic regression model procedure, this study revealed that age, place of residency, extent of disease, morphology and typography are significant predictors for colorectal cancer survival estimates. However, sex, grade and year of diagnosis were insignificant predictors.

The existing information from JCR was complete for the variables of age, sex, and place of residency. However, data on some variables was incomplete. This study supplemented JCR with additional information in order to improve the quality of cancer registry data and its completeness. For example, 25% of distance stage, 14% of morphology and 17% of disease grade data were completed as a result of additional collection. All information related to treatment (surgery, chemotherapy and radiotherapy) came from actively collecting new data. However, this study did not bring any improvements to the quality and completeness of the data on other information such as level of education, occupation, health insurance, smoking status, or marital status. It is important to note that patient outcome information was not collected by JCR, and that information on vital status for the study population was added to the JCR by this study.

Colorectal survival rates and age

This study, in line with other studies, showed poor survival with advancing age (138;140;145;190;247). This could be attributed to poor general health and the difficulties in prescribing cancer treatment (such as surgery) and possibly an association with more advanced disease stages (248). A study showed that survival for patients younger than 65 years improved over time compared with older patients. This improvement was attributed to the increase in the use of adjuvant treatment in younger patients as well as tolerance to surgery (148). The effect of adjuvant therapy on improving cancer–related survival rates was also reported for patients younger than 50 years with rectum cancer. Furthermore, less co-morbidity and emergency operations compared with older patients were identified as possible factors (143). Analysing the data obtained from Ontario cancer registry, the relative odds of early death at 1 year increased by 85 percent in age range 65-69 years compared with age range 40-49 years (145). Hazard ratios of death at 1 year for white and black patients; registered in the national cancer data base; was increased by 37 percent and 38 percent respectively in age range 61-64 compared with age 18-49 years (190). In Jordan, the high prevalence of non-communicable diseases (especially hypertension and diabetes) could be contributing to the poor health of the elderly population (3;4;125).

A worse prognosis of disease in young patients was reported by many researchers (139-143). Although the differences did not reach significant levels, this study revealed that younger age groups between 15 and 44 years generally had lower survival rates at all years of diagnosis for colon and rectum compared to patients' age groups 45-59 and 60-74. This was in line with studies (138;150). Study from China showed that the difference in survival rates among patients aged 40 years and younger, and older patients aged more

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than 40 years was insignificant in a study conducted on 230 colorectal cancer patients (140).

Colorectal cancer survival rates and place of residence

Variations in estimates of cancer survival between geographic locations are well documented in the literature (46;159;164;199;236;249-253). This study reported that patients living in the central part of Jordan had the highest 5-year observed survival rate for colorectal, colon and rectum cancers (at 60.1 percent, 61 percent and 58.5 percent, respectively) compared to the northern and southern regions. In Jordan, the central region has better health indicators compared to other region (22;46;236). Preventive programs such as screening were mostly established in the central region, leaving other regions lagging behind in this area. It is worth mentioning that patients from the south and north regions prefer coming to the central region to get their treatment. Kaplan-Meier shows that survival rates in the first year are almost the same among the three regions. Later though, discrepancies among the regions were observed, with the north and south regions showing a steady decrease, particularly the southern region (46;236). This finding might be attributable to poorer quality of health services in these regions. The association between CRC survival rates and place of residence remained statically significant after controlling for the effect of potential confounding variables.

This study revealed that patients from peripheral regions were more likely to die from CRC than those residing in the central region. Access to treatment services has been shown to influence cancer outcome; and high quality and timely treatment can lower the probability of early death among patients (46;159;164;199;236;250). Further research to study the

influence of spatial (location and distance) and non-spatial determinants (socio-economic and cultural factors) on survival differences is highly recommended.

Colorectal cancer survival rates and extent of disease

Stage of tumour at diagnosis is the most important predictor of survival. Patients' survival from CRC was estimated for the different stages of tumour recorded at the time of diagnosis. This study showed that more than half of the patients (59 percent) were presented with regional metastasis; 22.8 percent with distant metastasis, and only 11.2 percent with a localized CRC at diagnosis. This is an important result that should be taken into account in implementing CRC prevention and control strategies. In line with other studies, these findings indicate that survival rates become shorter as the cancer spread beyond the origin site. Thus the highest survival rate was found for patients with localized tumour and the lowest for the distant tumour stage (11;12;73;137;144;171;174;175). Supported by the literature, this result was found independent of patient's race (73;137), treatment type (174) and tumour site (175).

The study revealed that at year 5, relative survival rates of CRC cases with localized, regional and distant forms were 86.2 percent, 68.6 percent and 24.8 percent, respectively. The 5-year survival of colorectal cancer patients were 100 percent for Stage I, 68 percent for Stage II, 44 percent for Stage III and 2 percent for Stage IV (176). Others found that the 5-year survival of colorectal cancer patients were 89 percent for Dukes' stage A, 75 percent for Dukes' stage B, 49 percent for Dukes' stage C and 12 percent for Dukes' stage D (176). The differences between our results compared to other studies could be attributing to medical therapy, surgery type and screening programs and early diagnosis (130;254-

256). Moreover, this study revealed that a high percentage of CRC patients (13.8percent) were in the young age group (<40 year). CRC in the young patients appears to be more aggressive, to present with later stage, and to have poorer pathologic findings (142;146).

Moreover, this study shows that the survival rates for localized and regional colon cancer were better than those for rectum cancer in the same stages at 1-, 3- and 5-years of diagnosis. Alternatively, the rectum cancer data produced better survival rates than that of colon cancer throughout the first five years following diagnosis, which could be attributed to the extent of tumour invasion into the colon serosa and other adjacent tissues as this produces poorer survival rates of colorectal cancer patients (178).

Mucinous adenocarcinoma

Mucinous adenocarcinoma is a type of epithelial tumours that is classified by the WHO as tumours where the lesion is more than fifty percent composed of mucin (63). In this study, mucinous tumour was found to be uncommon, 7.8 percent of all CRC cases. This result was comparable to estimates reported by other population studies around the world, for example Iran (8.6 percent) (257), China (7 percent) (257-259). This study also revealed that CRC mucinous adenocarcinomas to be predominantly higher among older patients (> 50 years) which contradicts findings of other researchers (16;257-261). Alternatively, the study finding showing equal presence of mucinous adenocarcinoma among male and female patients, was similar to some studies (231), but conflicting with others which reported predominance among male patients (257;261;262). In addition, the study found mucinous adenocarcinomas to be more commonly present in the colon, which is in line with findings of several researchers (257-260;262;263).

As one of the poorly differentiated CRC tumours, mucinous adenocarcinoma has poor prognosis because of being usually presented at a later stage. Although still controversial, patients with CRC mucinous adenocarcinomas are reported to have poorer outcome when compared to those with non-mucinous adenocarcinoma (259;260;264). Results of this study support this notion, where the poorest survival rates among the CRC patients was observed among patients with mucinous tumours, (half of the patients died after less than 4 years from diagnosis). In addition, the five-year relative survival rate for mucinous adenocarcinoma of 46.4 percent was almost comparable to other studies (41.3 percent) (257), with a lower rate found among mucinous adenocarcinoma of the rectum (42.8 percent) than among the colon (52.4 percent); which might be due to specific biological behaviour of the tumour. Moreover, the study outcome of having mucinous tumors of the rectum associated with a higher risk of death than mucinous tumors of the colon is similar to findings of other studies (264).

The study also concluded that diagnosis with mucinous carcinoma was a predictive variable when calculating the hazard ratio using the cox logistic regression model, where patients with mucinous colorectal cancer had 1.5 times higher risk of death than those with adenocarcinoma (HR=1.5, 95percent CI: 1.2-1.9). This result might be attributed to the later staging of the mucinous adenocarcinomas, where the majority of the mucinous cancers in this study were found to be of a moderate grade (61.6 percent) and with a regional extent (64.86 percent), thus making mucinous type a significant predictor (16;265).

In conclusion, mucinous adenocarcinoma is an important factor to consider when treating CRC patients. Several studies concluded that mucinous histology to be an independent prognostic factor for poor prognosis of patients (16;257;259;266). Although many aspects of the mucinous histological type are still controversial, this study suggests that patients presented with an advanced grade of colorectal mucinous adenocarcinoma are at a higher risk of dying, thus requiring special attention when prescribing the treatment regimen.

Colorectal cancer survival rates and Treatment

Although information on treatment in our study is relatively incomplete, study findings revealed that RS for those CRC patients who underwent surgery to be consistently higher than that of patients who did not have surgery. This pattern was observed for colon and rectum models alike. The difference between both groups in this model was clearly observed over all time periods as well. Moreover, those who underwent emergency surgery had a higher risk of death than those who underwent an elective one. In addition, those who did not get chemotherapy treatment had a higher risk compared to those who did. On the other hand, study results indicated that patients who received radiotherapy had lower risk of death during the first year from diagnosis compared to those who received no such treatment, and that this relationship reversed subsequently.

Appropriate surgery is recognized as the most important aspect of CRC treatment and as a necessary curative treatment modality for CRC (18;77). However, the inclusion of other modalities in the treatment of CRC, like chemotherapy and radiotherapy, can reduce the probability of disease recurrence (18;108). Albeit having surgery as the backbone for CRC

management, the use of adjuvant chemotherapy and radiotherapy to improve survival of CRC patients has been on the rise (18;77;111;113;114;267). In Jordan, chemotherapy and radiotherapy treatment have been well developed specifically at the tertiary healthcare facilities. Moreover, preoperative and postoperative chemotherapy treatment became more common treatment for colorectal patients with advanced stages.

Regarding to our result concerning radiotherapy treatment, we believe that such a result is an artefact because those who died early were not offered radiotherapy. In addition, radiotherapy is rarely included as part of colon cancer treatment, and is a common treatment modality for rectum cancer patients. Radiotherapy tends to be given after surgery in colon cancer; hence a survivor bias occurs in the observed outcomes. However, radiotherapy is given pre-operatively in rectal cancers, the effect of which appears much later.

It is worth noting that this study lacked the inclusion of specific information on chemotherapy and radiotherapy treatment regimens, such as length of treatment, and absence of information about complications during or after primary surgery. Such information is not collected by JCR and was not available on patients' medical records.

The study hazard ratios were calculated using the Cox logistic regression model. Two models were examined and presented based on treatment (Model 1 without treatment and model 2 with treatment as a predictor). The rationale behind running the cox regression model without the treatment variable lies in that treatment variables are considered confounders because they are associated with better survival, and that the probability of

receiving treatment is dependent on the survival time (i.e. patients have to live longer in order to be able to receive treatment). In addition, the reason for receiving treatment can play an important role in confounding its effect on the survival rate, thus masking the effect of other important predictors. Based on this argument, this study considers Model 1 as the main predictive model for calculating the hazard ratios when adjusting for important variables that are associated with colorectal cancer survival.

Thirty-day postoperative mortality

Addressing 30-days postoperative mortality can enrich the attempt to understand CRC survival and its associated factors or predictors. This study provides information related to the risk of surgical treatment which should enable informed decision-making by clinicians. The study indicated that during the study period, 4.8 percent of patients who underwent surgery had died within 30 days of surgery. When examining the factors that might have influenced the 30-days postoperative mortality, data indicated higher mortality among patients who were elderly (over 65 years of age), those with distant tumours and those who were operated upon as an emergency.

When compared to other studies, the overall 4.8percent 30-days postoperative mortality seen in this study was found to be lower than that of a population-based study done in the United Kingdom (6.7 percent) and of another nationwide cohort study conducted within the entire Danish population (8.8percent) (268;269). Both the UK and Denmark studies supported the results of this study in that the elderly and those having an emergency type of operation were found to have higher mortality within 30 days postoperatively. Differences in the 30-day postoperative mortality rates between colon and rectum cancer

seen in this study, contradicted the results of the population-based studies done in the UK and Denmark which reported higher postoperative mortality after 30 days from colon cancer surgery than after rectal cancer surgery. Higher postoperative mortality during the first 30 day from surgery, for patients with distant tumours found in this study, was confirmed by results from the UK study.

The increase in the incidence of CRC in this study and the noticeable decline in the relative survival rate among the elderly population, raise a question of whether these results are related to greater risk of dying from surgical treatment; especially when considering the significantly higher 30-days postoperative mortality rate among this group. Even though elderly people might be presented with comorbidities and a generally weaker health status, this notion should not pose as a reason for precluding them from surgery. In this arena, a study done in the Netherlands to support the decision of surgical treatment in octogenarian and nonagenarian patients with cancer reported 30 day postoperative CRC mortality rates to increase from 8percent in patients aged 80-84 years, to 13percent in patients aged 85-89 years and to 20 percent in those over 90 years; thus concluding that surgery resection can be performed at an acceptable risk in the elderly with CRC (270).

CHAPTER 7 – COLORECTAL CANCER SURVIVAL AND TREATMENT SITES

7.1 Introduction

There is no evidence that attempts to assess the performance of the health care system in Jordan in relation to survival outcome for long treatment cases such as cancer. Despite the documented wide health coverage in Jordan, there remains a need to assess differences in the responsiveness and function of major health providers in association with treatment outcomes for serious and long-term illnesses such as cancer. While public health insurance (civil and RMS) is a crucial source of coverage for the majority of Jordanians, the KHCC and teaching hospital provide a safety net for many cancer patients across Jordan.

One of the objectives of this study was to examine the usage of treatment sites in association with survival probability of colorectal cancer patients by developing Hazard Ratios using the Cox Proportional Hazard Model. The study used a national population sample obtained from the JCR, which included all Jordanian patients diagnosed with first invasive primary colorectal cancer during the period 01 January 2003 through 31 December 2007. Data on the treatment site was collected by identifying the main source of medical services sought by the patient during the course of cancer treatment. Treatment sites were mainly categorized according to payment regimens, which is the main factor that is usually considered when describing the health care system in Jordan.

7.2 Survival probability of colorectal cancer by treatment site

The Kaplan-Meier method was used to determine the observed cumulative survival probability over time by calculating the proportion surviving after being diagnosed with colorectal cancer. Five year survival probabilities for colorectal, colon and rectum cancer were developed to compare the overall survival probability across the different treatment site categories.

Figures 24a, 24b and 24c show that there is a clear grouping between private; KHCC and others; and teaching and public. Patients who got treatment at private hospitals had better survival outcomes when compared to all the other treatment sites, followed by patients who got treatment at KHCC. However patients who received treatment at public or teaching hospitals had the lowest survival probability. Further stratification of data by cancer location showed that this relationship retained a statistically significant level for colon (Log-Rank test, P-value < 0.001) and for rectum (Log-Rank test, P-value < 0.001) cancer alike (Figure 24b and 24c).

Figure 24a: Observed survival probability of colorectal cancer cases by treatment site (2003-2007), Jordan

P-value < 0.0001

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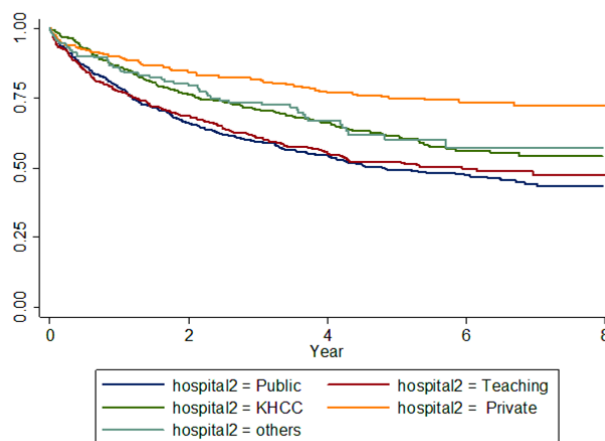
Figure 24b: Observed survival probability of colon cancer cases by treatment site (2003-2007), Jordan
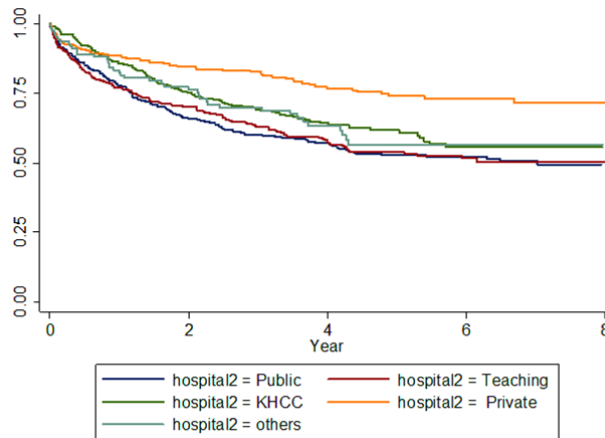
P-value < 0.0001

Figure 24c: Observed survival probability of rectum cancer cases by treatment site (2003-2007), Jordan
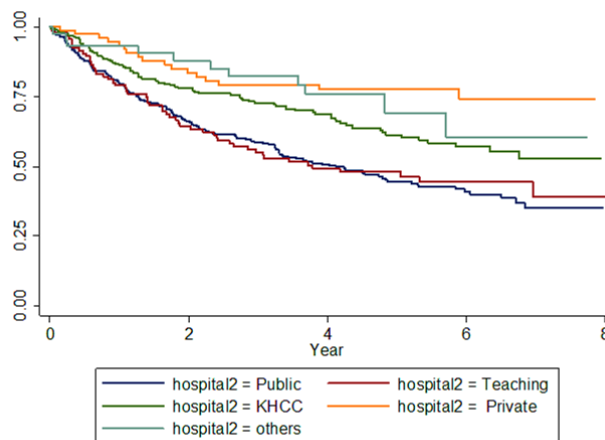
P-value < 0.0001

7.3 Hazard ratio for colorectal cancer survival and treatment site

Hazard ratios for colorectal survival by treatment site were calculated using the Cox proportional hazard model to adjust for age, extent of disease, place of residence, surgery, chemotherapy, radiotherapy and intent of treatment. Results showed that getting treatment at KHCC or getting the treatment at one of the private sector hospitals to be significant

independent predictors of survival in colorectal cancer. Correspondingly, patients who received treatment at KHCC (HR=0.63, 96percent CI: 0.52-0.76) or at private sector hospitals (HR=0.40, 96percent CI: 0.31-0.52) had a 37 percent and 60 percent lower risk of death compared with those who received the treatment at public sector hospitals (Table 33).

Table 33: Hazard ratios in colorectal cancer in treatment sites adjusted by Cox proportional hazard model

Site	Hazard ratio	[95 percent CI)	
		Upper limit	Lower limit
Public	1.00		
Teaching	0.82	.69	1.1
KHCC	0.63	0.52	0.76
Private	0.40	0.31	0.52
Others	0.57	0.42	0.78

*The model adjusted for age, sex, place of residence, extent of disease, grade, and morphology.

Table 34 shows results of cox proportional hazard models for each treatment site separately displaying unadjusted and adjusted hazard ratio for CRC patients by each treatment site. The overall unadjusted HRs for the selected variables showed that age, place of residence, extent of disease, morphology, and grade as significant predictors to CRC survival. However, sex and topography variables did not reach the level of significance.

For further exploration of the CRC cancer survival according to treatment sites, Cox Proportional Hazard modalities of the effect of selected characteristics on treatment sites were examined. In addition to age and sex as constant variables for each adjusted model, only significant predictors were included in each adjusted treatment site models (p-value ≤

0.2). The unadjusted HRs indicated that extent of disease were only strong significant predictors for CRC survival in all four adjusted treatment sites models. Morphology was a significant predictor for public, teaching, and KHCC hospitals but not the private ones. Moreover, age was a significant predictor for both public and teaching models only; indicating that CRC patients aged 65 year or older were 1.4 and 2 times more likely to die at these type of hospitals compared to those aged 65 year or less at each of the hospitals(HR=1.4, P-value ≤ 0.001); (HR=2.0, P-value ≤ 0.001) respectively.

For the adjusted HR model of private sector treatment site place of residency was a statistically significant predictor for CRC, where CRC patient who resided in the southern part of the country were 2.5 more likely to die compared to those who reside in the middle part of the country (HR=2.5, p-value = 0.012). However; sex and topography were insignificant predictors for all four models.

Table 34: Cox Proportional Hazard Models for death after colorectal cancer according to the effect of selected characteristics on treatment sites, Jordan (2003-2007)

Variable	Overall Unadjusted HR (95percent CI)	Public hospitals Unadjusted HR (P-value)	Adjusted HR (P-value)	Teaching hospitals Unadjusted HR (P-value)	Adjusted HR (P-value)	KHCC Unadjusted HR (P-value)	Adjusted HR (P-value)	Private hospitals Unadjusted HR (P-value)	Adjusted HR (P-value)
Sex									
Male	1	1	1	1	1	1	1	1	1
Female	0.91(0.79-1.1)	0.97 (0.809)	1.0 (0.780)	0.78 (0.129)	0.92 (0.625)	0.95 (0.774)	1.1 (0.473)	0.93 (0.783)	0.98 (0.954)
Age									
< 65y	1	1	1	1	1	1	1	1	1
>= 65 y	1.3(1.1-1.5)	1.1 (0.706)	1.4 (0.001)	1 .7 (0.001)	2.0 (0.001)	1.3 (0.120)	1.4 (0.080)	0.95 (0.840)	1.2 (0.491)
Place of residence									
Middle	1	1	1	1		1	1	1	1
North/South	1.1(1.0-1.4)	1.0 (0.756)	1.1 (0.176)	1.0 (0.860)		1.3 (0.163)	1.3 (0.195)	3.1 (0.001)	2.5 (0.012)
Extent of disease									
Localized	1	1	1	1	1	1	1	1	1
Regional	2.2 (1.5-3.1)	1.6 (0.044)	2.2 (0.001)	3.2 (0.022)	3.1 (0.031)	2.6 (0.039)	2.7 (0.030)	4.9 (0.008)	5.6 (0.005)
Distant metastasis	8.4 (5.9-11.9)	6.1 (0.001)	8.1 (0.001)	11.3 (0.001)	12.7 (0.001)	12.3 (0.001)	13.1 (0.001)	19.4 (0.001)	17.7 (0.001)
Topography									
Colon	1	1	1	1		1		1	
Rectum	1.1 (0.92-1.2)	1.2 (0.097)	1.1 (0.261)	1.2 (0.288)		0.94 (0.689)		0.86 (0.616)	
Grade									
Well	1	1	1	1	1	1		1	1
Moderate	1.3 (.93-1.8)	1.4 (0.194)	1.1 (0.561)	1.4 (0.386)	1.2 (0.685)	0.66 (0.296)		2.6 (0.186)	1.9 (0.375)
Poor/ anaplastic	1.9 (1.4-2.8)	1.9 (0.020)	1.4 (0.095)	1.7 (0.162)	1.3 (0.443)	1.4 (0.391)		4.1 (0.057)	2.6 (0.206)
Morphology									
Adenocarcinoma	1	1	1	1	1	1	1	1	
Mucinous	1.4 (1.1- 1.8)	1.4 (0.096)	1.4 (0.013)	1.2 (0.579)	1.3 (0.386)	1.7 (0.030)	1.8 (0.025)	1.5 (0.304)	
NOS/others	0.93(0.70- 1.2)	0.79 (0.359)	0.77 (0.096)	0.62 (0.003)	0.32 (0.002)	1.3 (0.450)	2.1 (0.045)	0.91 (0.838)	

7.4 Summary and Discussion

This chapter discussed the findings in relation to treatment site usage, survival probability by treatment site and hazard ratios (using the Cox model) associated with treatment sites. The study revealed that in terms of treatment sites (i.e. hospitals), 32.4 percent of cases were treated at public health facilities; 23.42 percent were treated at KHCC; 18.4 percent were treated at teaching hospitals; and 16.82 percent were treated at private health facilities. After adjusting for age, extent of disease, place of residence, surgery, chemotherapy, radiotherapy and intent of treatment, the Cox proportional hazard model showed that getting treatment at KHCC or at one of the private sector hospitals was a significant independent predictor of survival in colorectal cancer. Patients who received CRC treatment at KHCC or at private sector hospitals had a lower risk of death compared with those who received the treatment at public sector hospitals.

In conclusion, survival in public hospitals is less than half that in private hospitals in Jordan after adjustment for several main casemix variables. The public health impacts of such differences are very large and the explanations therefore need to be understood.

Health care system

Jordan's health care system is a complex amalgam of three major sectors: public, private and donors. Patients receive treatment according to their type of health insurance, noting that about 79 percent of the population in Jordan is covered by formal civil health insurance. Moreover, MOH is the largest health insurer (34 percent) followed by RMS (26 percent), private firms (9 percent), and university hospitals (1.3 percent) (49). Individuals certified as poor, the disabled, children below the age of six years and blood donors,

pregnant women and elderly above 60 are also formally treated in the public health sector (MOH and RMS). However, private hospitals and non-profit centres cover individuals who are able to pay the cost of treatment out of pocket or who have private insurance. Colorectal survival is very much dependent on socioeconomic status and differences between treatment sites might reflect this as a result of selection bias (62). Moreover, there is a belief that hospitals could be more efficiently operated and quality of patient care enhanced if autonomy was granted to them (236). In addition, Amman, as the capital, attracts the majority of investments, including healthcare; thus, most of the private hospitals are mainly located in Amman.

What can be observed is that hospitals (like KHCC) that focus specifically on cancer treatment combined with an institutional goal of continuous improvement to quality of healthcare might be able to achieve better performance results than public hospitals. Results of this study present evidence and hence an opportunity for the public health sector to invest in aspects of health-care management, quality and infrastructure in an attempt to impact the outcome of cancer.

Jordan was ranked by the World Bank to be the number one health care service provider in the region and among the top five in the world, as well as being the top medical tourism destination in the Middle East and North Africa (26). In 2007, total health expenditures – both public and private was estimated at 1.016 million JD, or 177.5 JD per capita (253 US dollars). This is equivalent to 9.05 percent of GDP which is comparable to figures of some developing countries and considered among the highest in the Middle East and North Africa (MENA) region. The government share in the financing of health expenditures has increased from 43 percent in 1998 to 57 percent in 2008 (46;236).

Curative care, in Jordan like many other developing countries, takes up a disproportionately large share of public spending on health. During the period 1998-2007, the share of curative care increased. Expenditure on curative care was about 79 to 82 percent of the total state health expenditure, while the proportion spent on primary health care was less than 20 percent (23;25;46). Overall spending has increased in nominal terms over the past six years and has grown slightly more rapidly than GDP. Nevertheless, Jordan's health care spending, whether measured in per capita U.S. dollar terms or as a share of GDP, is high compared to other countries of the MENA region and compared to other middle-income countries (2).

About 79 percent of the population in Jordan is covered by formal health insurance. In addition to its general public health functions, the MOH is responsible for administering the CHIP that covers civil servants and their dependents. Individuals certified as poor, the disabled, children below the age of six years, and blood donors, pregnant women and the elderly (above 60 years of age) are also formally covered under the CHIP. In addition, some costly diseases, including cancer and its side effects, are also insured according to special regulations determined by the Health Insurance bylaw (46;49) . All of these aforementioned factors have contributed to the good survival estimates of colorectal cancer in Jordan.

A major influence on quality in healthcare performance (particularly in recent years) has been the goal of maintaining Jordan's competitiveness as a destination in the international medical tourism industry. This has had a spillover effect on healthcare performance

characteristics, especially in the private sector hospitals that seek to compete internationally based on 'price advantage' while offering equivalent medical standards and patient support services that could be expected in North America and Europe.

After adjusting for age, extent of disease, place of residence, surgery, chemotherapy, radiotherapy and intent of treatment, the Cox proportional hazard model showed that getting treatment at KHCC or at one of the private sector hospitals was a significant independent predictor of survival in colorectal cancer. Patients who received treatment at KHCC or at private sector hospitals had a lower risk of death compared with those who received the treatment at public sector hospitals.

Aspects of health-care

Although without a comprehensive assessment of the underlying factors that might be related to the disparities in survival of colorectal cancer among types of treatment sites, it is possible to set forth explanations or assumptions for the results based on best available information. Therefore, the following interpretations are presented to support the variations in CRC survival in association with treatment sites presented in this study.

Health-care Management

In a study that aimed at exploring the different aspects of short and long term CRC survival in Denmark, delay for rectum cancer treatment, and emergency post-operative complications were reported as strong independent risk factors for death (271). Although specific information related to treatment regimens and facility features, provider delay ≥ 60

days, hospital delays $\geq$ 30 days or $\geq$ 60 days cannot be addressed in the present study, some elements related to health-care management can be noted as possible factors that might generally influence the outcome of long-term illnesses.

Consequently, private hospitals and KHCC utilize treatment protocols that conform with international standards; the public hospitals do not (necessarily) utilize international standards. In addition, treatment at KHCC and private hospitals is based on a team approach. For example, KHCC utilizes a team of health providers that is comprised of "board certified oncologists, surgeons, radiologists, radiation oncologists, pathologists, nurses, and ancillary service providers that work together to treat and follow up every case from start to finish" (237).

Not only have the private hospitals and KHCC looked to North American and European treatment standards, they have hired medical staff (including not only doctors, but nurses and other support staff) with qualifications from western countries (i.e. specifically North America and Europe). Moreover, the role of continuing professional education for physicians and other staff has also played a strong role in improved performance in the private sector and KHCC with access to training that provides the staff with the most up-to-date methods of treatment.

Recently the private hospitals in Jordan adopted a new team approach in cancer care management by establishing multimodality clinics in which a treatment plan is identified for each cancer patient where a group of no fewer than three specialists are engaged. Each clinic includes a medical oncologist, a surgical oncologist and a radiation oncologist, in

addition to other specialized physicians needed for particular treatments. Recognizing that prevention is the best medicine, lately three awareness clinics were established: the Diet Clinic, the Lifestyle Clinic and the Stop-Smoking Clinic. In addition, screening clinics have been established for different types of cancer (colorectal, breast, cervical, prostate, testicular, and skin). Moreover, these private hospitals offer psychological counselling, patient support, education of families of cancer patients, and after-therapy care in addition to the specific cancer treatment.

A culture of Quality

Quality of care allows different countries to compare performance of their health care system (196;272). The literature provides evidence on the relation of quality of care and the relative survival of cancer. For example inequalities in access to and receipt of quality health care were reported as possible associates to disparities in cancer survival between African and White Americans (273).

In Jordan, a strong culture of quality prevails in the healthcare sector with a greater emphasis and attention on quality aspects in the private sector. For example, 11 hospitals have been accredited by the Joint Commission International (JCI); 12 hospitals have been accredited by the Health Care Accreditation Council (HCAC) in cooperation with ISQua; five of these hospitals have both accreditations. In addition, there is a national award for quality (the King Abdullah II Award for Excellence) for which both private and public hospitals can compete; one of the private hospitals has won the award two years in a row.

The influence of accreditation and the possibilities for twinning also enhance the performance of an institution. While twinned projects are usually formed between a facility in a lesser developed country and one in a more developed region (such as North America or Europe), KHCC provides an example of how that dynamic can be reversed: In January 2011, KHCC "entered a partnership and twinning deal with the Hassan II University Hospital in Fes, Morocco, to increase the level of care offered to patients…the agreement…involves staff training, capacity building and experience sharing, specifically in the segment of quality assurance and hospital accreditation. The Hassan II Hospital is initiating the process of securing accreditation as a general hospital from the Joint Commission International" (272).

Investment in infrastructure

Differences in levels of institutional investment contribute to improved performance in the private sector compared with the public, as well. For example: Private hospitals have greater availability for appointments and surgeries as they carry an overall lower patient load than in the public hospitals. There is less frequent patient follow up in public hospitals with longer intervals between appointments; there is also less availability of all diagnostic equipment (such as CT scan and MRI) in public hospitals, making patient follow up more difficult.

Even such basic requirements as well-maintained patient records systems may be affected by whether or not an institution has had the resources to invest in computerization. Financial considerations influence the ability of an institution to provide proper recordkeeping, but standards of quality and performance contribute, as well. The private

hospitals that are accredited have committed themselves to maintaining specific standards of process performance that have been proven to be more efficient and robust in a variety of treatment sites across the world; simply following those commitments leads to better quality of care, as well.

In 2007, KHCC became the first hospital outside the U.S. to be JCI-accredited as a cancer centre. During the intervening years, KHCC has introduced more and varied auxillary services while continuing to strive for improved process performance. Some examples: Thirty-plus professionals providing psychosocial services for inpatients, outpatients, family members and healthcare staff; pain management centre for adults based on pain nurse-anaesthesia supervised concept; a paediatric pain management team that includes a paediatric haematologist/oncologist, a general paediatrician and a nurse coordinator; a variety of support groups based on various cancer types and follow-up needs; and spiritual care for both Moslems and Christians. In addition, KHCC assists Jordanian patients to petition the Royal Court for financial assistance when patients do not have insurance or for services not covered by insurance. While none of these examples is likely to independently influence survival rates, taken altogether they show that private sector hospitals are more likely to comprehensively care for cancer patients.

Optimizing insurance coverage

Although issues related to health insurance coverage are not clinical issues, they are important dimensions that need to be considered because they might affect cancer survival rates (197;199;201). Consequently, a plausible question that is worth considering when exploring the survival discrepancies between the different treatment sites is whether

patients are getting maximum potential services from their CHIP and the Health Insurance bylaw. In addition, assessing coverage gaps in the CHIP that is provided to the majority of the Jordanian population and the type of health provision provided to the elderly and to those patients living in more rural areas (particularly in the south of Jordan) are essential aspects to note.

Eminently, KHCC offers a variety of payment/financing assistance including, as a last resort, advocating on the patient's behalf for assistance from the Royal Court. This suggests that some Jordanian patients might not have health insurance or that the CHIP doesn't fully cover all areas of care. In most cases, patients who have no insurance are treated at KHCC within a specific programme that assists them in getting financial assistance to cover their treatment.

CHAPTER 8 – COLORECTAL CANCER SURVIVAL AND DIABETES MELLITUS

8.1 Introduction

Recently, the International Diabetes Federation (IDF) estimated as many as 183 million people worldwide, or half of those who have diabetes, to be unaware of their condition (274). In 'middle income' MENA countries, the percentage of undiagnosed diabetics increases to 61.6 percent of the total number of diabetes cases (274). In the last two decades, diagnosed cases of diabetes mellitus in Jordan increased by three folds; from 6.8 percent in 1996 to 19.5 percent in 2007. Moreover, published figures denote an estimated 12 percent of Jordan's population to have impaired fasting glucose (3;125). In addition, crude population projection estimates suggest that approximately one to three million individuals in Jordan will have diabetes by 2050 depending on changes in disease prevalence and the growth of the population (45).

One of the aims of this study was to explore the effect of diabetes mellitus (one of the most prevalent comorbidities in Jordan) on colorectal cancer survival among Jordanians. This chapter examines the survival probability for colorectal cancer among patients with history of diabetes and the different correlates affecting this association.

8.2 Survival probability of colorectal cancer by diabetes mellitus

As an important comorbidity, information collected from the medical records of each patient on the history status of diabetes was carried out in order to study its relationship with colorectal cancer survival. The study population was divided into two groups based on the history status of diabetes (diabetic and non-diabetic).

The Kaplan-Meier method was used to determine the observed cumulative survival probability over time by calculating the proportion surviving after being diagnosed with colorectal cancer. Five year prognostic probabilities for colorectal, colon and rectum cancer were developed to compare the survival relationships between patients with diabetes and no diabetes. According to hospital medical records, 306 CRC patients were detected as diagnosed diabetic patients, which consisted of 16.2 percent of the study population.

Table 35 summarizes the baseline characteristics of colon patients categorized according to presence of diabetes. Only colon cancer cases are presented because based on the logrank test the relationship between colon cancer and diabetes was found significant, and thus worth further exploration. Compared to patients without pre-existing diabetes, patients with diabetes were significantly older. Significant differences were reported for extent of disease and predictors of undergoing surgery between the two groups. However, there were no significant differences with regard to sex, morphology, histology grade, chemotherapy and radiotherapy.

Table 35: Baseline characteristics of patients with colon cancer according to diabetic status Jordan, (2003-2007)			
Variable	Diabetes (percent) (n= 306)	No diabetes (percent) (n= 593)	P-value
Sex			
Male	159 (51.9)	239 (56.5)	0.157
Female	147 (49.3)	184 (43.5)	
Age			
15-44	9 (4.1)	131 (30.9)	0.000
45-59	72 (32.29)	122 (28.8)	
60-74	109 (48.8)	142 (33.7)	
≥75	33 (14.80)	28 (6.6)	
Extent of disease			
Localized	30 (14.2)	31 (7.7)	0.036
Regional	133 (62.7)	269 (66.4)	
Distant	49 (23.1)	105 (25.9)	
Morphology			
Adenocarcinoma	188 (85.1)	344 (81.9)	0.249
Mucinous and serous	14 (6.3)	42 (10.0)	
Neoplasm, NOS	14 (6.3)	19 (4.5)	
Others	6(2.3)	15 (3.6)	
Grade			
Well	13 (6.8)	30 (8.1)	0.304
Moderate	149 (78.4)	269 (72.5)	
Poor/ anaplastic	28 (14.7)	72 (19.4)	
Surgery			
Yes	158 (70.9)	345 (81.6)	0.002
No	65 (29.2)	78 (18.4)	
Chemotherapy			
Yes	91 (85.1)	246 (91.4)	0.066
No	16 (14.9)	23 (8.6)	
Radiotherapy			
Yes	17 (7.6)	44 (10.4)	0.251
No	206 (92.4)	379 (89.6)	

Using Kaplan-Meier survival analysis, the relation between colorectal cancer survival estimates and diabetes mellitus patients was explored using the Log-Rank test (Figure

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25a). It was found that the mean survival for colorectal cancer patients with diabetes mellitus was significantly lower than that for patients without diabetes (Log-Rank test, p=0.0359). By further stratification, it was found that this relation was statistically significant for colon (Log-Rank test, P-value 0.0262) as seen in Figure 25b, but not for rectum (Log-Rank test, P-value 0.6337) cancer as shown in Figure 25c.

Figure 25a: Observed survival probability of colorectal cancer cases by diabetes mellitus status, (2003-2007), Jordan
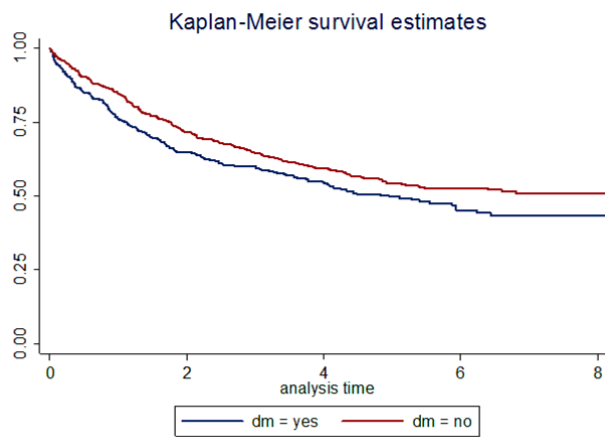
(P-value 0.0359)

Figure 25b: Observed survival probability of colon cancer cases by diabetes mellitus status, (2003-2007), Jordan
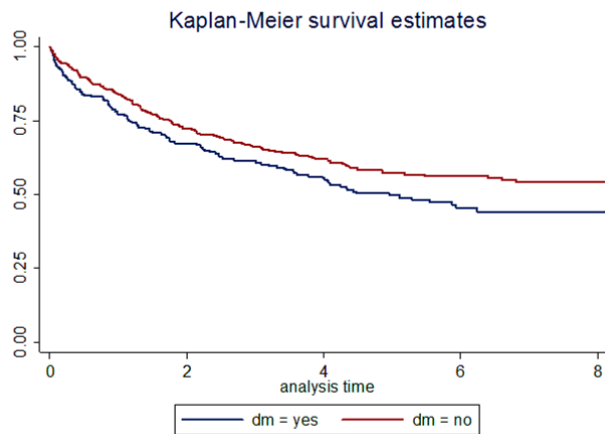
(P-value 0.0262)

Figure 25c: Observed survival probability of rectum cancer cases by diabetes mellitus status, (2003-2007), Jordan

Kaplan-Meier survival estimates
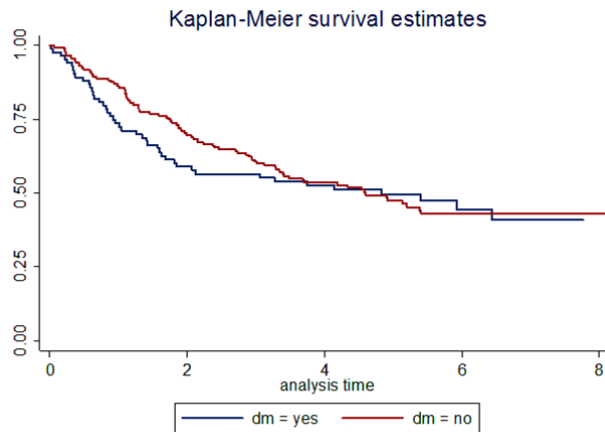
(P-value 0.6337)

When examining the extent of the disease, diabetic patients with a regional extent of the disease were found to have a significantly lower survival time than non-diabetics (Log-Rank test, P-value 0.0093) (Figure 26b). No significant differences in survival time were found in relation to diabetes when examining localized (Figure 26a) and metastatic extent of the disease (Figure 26c).

Figure 26a: Observed survival probability of colon cancer cases by localized extent of the disease, (2003-2007) Jordan

Kaplan-Meier survival estimates

(P-value 0.1511)

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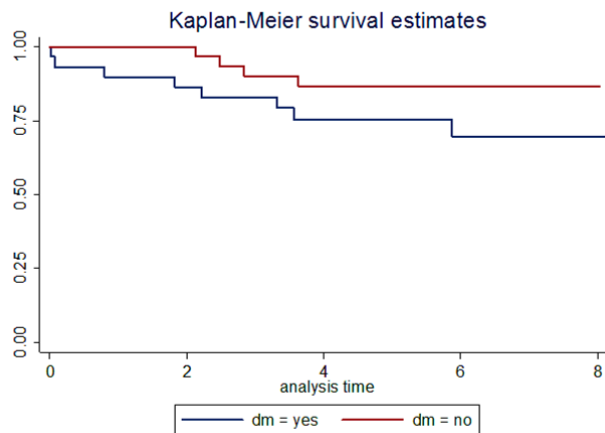
Figure 26b: Observed survival probability of colon cancer cases by regional extent of the disease (2003-2007), Jordan
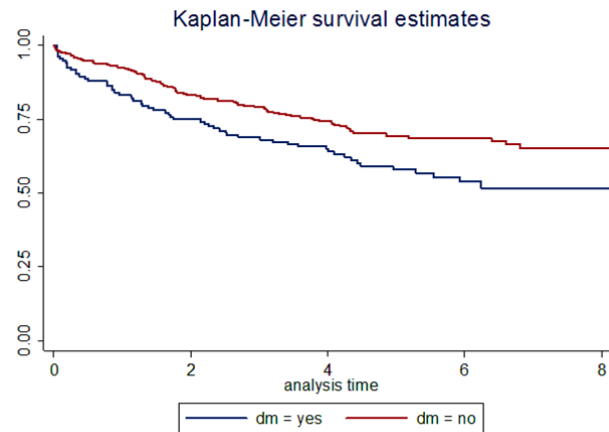
(P-value 0.0093)

Figure 26c: Observed survival probability of colon cancer cases by metastasis extent of the disease (2003-2007), Jordan
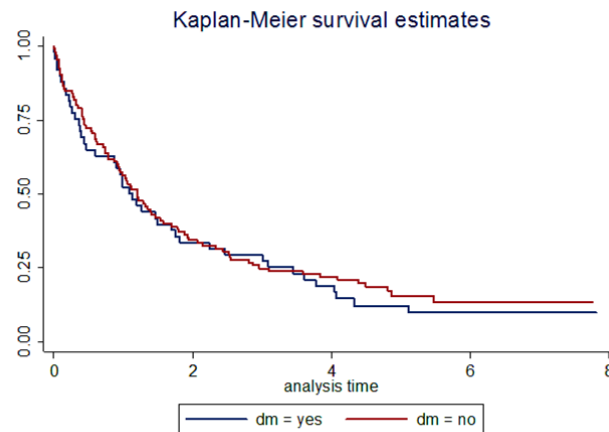
(P-value 0.5598)

8.3 Hazard Ratio for colorectal cancer survival and diabetes mellitus

The status of diabetes was examined in relation to the correlates of age, sex, clinical characteristics (e.g. morphology, grade, and extent of disease) and tumour treatment. Hazard ratios were calculated using the Cox Logistic regression model for diabetes, sex, age, year of diagnosis, extent of disease, morphology, grade, surgery, chemotherapy, and radiotherapy. These ratios were first estimated as crude using a univariate analysis to identify the potentially important prognostic variables-effect of different predictors on

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survival rate (e.g. age, sex, stage, site, grade and type of treatment), followed by a multivariate analysis to identify the prognostic factors for predicting observed survival for colorectal cancer in relation to diabetes. Only significant variables from the univariate analysis were included in the multivariate analysis. Table 36 summarizes the univariate and multivariate analysis of prognostic factors predicting observed survival.

Diabetes mellitus was identified as a predictor associated with lower observed survival in multivariate analysis, where diabetic patients were one and one-half times more likely to be at risk of death compared to non-diabetic patients. Age group 75 years or older, regional and distant metastasis of disease were shown to be independent prognostic factors for observed survival in multivariate analysis.

Table 36: Prognostic factors for observed survival in patients with colon cancer and diabetes mellitus (n=899) according to univariate and multivariate analysis

Variable	Univariate analysis			Multivariate analysis		
	HR	95perc	P–	HR	95perc	P–
Diabetes Mellitus						
No	1		0.0285	1		
Yes	1.3	1.1-1.6		1.5	1.1-1.9	0.011*
Sex				---------	---------	---------
Male	1		0.8857	---------	---------	---------
Female	1.1	.81- 1.3		---------	---------	---------
Age						
15-44	1		0.0424	1		
45-59	.94	.67-1.3		.92	.63- 1.3	0.688
60-74	.91	.66- 1.3		.82	.57-1.2	0.328
≥75	1.6	1.1-2.3		2.1	1.3-3.4	0.002*
Year of diagnosis	1.03	.94-1.1	0.5662	---------	---------	---------
Extent of disease			0.0000			
Localized	1			1		
Regional	1.9	1.1-3.5		2.2	1.2-4.2	0.017*
Distant	8.9	4.9-		11.3	5.7-	0.000*
Morphology				---------	---------	---------
Adenocarcinoma	1		0.3264	---------	---------	---------
Mucinous / serous/	1.2	.86-1.5		---------	---------	---------
Grade			0.0062			
Well	1			1		
Moderate	1.8	1.1-3.4		1.6	.88-3.0	0.116
Poor/ anaplastic	2.5	1.3-4.9		1.4	.76-2.8	0.239
Surgery						
No	2.1	1.6-2.7	0.0000	.77	.55-1.2	0.122
Yes	1			1		
Chemotherapy						
No	1.5	.88-1.5	0.0982			
Yes	1					
Radiotherapy			0.8893			
No	.97	.67- 1.4				
Yes	1					

NOTE: only significant variables in univariate analysis were entered into the multivariate analysis

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8.4 Summary and Discussion

The relationship between survival from colorectal cancer and diabetes mellitus was examined by analysing the data on 306 diabetic patients out of the total study population of 899. Analysis was done with respect to age, sex, clinical characteristics (e.g. morphology, grade, and extent of disease) and tumour treatment. Prognostic probabilities were compared with various patient characteristics and clinical characteristics as well.

Diabetes mellitus was identified as a predictor associated with lower observed survival time for colon cancer in multivariate analysis, where diabetic patients were one and one-half times more likely to be at risk of death compared to non-diabetic patients. In addition to diabetes, being 75 years of age or older and/or having regional and distant metastasis of disease were shown in multivariate analysis to be independent prognostic factors for observed survival.

The study results for Jordan were not very different from those of other countries (187-189; 191; 192; 194). However, due to the anticipated increase of the diabetic population over the next few decades, the need to examine the association between diabetes and CRC survival in light of other predictors poses as a priority area that needs to be addressed in the future.

The positive association observed in this study was consistent with similar studies done in other countries (116-119; 122). However, there is insufficient evidence to largely support the association between diabetes and colon cancer survival probability in Jordan. Additional follow up and larger scale studies need to be implemented in Jordan in order to

depict the association of diabetes with the prognostic probability of colon cancer. Such studies present a priority in light of the escalating prevalence of diabetes in Jordan.

It is expected that Jordan's undiagnosed diabetic population is as numerous as the diagnosed group. In other words, for each new case of colorectal cancer, there is a strong possibility that the patient already has diabetes. Detection and treatment protocols urgently need to be adjusted for this potential reality.

Although the literature strongly supports the association between diabetes and an increased risk of colorectal cancer (116-119; 122; 187-189; 191; 192; 194), such evidence remains non-existent in the Eastern Mediterranean Region, including in Jordan. Therefore, this study comes as one of the first attempts to explore the relationship between diabetes and the prognostic survival of colorectal cancer in Jordan, where results showed a lower 5-year survival probability for colorectal cancer patients who have diabetes than for non-diabetics (Log-Rank test, p=0.0359).

These findings are consistent with results of a study done in China where diabetic patients were found to have significantly lower 5-year survival rate when compared to the non-diabetics (275). Similarly, several meta-analysis reports support the notion that diabetes is positively associated with increased colorectal cancer outcome and mortality (116-118;121;123;276-278). The findings are also uniform with the results of a recent large population-based controlled cohort study done in Taiwan on a total of 37,001 diabetic patients and 148,004 controls, where diabetes was reported to increase the risk of colorectal cancer (279).

A focus on colon cancer

Even though studies investigating the association of diabetes and the outcome of colon cancer are not available in Jordan, global evidence on the prognostic survival (outcome) of colon cancer in association with diabetes remains controversial, especially when examining the relationship between diabetes and the outcome in relation to the extent of disease and other important independent predictors.

Results of the stratified analysis for colorectal cancer data and diabetes in this study revealed a statistically significant association between diabetes and prognostic survival of colon cancer (Log-Rank test, p=0.0262) compared to non-diabetics. Cox multivariate regression analysis showed that diabetic patients with colon cancer have one and one-half times the likelihood of mortality than non-diabetic patients. These findings suggested a decreased 5-year survival risk among diabetic patients with colon cancer (HR=1.5, 95% CI: 1.1-1.9) in Jordan, which were found to be consistent with results of a studies done in Taiwan and China, which reported a negative prognostic impact of diabetes on the overall survival in patients with colon cancer (120;122).

Age and extent of disease as main predictors to colon cancer

The present results are also in agreement with the findings of a large prospective multi-ethnic cohort study done in Los Angeles County on a five racial/ethnic populations (European, American, African American, Native Hawaiians, Japanese Americans and Latinos). The study reported diabetes as a significant factor associated with colorectal

cancer in all ethnic groups except among Native Hawaiians and African Americans with a significantly increased risk for colon cancer compared to a non-significant overall positive association for rectum cancer (280).

The results of this study are also supported by results of a cohort study of 256,036 diabetic patients done in Taiwan to study the age and sex-specific mortality rates in diabetic patients and their mortality rate ratios compared to the general population. The study reported a significantly higher risk of mortality from colon cancer for the diabetic patients compared to the general population, with the magnitude increasing with the decrease of age (281). Results of the multivariate Cox Regression for this study found that the risk of predicting survival among diabetic patients to be higher among patients who were 75 years or older (HR=2.1, 96% CI = 1.3-3.4), and/or having regional (HR=2.2, 96% CI = 1.2-4.2) or distant (HR=11.3, 96% CI = 5.7-22.3) metastasis of the disease. Among the few studies that were found to investigate similar associations was a retrospective multi-ethnic cohort study which reported significant increases in the risk of both regional and distant cancer with no differences between males and females (280).

CHAPTER 9 – SUMMARY AND RECOMMENDATION

This section includes is the major hub of this study because it explores study implications for practice as well as recommendations for further research in the area of colorectal cancer. Recommendations presented in this chapter are mainly built around the results of this study.

9.1 Study overview

CRC is a common form of cancer that is receiving great interest especially when it comes to identifying its associated risk factors. The literature provides supporting evidence for the need to concentrate on treatment and early recognition of CRC in order to improve its overall survival. Improved population coverage by preventive programmes, such as organized screening programmes, can result in a decrease or even stabilization in CRC incidence rate. This study provides evidence that can benefit CRC mortality in Jordan, while taking into consideration other variables of interests, such as socio-demographic, clinical and treatment characteristics and diabetes mellitus as an important comorbidity.

This study is a population-based survival study of colorectal cancer in Jordan. The study population consisted of 1,896 patients diagnosed during the period 2003 through 2007. The study aimed to: 1) produce estimates of observed and relative survivals for Jordanian CRC patients; 2) compare colorectal cancer survival among Jordanian patients with other comparable countries; and 3) explain possible differences. The study investigated the possible effects of socio-demographic patient status, the clinical manifestations and treatment of the tumour on survival of CRC in Jordan.

The study was carried out at the national level by investigating data from the JCR, Jordan CRB, hospitals and laboratories - both governmental and non-governmental sectors in Jordan. The sample consisted of all Jordanian CRC patients (aged 15 years and above) who were diagnosed with invasive primary CRC (C18-C20.9) during the period of 01 January 2003 through 31 December 2007 and registered in the JCR with verified histopathology report. To the best of the investigator's knowledge, this study represents the first attempt to examine and study colorectal cancer survival data of the Jordanian population.

9.2 Addressing the research questions

The study focused on six research questions introduced in Section 1.4.1 as the following:

RQ1: *What are the observed and relative 5-year survival rates of colorectal cancer among Jordanian patients diagnosed in 2003-2007?*

RQ2: *Do survival rates from colorectal cancer differ between Jordan and other comparable countries, and if so, how can this be explained?*

RQ3: *Do socio-demographic characteristics (e.g. age, sex, and place of residency) affect the survival rate of colorectal cancer in Jordan?*

RQ4: *Do the patient clinical manifestations (site, histopathology, grade, stage) and treatment of the tumour affect the survival rate of colorectal cancer in Jordan?*

RQ5: *Are there differences of colorectal cancer survival estimates across treatment sites within Jordan and how could they be explained?*

RQ6: *Does diabetes mellitus affect the survival of colorectal cancer among Jordanian patients?*

Answers to the research questions are presented and discussed in the summary of the main findings under chapters 4 through 9 of this document.

9.3 Summary of the main findings

The study consisted of a total of 1,896 study participants with 62.4 percent of colon cancer and 37.6 percent of rectum cancer cases. While half of the sample (50.5 percent) was aged 60 years and above, 55.5 percent were males and 75.9 percent was living in the central region of Jordan. By the end of the five year study period, 40.3 percent of the study participants had died with more deaths occurring among the male population 442 (57.9 percent).

Incidence rates were calculated using data from newly diagnosed CRC patients aged 15 years through 74 years (1,704 cases). The 5-year overall crude CRC incidence rate was 5.6 per 100,000 males and 5.1 per 100,000 females. Further examination of the crude incidence rates revealed higher colon and rectum cancer incidence rates among males (colon cancer: 5.4 per 100,000 males and 4.1 per 100,000 females, rectum cancer: 3.0 per 100.1000 males and 2.4 per 100,000 females). The overall colorectal ASR was higher among males with a male/female ratio of 1.2:1 (15.5 per 100,000 males and 12.5 per 100,000 females).

The 5-year observed and relative survival rates of colorectal cancer were 57.7 percent, and 61.3 percent respectively. The 5-year observed survival rates for colon and rectum cancers were 59.1 percent and 55.4 percent respectively, the corresponding relative survival rates were 63.2 percent and 58.3 percent respectively. The age-standardized relative survival

rate for the overall cases of colorectal cancer at 5 years of diagnosis was 58.1 percent. It was slightly better for rectum (59.2 percent) compared with (57.8 percent) colon.

This study revealed that age, place of residence, extent of disease, and morphology had significant effects on the colorectal cancer survival estimates: the oldest age group had worse survival estimates compared with the younger age groups; the highest survival estimates were obtained for patients living in the middle of the country compared with those living in the north and the south; and poorer survival rates are associated with distant and regional tumours compared with localized tumours.

Survival was significantly higher for patients who underwent surgery than for those patients who did not. Although not of significant value, patients who received chemotherapy treatment had better survival for almost the first four years; later, though, patients who didn't receive chemotherapy treatment had better survival. Similarly, colon cancer patients who received chemotherapy treatment had better survival rates for nearly four years afterward; but beyond that time, those patients who didn't receive chemotherapy treatment had a slightly better survival. Alternatively, rectum cancer patients who received chemotherapy had better survival rates for the first two years; but after that time those patients who didn't receive chemotherapy had higher survival rates.

In terms of treatment sites (hospitals), results showed that 32.4 percent of cases were treated at public health facilities, 23.4 percent at King Hussein Cancer Center (KHCC), 18.4 percent at the teaching hospitals, 16.8 percent at the private health facilities, and only 9.1 percent at other sites. The results of Cox proportional hazards ratios, after adjusting for

age, sex, place of residence, extent of disease, topography, morphology, and grade have shown that patients who received treatment in private hospitals as well as in the King Hussein Cancer Center, had better survival rates compared with those who received their treatment in the public sector.

Finally, this study revealed a significant relationship between diabetes mellitus and colon cancer survival; diabetic patients with colon cancer were less likely to survive compared to non-diabetic patients with colon cancer. However, no significant association was observed regarding diabetic patients with rectum cancer. On the other hand, this study did not report significant relationships between CRC and sex, topography, grade and radiotherapy treatment.

9.4 Strengths and limitations

As with any other research, this study comes with strengths and limitations that need to be set forth in order to provide an advantage to other investigators.

9.4.1 Strengths and challenges

The following list of strengths is presented to optimize the study results and project the main advantages believed to prompt prominence to benefiting from the survival analysis of colorectal cancer undertaken in this study.

- *Study significance:* Results of this study hold important significance because it is the first colorectal cancer survival study done to estimate survival rates among colorectal

cancer patients in Jordan and compare these estimates with similar ones in other populations. The study instrument was designed to gather information on socio-demographic characteristics, clinical and histo-pathological information, treatment, co-morbidities and information about patients' vital status. Therefore the study holds prominence because it allowed for examining the relationship between colorectal cancer survival estimates and various potential predictors.

–   *Study methodology:* The study was carried out at the national level using a relatively large sample (1,896) that allowed examination of subgroups among the Jordanian population. In addition to using the routine JCR population-based data base, active strategies were utilized for collecting more clinical information on treatment, and diabetes mellitus as an example of co-morbidity and the site of receiving health care services, thus enabling review of hospital records and pathological laboratory reports at the national level. Furthermore, the five year study period is relatively a suitable follow up period that allowed for the detection of any plausible survival trends in the population of interest.

–   *Statistical analysis:* In this study, advanced statistical principles were employed along with advanced methods and applications of cancer survival using population-based data. The investigator took into account several statistical methodological issues in order to minimize bias and allow for comparisons when interpreting survival functions. More explicitly, the investigator used different statistical methods, such as calculating relative survival rates, age standardized survival rates and Cox ratios in order to control for variables that might have had an effect on the survival rates. This allowed for the

control of confounding variables thus allowing for causal inference to ascertain that the observed differences in survival were of a real causal effect rather than due to differences in the nature of the groups that were being compared. Moreover, special precautions were taken into account when interpreting survival data by referring to the particular statistical method that was used.

- *Case ascertainment:* Using the JCR data base for case ascertainment/recruitment allowed for a nearly comprehensive inclusion of patients diagnosed with colorectal cancer during the five year study period in Jordan. Furthermore, verified by histopathology reports, the JCR was used to ascertain cases that had colon or rectum cancer as the primary diagnosis of cancer. Matching the national ID number of recruited cases to vital records mortality information at the Civil Registration Bureau data base enabled accurate and complete ascertaining of death information due to the reliability and completeness of vital recording at the Bureau. In addition, actively collecting information from medical records and pathological laboratory reports at hospitals was an appropriate strategy utilized to compensate for missing clinical information at the JCR (such as the site, stage and grade of the cancer). In many hospitals the data related to patient treatment was available and medical records were found to be good resources to complete the missing information gap at the JCR.

9.4.2 Limitations

The following list of limitations is presented in order to outline confinements and constraints for other researchers who are keen at undertaking similar studies. The list includes bias that might have influenced the estimates, and hence the validity of

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comparisons among groups. These limitations are by no means exhaustive and are presented in order of importance.

- *Complete Approach for estimating survival:* In this study, the estimate of patient survival was made using the complete approach. This approach allows for inclusion of all patients in the study period (2003-2007). Besides including patients diagnosed more than five years ago the approach also allows for including recently diagnosed patients, even though they were not followed for five years. Although the complete approach is more up-to date than the cohort approach estimates, it remains subject to influence by survival estimates of patients who were diagnosed in the preceding years. In particular, it usually underestimates the relative survival ratio (213;214;241).

- *Record keeping:* Jordan, as many other developing countries, still suffers from inadequate clinical follow-up systems in hospitals and an absence of computerized patient records' systems. Most of the hospitals do not apply ICD coding; data is not standardized and most of the time hospitals do not provide timely patient discharge summaries. For example, during the data collection phase, it was noted that the hospitals and pathology laboratories collect the stage of the colorectal cancer information using Duke's or TNM systems; however the JCR uses the SEER Summary Staging approach. In addition, most of the hospitals do not have written policies and procedures for medical records upkeep, and do not conduct periodic quality reviews for accuracy and completeness of information. Even though, reviewing individual medical records was very beneficial to figure out the type of treatment the patient received as well as to fill the gap of missing information from the JCR, the quality of recording and maintaining updated information was found to be inadequate. Moreover, using

routinely collected data such as that of the JCR introduces an error effect especially when data quality monitoring measures are lacking.

– *Death certificate registration:* The proportion with microscopic verification, autopsy diagnosis, or of those dying within one month of diagnosis could be factors that influence the survival estimates, thus affecting the external validity of regional and international comparisons (242). This study addressed some points regarding quality of data as important limitations. For example, the total number of CRC cases reported to the JCR during the study period was 1,896 of which 99.1 percent was microscopically verified, which is considered a good indicator of quality (58;243). By restricting the sample and excluding patients with no histology, survival will be higher than if all patients were included, however, due to the very small proportion of patients with no histopathology reports (<1%) this type of bias is unlikely to have had a significant effect on the results. In addition, more than one-third (37 percent) of the colorectal cases were coded as "Colon, NOS". While this issue affects the specificity of the data, it does not affect the overall incidence of CRC (65). However, non-usage of additional sources of information e.g. death certificates limits the completeness of data at the JCR. In 2003, the Jordan Ministry of Health updated its death certificate according to international standards. The improving of quality of death certificate and increasing the coverage and utilization of medical death certificates allows mortality statistics to be used with greater confidence for causes of death. However even mandatory death certification requires basic additional information to enable verification of the causes of death statistics with other sources. Recently, the JCR started using death certificates as a reliable source of information.

- *Incomplete ascertainment of cases (incidence) and incomplete ascertainment* of death in registered cancer patients are factors that may cause bias in comparative survival estimates (244). In this study Cancer registration in Jordan only started in 1996 and, as with any newly established registry, there were some difficulties in ascertaining all cases and gathering all the required information as well as in coding and validation procedures. Completeness and reliability are important components to assess the quality of cancer registries (245;246). External assessors assessed completeness and reliability of the JCR data in 1998 where registrations at the JCR were determined to be 88 percent complete. Such a completeness rate is considered good for a newly establish registry (57). Moreover, In Jordan, the reporting of incident cancer cases is obligatory by law, and it is obligatory to get treatment, thus incomplete ascertainment of incidence cases (incidence) is probably to be relatively limited. Regarding to ascertainment of death in registered cancer patients, we actively followed up with CRB to ascertain the vital status of the patients. CRB, a part of the Ministry of Interior in Jordan, has very advanced civil registration system. As a result, such type of bias may still exist in this study, but with a minor effect on our survival estimates.

- *Completeness of data:* The validity and strength of the incidence data affects the survival inferences in the study. Hypothetically, JCR should have on record, documentation of all diagnosed colorectal cancer cases in Jordan. However, because the JCR is a fairly new entity (established in 1996), and as with any newly established registry, there are predominant difficulties in ascertaining all cases and gathering all the required information as well as in coding and validation procedures. Although the JCR collects data on CRC from all related health facilities (i.e. Ministry of Health, the

Royal Medical Services, universities and private as well as public-sector pathology laboratories) using active and passive methods of case finding, so far the registry collects only the basic information of the patients (i.e. four digit name, sex, age, ID, nationality, stage, morphology, topography, behaviour, site of treatment and place of residency). However, other information such as level of education, occupation, health insurance, smoking status, treatment, marital status and patient outcome are not collected.

Moreover, the researcher was able to collect information only about diabetes mellitus, because absence of information related to other comorbidities was incomplete. In addition, information about other comorbidity risk factors e.g. smoking, obesity, hypertension, and physical inactivity and other factors were not collected by JCR and it was not available in patients' medical records. These comorbidities factors are associated with poorer survival (187;189;191;192;282), and lack of information about them poses as a limitation to the study.

The association between colorectal cancer and diabetes remains of a complex nature when considering the variety of variables and predictors that might affect such an association. Other comorbidities such as hypertension and cardiovascular disease are among such leading variables. In addition, factors affecting the progress and control of diabetes might be important predictors that need to be controlled when examining the association of diabetes with cancer survival. Not including some of these factors in this study should be noted as a study limitation, especially given that some of these factors are mentioned in the literature, such as: quality of diabetic care, type of diabetic treatment, duration of diabetes.

Other comorbidities, such as cholesterol, hypertension or cardiovascular diseases, might also significantly affect the mortality from colorectal cancer (161;162;171;172;186-192). In addition, behavioural risk factors affecting diabetes and cancer, such as smoking and obesity, ought to be considered when examining the association under study. In summary, this study did not control all causes that might be associated with mortality, for which we offer a recommendation to undertake a more comprehensive study in the future to help ascertain the association between diabetes and prognostic probability of CRC.

- *A multifaceted research problem:* CRC is a multifaceted health problem with a wide range of risk factors that ought to be considered when determining the hazard risk. Such an assumption maximizes the need to combine information that can possibly add value to the current focus of the study, such as: behaviour, lifestyle, social support and other pertinent risk factors. In addition, examining the association of treatment site and survival of colorectal cancer does not come free of limitations. The most important limitation lies in the information collected on the different treatment sites from the patients' perspective. Responsiveness of the health care system in terms of patient satisfaction, trust and acceptance of treatment are important elements that were not addressed in this study. In addition, including health-care management aspects and focusing on health insurance of patients are major areas that could have added value to the results.

- *Survival differences:* Although the study used the log rank test and the cox proportional hazard regression analysis to examine factors that affect survival differences, several factors can affect these differences especially if they are related to issues beyond the control of the study design. For example, adjusting for the rate of disease progression of cancer in this study was limited by the type of study design because the progression depends on the length of time of the preclinical phase, usually referred to as length bias. Similarly, the lead time bias which is the effect of early detection of cancer on survival could have influenced the association between treatment and survival and should have therefore been controlled for when examining the association between cancer survival and type of treatment. Subsequently, including the stage of disease and year of diagnosis as predictors in this study was insufficient to control for such bias. Colorectal cancer survival is determined by socio-economic status and the socio-economic selection biases of different hospitals (e.g. those that only accept patients who can pay directly or who are privately insured) may explain the observed differences in outcomes between hospitals.

9.5 Recommendations

As the first colorectal cancer survival study in Jordan, this study brings interesting and important findings that should serve as a call for action to policymakers and program planners in Jordan. The main findings worth noting include: 1) high incidence of colorectal cancer in younger patients, 2) poorer survival in younger patients, 3) very large variations in survival between hospitals and 4) large effect of diabetes mellitus on survival – which, given the high prevalence of 19 percent, has very large implications for public health. Therefore, these results provide a foundation of evidence and an essential element for raising public awareness, advocacy and improving health care service delivery. Continued

monitoring and evaluation of the colorectal survival estimates is a vital component to developing future targeted and effective programs and policies in Jordan. In addition, expanding the establishment of the estimates of survival among Jordanian patients with other types of cancers in Jordan is highly recommended.

Due to the scarcity of colorectal cancer survival estimates from the Eastern Mediterranean countries, and the availability of only a few studies in less developed countries, this study can serve as a model for the region to assist other countries to ascertain national colorectal cancer survival estimates as well as survival estimates for other types of cancers.

Results of this study prompted a set of recommendations to assist national efforts in preventing and controlling colorectal cancer. Attempts were made to extend recommendations that are applicable to countries of similar nature to Jordan. The recommendations presented herewith were grouped alongside core areas that are necessary for advancing national strategies and actions in the combat against the burden of colorectal cancer.

9.5.1 Strengthen health service provision

Mandate early detection programs especially in the older adult population. The study, in line with other studies, showed poor survival with advancing age; people aged 75 years and above had approximately a two-times higher risk of death than those aged 44 years or less. This could be attributed to poor general health for CRC patients and the difficulties in prescribing cancer treatment (such as surgery) and possibly an association with more advanced disease stages. Specifically for Jordan, the high prevalence of non-communicable diseases like hypertension, cardiovascular diseases and diabetes could be contributing to

the poor health of the elderly population. Health care professionals should be encouraged to pay special attention and focus on older patients.

On the other hand, screening programmes are considered to be the cornerstone of prevention for colorectal cancer. However, due to the limited available financial resources allocated to health care, caution should be exercised toward other considerations in the control of the low risk of CRC in Jordan as a country with low financial resources compared with the developed countries. In addition, this study revealed that 14 percent of the CRC among patients aged 40 years or less. In the event of implementing screening activities, age at diagnosis of CRC should be taken into consideration. In light of this finding, this study recommends further investigation to investigate CRC among the middle aged Jordanian population in order to attest the need to introduce screening at a younger age whenever possible.

Develop appropriate protocols and clinical practice guidelines for the management of colorectal cancer. This study revealed that there is statistically significant difference in CRC survival estimates in relation to treatment sites, where patients who received CRC treatment at private sector hospitals and King Hussein Cancer Center had lower risk of dying compared to those who received treatment at public sector hospitals. This result calls for an urgent action to adopt measures that can resolve any discrepancies in the survival estimates across various local treatment sites. Treatment protocols should be unified and developed to conform with international standards and the multidisciplinary Team Approach to Healthcare. These treatment protocols and strategies should be applied uniformly to allow for the provision of effective and efficient care to CRC patients across Jordan.

In addition, bringing qualified staff to the public sector health facilities should be taken into consideration as well as the provision of continuing professional education to physicians and other staff. The study also recommends evaluating the affordability and accessibility of diagnostic equipment and procedures at public hospitals and making essential upgrades for improving the quality of care. In addition, the study recommends pursuing accreditation of public service hospitals as an opportunity for improving the quality of services, with a proposition to consider twinning of cancer services across hospitals in order to enhance performance across Jordan. Therefore, the study recommends introducing managed clinical networks as an approach for reducing the variation in survival between the different hospitals as a worthwhile suggestion to be considered.

Develop and endorse national guidelines for effective colorectal cancer management in diabetic patients. The researcher believes that this is the first study from the region to examine the relationship of colorectal cancer and diabetes. Furthermore, based on the in depth literature review, the researcher did not find any peer reviewed articles that address the relationship between CRC and diabetes mellitus in Jordan nor in any other countries where diabetes is known to be highly prevalent. The high prevalence of diabetes mellitus in Jordan and the significant relationship between colon cancer survival estimates and diabetes mellitus that was detected in this study, call for intensifying efforts to promote measures that can improve and advance the management of diabetes in CRC patients. Therefore, program planners should consider developing and adopting guidelines for effective management of diabetes in the presence of CRC cancer. The study stresses the need to intensify public health efforts in preventing and controlling diabetes. This together with conducting further research to investigate the increased mortality among diabetic

CRC patients are worthwhile recommendations to be considered by health planners and policy makers.

Due to the limited local financial resources and the tremendous impact of cancer on public health in light of the escalating health care cost, strategies for prevention and control are becoming increasingly more important. Consequently, raising awareness of CRC risk factors, symptoms and early warning signs in the general population could help reduce incidence, ensure earlier detection and thus improve survival rates. Adopting a policy for introducing community programs to raise public awareness regarding the early warning signs of CRC as a primary prevention strategy is highly recommend. Therefore, the study recommends for policymakers and researchers the need to explore more fully the viability of establishing a CRC screening programme and to adapt the CRC national screening guidelines according the country's needs.

9.5.2 Assure provision of health care by expanding services

Expand cancer treatment sites beyond the central region of Jordan. The survival rates in the central region of the country were found to be higher than those in the north and south. Patients who resided in the central region of Jordan had a 27 percent lower risk of death compared with those who resided in the north. This could be attributed to the concentrated development plans targeting the centre of the country since the establishment of Jordan. Infrastructure and healthcare have significantly improved in this region compared to those services offered in the north and south. However, one of the contributing factors that should be considered is the widespread existence of the private sector hospitals and treatment sites in the central region as well as the centralized

government structure in Jordan. Accessibility, affordability and quality of health services across the regions of Jordan should be addressed. Furthermore, socio-demographic potential predictors of the colorectal cancer survival estimates should be also examined. Finally, the on-going development of health services implemented in the northern and southern regions of the country should be monitored to identify gaps and areas of improvement. Further research to study the influence of spatial (location and distance) and non-spatial determinants (socio-economic and cultural factors) on survival differences is highly recommended.

9.5.3 Improve monitoring by promoting policy and research

Conduct studies to examine the role of lifestyle habits in colorectal cancer. Jordan is experiencing demographic and epidemiological transitions where the life expectancy is increasing and infectious diseases are declining and chronic diseases, such as cancer, are becoming more predominant. Sedentary lifestyle, high fat diet, obesity, physical inactivity and smoking are becoming common in Jordan. Therefore, it seems reasonable to hypothesize that the incidence of colorectal cancers in Jordan is likely to increase steeply in the next coming years in light of the expected increase in these modifiable risk factors. In addition, this study showed that the overall Age Standardized Rate for CRC to be 15.5 per 100 000 males and 12.5 per 100 000 females, which is considered low compared to developed countries but yet similar to CRC incidence rates in other countries in the region. However, colon cancer in the Jordanian population is one of the highest in comparison to the various regional countries for both sexes; while at the same time, rectum cancer was one of the highest among females. These variations could be attributed to differences in food and lifestyle habits within the region. Therefore, this study recommends undertaking

epidemiological analytical studies to further investigate the role of different lifestyle attributes on colorectal cancer survival. In addition, the study recommends conducting further studies to better understand the differences in incidence among different neighboring countries in the Eastern Mediterranean region.

Conduct studies to explore the age and sex differences in colorectal cancer. This study was found to be in line with other studies from the region where a large proportion (13.8 percent) of diagnosed colorectal cancers cases occurred in patients who were aged 40 years and less. However, in the developed countries, only 2 to 8 percent of the colorectal cancers occur in young people. Although this might be due to the high percentage of young population in Jordan, it can also suggest a lower recording of cases among the elderly. Moreover, age specific rates among patients in Jordan for individuals aged 65 years or less were found to be more pronounced when compared to developed countries. Nevertheless, being 'affected at an early age' is a significant group characteristic and is an important result that should be taken into account in implementing CRC prevention and control strategies. As a result there is an urgent need to better understand the local CRC burden by conducting further studies to explore the age differences and causality for high occurrence of colorectal cancer among the young age groups (i.e. less than 40 years of age). Such studies can provide an explanation as to why the disease occurs at such early ages in Jordan.

Implement research studies to investigate the relationship between diabetes and colorectal cancer. Although the relationship between colorectal survival and diabetes mellitus is still not well established in the literature, this study provided an added value to the available works in this field. Nevertheless, further clinical studies are needed to

investigate whether diabetes mellitus influences the outcome of CRC as well as investigate the possible association between CRC survival and the level of diabetes control. Although this study mainly detected a relationship between cancer survival and diabetes in patients with a regional extent of colorectal cancer, undertaking clinical studies to ascertain the underlying mechanism(s) that affect cancer survival in diabetic patients is needed. Further investigation of the role of co-morbidities and their risk factors, such as obesity, on CRC survival can play an important role in identifying prevention and treatment strategies.

Promote decision-finding evidence in public health policy leaders. The findings from this study indicated that survival rates were reduced as the cancer spread beyond its site of origin; the highest survival rate was found for patients with localized tumour stage and the lowest for those with distant tumour stage. In addition, the study results showed that more than half of the patients had regional metastasis at the time of diagnosis, 22.8 percent had distant metastasis and only 11.2 percent had localized CRC at diagnosis.

Having overall good survival estimates of CRC with such advanced stage descriptions at the time of diagnosis could be attributed to the advanced curative care in Jordan. Curative care takes up a disproportionately large share of public spending on health (about 79 to 82 percent of the total state health expenditure, while the proportion spent on primary health care is below 20 percent).

Moreover, the study showed that treatment was better in some sectors (i.e. geographic, as well as public versus private), than in others. This raises questions that have implications for policy considerations: Why is there a difference in geographic survival rates? Can

something be done to improve the situation? While it might not be economically attractive for private hospitals to build new centres in the south of the country, is there any 'scaled back' version that could significantly impact survival rates? For example, JCI literature describes cancer-specific accredited treatment centres (such as KHCC). In the U.S., Mayo Clinic not only operates inpatient cancer hospitals in the state of Minnesota, but also provides several day-patient satellites in less-densely populated areas of the state. Could this model be successfully applied in Jordan by KHCCH? Or, might it be feasible to establish some form of twinning between private hospitals from Amman with public treatment centres in other parts of the country? What might the likely impact on CRC survival rates be? All these questions should steer decision-finding evidence to assist policy makers and program planners in providing optimal and essential CRC care.

In this study we estimated the survival estimated based on the available Jordanian data. Information about the socio-economic factors was available neither in medical records nor in JCR. This leaves questions about the nature and extent of variations in survival according to personal characteristics reflecting socio-economic status. It may be that additional data on income and health-related behaviours could be gathered routinely to help understand these influences. Issues such as this should be taken into consideration for future in-depth research to provide greater insights into determinants of outcomes.

In conclusion, there are potential policy issues that can enhance efforts for better prevention and management of colorectal cancer in Jordan, albeit the evidence provided in this study which discloses a better than expected colorectal survival rates. It is recommended that policy makers and health researchers investigate more fully the reasons behind the phenomenon of regional differences, and, in particular, to examine the

associated factors of use of health services in the southern region. It is also recommended that policy makers implement strategies for primary and secondary prevention since such strategies are becoming increasingly important for Jordan.

9.5.4 Improve and strengthen data quality measures

Improve completeness and quality of Jordan Cancer Registry. As mentioned earlier, the national JCR was established in 1996 in collaboration with NCI-USA and the MECC. External assessors evaluated completeness and reliability of the JCR data in 1998 and registrations at the JCR were determined to be 88 percent complete. Such a completeness rate is considered good for a newly established registry. However, when collecting information from JCR, there were some difficulties in ascertaining all cases and gathering all the required information as well as in coding and validation procedures, which in turn call for employing further data quality control measures.

JCR collects data on CRC from all related health facilities; i.e. Ministry of Health, the Royal Medical Services, universities and private as well as public-sector pathology laboratories; and uses active and passive methods of case finding, thus far the registry only collects the basic information of the patients (e.g. four digit name, sex, age, ID, nationality, stage, morphology, topography, behaviour, site of treatment and place of residency), However, other useful information (such as level of education, marital status, occupational status, health insurance, smoking status, treatment and patient outcome) are not collected. The study recommends increasing the awareness of JCR staff of the importance of quality and benefits of the registry and increasing the active data collection registry. Nowadays the cancer registry role has developed beyond providing cancer counts and incidence.

Therefore, the study recommends that JCR consider scaling up its role to include following-up with cancer patients in order to monitor the quality of cancer services they receive.

Establish linkages and networking to improve information sharing. Currently there is no direct electronic network between the JCR and the CRB. Thus, it is recommended to establish such a link to support completeness, accuracy and timeliness of the vital status of cancer patients.

Jordan still suffers from absence/inadequate computerized patient records' systems, particularly in public health hospitals. However, KHCC and many of the private hospitals do have such computerized systems. It is recommended that JCR enhance the quality of its data by collaborating with the already-computerized hospitals in establishing a directly linked electronic network.

Improve patient medical records and establish quality improvement systems. In this study the medical records were an important source of data. Reviewing the medical records was very beneficial to better understand the type of treatment administered as well as to attempt to fill the gaps in information missing from JCR. However, Jordan, as in many other developing countries, still suffers from inadequate clinical follow-up systems in hospitals and an absence of computerized patient records' systems. Medical records with missing data are very common. Most of the hospitals do not have written policies and procedures for medical records upkeep. Moreover, few of the hospitals conduct periodic quality reviews for accuracy and completeness of information. Cancer registries should

foster awareness of the importance and uses of the valuable data that they collect. Clinicians and pathologists should recognize their potential contribution in improving the quality of cancer registry data. Well-maintained patient records' systems should be implemented irrespective to whether or not an institution has its own resources to invest in computerization; where institutional funds are lacking, the government should assist. Providing proper recordkeeping, standards of quality and performance should be implemented as well. All of these steps lead toward continuous improvement in the quality of services provided.

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APPENIX 1: MDG PROGRESS INDEX SCORE FOR JORDAN

MDG Progress Index Scorecard - Jordan   Score: 4.5

MDG 1A: Extreme Poverty
Halve Proportion of Population Under $1.25/day

MDG 1C: Hunger
Halve the Proportion of Undernourished Population

MDG 2: Education
Achieve Universal Primary Education

MDG 3: Gender Equality
Achieve Gender Parity in Schooling

MDG 4: Child Mortality
Reduce Child Mortality By Two-Thirds

MDG 5: Maternal Health
Reduce Maternal Mortality by Three-Quarters

MDG 6: Combat HIV/AIDS
Halt and Begin to Reverse the Spread of HIV/AIDS

Insufficient Data Available

MDG 7: Environmental Sustainability
Halve the Proportion of People Without Access to Safe Drinking Water

Score = 0   Score = 0.5   Score = 1

For more information:
"Who Are the MDG Trailblazers? A New MDG Progress Index",
by Benjamin Leo and Julia Barmeier.
http://www.cgdev.org/content/publications/detail/1424377

Sources: World Bank, World Development Indicators 2011
The Lancet: Maternal Mortality for 181 Countries

APPENDIX 2: OBSERVED AND RELATIVE SURVIVAL RATES BY SEX AND

YEAR OF DIAGNOSIS

Table A.1: Observed (OS) and relative survival (RS) estimates for patients diagnosed with colorectal cancer during 2003-2007, Jordan

Year	Male			Female			Overall		
	No.	OS percent	RS percent	No.	OS percent	RS percent	No.	OS percent	RS percent
0.0- 0.1	1 053	95.9	95.9	843	96.9	96.9	1 896	96.3	96.4
0.1-0.2	1 001	94.1	94.1	814	94.8	94.9	1 815	94.4	94.5
0.2- 0.3	976	92.2	92.4	788	93.4	93.5	1 764	92.8	92.9
0.3- 0.4	953	90.1	90.3	772	91.8	91.9	1 725	90.9	91.1
0.4- 0.5	925	88.7	89.0	756	89.4	89.5	1 681	89.0	89.2
05- 0.6	907	87.3	87.6	734	87.7	87.8	1 641	87.5	87.7
0.6- 0.7	889	85.9	86.3	714	86.7	86.8	1 603	86.3	86.5
0.7- 0.8	872	85.3	85.6	705	85.6	85.8	1 577	85.4	85.7
0.8- 0.9	862	83.5	83.9	693	84.2	84.4	1 555	83.8	84.2
0.9- 1.0	840	82.2	82.6	681	83.3	83.6	1 521	82.7	83.1
1.0- 1.5	825	76.4	77.1	671	78.3	78.7	1 496	77.3	77.9
1.5- 2.0	761	71.9	73.1	620	74.5	75.1	1 381	73.1	73.9
2.0- 2.5	713	67.9	69.3	587	71.5	72.2	1 300	69.5	70.6
2.5- 3.0	668	65.2	66.9	557	69.7	70.6	1 225	67.2	68.6
3.0- 4.0	641	60.1	62.9	542	64.7	66.3	1 183	62.1	64.5
4.0- 5.0	541	55.9	60.1	372	59.8	62.3	823	57.7	61.3

Table A.2: Observed (OS) and relative survival (RS) estimates for patients diagnosed with colon cancer during 2003-2007, Jordan

Year	Male			Female			Overall		
	No.	OS percent	RS percent	No.	OS percent	RS percent	No.	OS percent	RS percent
0.0- 0.1	658	94.8	95.3	643	96.1	96.1	1 420	95.6	95.7
0.1-0.2	617	92.3	93.1	615	93.6	93.7	1 348	93.3	93.4
0.2- 0.3	597	90.5	91.3	592	92.2	92.3	1 304	91.6	91.8
0.3- 0.4	581	88.3	89.2	581	90.7	90.8	1 275	89.8	89.9
0.4- 0.5	563	86.9	87.7	570	88.3	88.5	1 243	87.9	88.1
05- 0.6	552	86.1	86.3	553	87.1	87.2	1 212	86.5	86.7
0.6- 0.7	539	84.9	85.3	539	85.9	86.1	1 183	85.4	85.7
0.7- 0.8	532	84.3	84.7	532	84.6	84.8	1 165	84.4	84.8
0.8- 0.9	524	82.4	82.8	521	83.8	84.0	1 146	83.0	83.4
0.9- 1.0	509	81.4	81.9	515	83.0	83.3	1 124	82.1	82.5
1.0- 1.5	500	76.4	77.2	510	78.1	78.5	1 110	77.2	77.8
1.5- 2.0	464	72.0	73.1	471	75.1	75.7	1 029	73.4	74.2
2.0- 2.5	438	68.0	69.5	452	71.9	72.7	977	69.8	70.9
2.5- 3.0	410	66.1	68.0	429	69.9	70.9	920	67.8	69.3
3.0- 4.0	399	63.8	63.7	416	69.9	67.4	893	62.9	65.4
4.0- 5.0	282	56.9	61.8	290	65.7	63.7	626	58.8	62.7

Table A.3: Observed (OS) and relative survival (RS) estimates for patients diagnosed with rectum cancer during 2003-2007, Jordan

Year	Male			Female			Overall		
	No.	OS percent	RS percent	No.	OS percent	RS percent	No.	OS percent	RS percent
0.0- 0.1	276	97.8	97.9	200	99.5	99.5	476	98.5	98.6
0.1-0.2	268	97.1	97.2	199	99.0	99.0	467	97.9	97.9
0.2- 0.3	264	95.3	95.4	196	97.5	97.5	460	96.2	96.3
0.3- 0.4	259	93.4	93.6	191	95.4	95.5	450	94.3	94.4
0.4- 0.5	252	92.3	92.5	186	92.9	92.9	438	92.5	92.7
05- 0.6	248	91.2	91.5	181	89.8	89.9	429	90.6	90.8
0.6- 0.7	245	88.9	89.3	175	89.3	89.4	420	89.1	89.3
0.7- 0.8	239	88.2	88.6	173	88.8	88.9	412	88.4	88.7
0.8- 0.9	237	86.7	87.1	172	85.7	85.8	409	86.3	86.6
0.9- 1.0	231	84.5	84.9	166	84.6	84.8	397	84.5	84.9
1.0- 1.5	225	76.6	77.2	161	79.3	79.7	386	77.7	78.2
1.5- 2.0	203	71.9	72.9	149	72.9	73.3	352	72.4	73.1
2.0- 2.5	188	67.8	69.1	135	70.2	70.8	323	68.8	69.8
2.5- 3.0	177	62.8	64.3	128	69.1	69.9	305	65.4	66.6
3.0- 4.0	164	58.5	60.8	126	61.5	62.8	290	59.7	61.7
4.0- 5.0	115	53.2	56.8	82	55.8	57.8	197	54.3	57.2

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Colorectal cancer survival in Jordan (2003-2007)

Information collection instrument

Number of case: ------------

1. **Cancer registry**

National ID: ☐☐☐☐☐☐☐☐☐

Name: ---

Sex   Male   ☐   Female   ☐

Age   ☐☐

4- Address: **Governorate:** ----------------------------------

   District:--------------------------------------

Date of diagnosis: DD/MM/YYYY

Site of the tumor (Topography) according to ICD (O3):

Morphology ICD (O3): --

Staging:
TNM classification: 1- Stage I   2- Stage II   3-stage III   4- stage IV

                5- unknown

Dukes Classification: 1- Stage A   2- Stage B   3-Stage C   4- Stage D

5- unknown

Summary stage: 0 1   2 3 4 5 6 7 9

Extent of disease   1- Local   2 - Regional   3 - Distant metastasis

Grade and differentiation: 1. Well   2. Moderate   3. Poor   4.anaplastic
                       5.Unknown

Treatment: 1. Palliative treatment   2. Curative treatment:

If curative specify: 1.surgey   2.chemotherapy   3.radiotherapy

Vital status : 1- A live   2-dead   3-unknown

Date of last visit: DD/MM/YYYY

Time passed (months) from date of diagnosis to date of last visit:------------

Cause of death: 1- Cancer   2- Other causes (specify):-----------------------

   2. **Medical records:**

Hospital name: …………………………………………

Patient's record serial number:…………………………………..

Patient's doctor name: ……………………………

Smoking status   Yes   No

Occupation:…………………………………….

Level of education :---

Family history :   1- yes   2- no   which relative

Any benign tumors (adenomatous polyp)

Last contact date: DD/MM/YYYY

Co-morbidity: 1. diabetes ………………..for …………years
                   2.Hypertension   3.cholesterol 4.obesity

Case summary: ---

Admission history: -main symptom (presenting) ------------------------------------

----

Emergency or elective……………………………

Endoscopy done   1- yes   Date : dd/mm/yyyy   2- no

Main source of medical services:
1. MOH 2.University   3.Military   4.UNRWA 5. Private
6. Other (specify)………………………………………

Health insurance status:
Having health insurance: Yes   No

Type of health insurance: ……………………………………..

Treatment:

1.surgey 2.chemotherapy 3.radiotherapy (you can circle more than one)

Surgery:

Date of surgery: DD/MM/YYYY

Type of surgery: emergency   elective

Surgery procedure:

Date of starting chemotherapy: DD/MM/YYYY

Frequency:----------------------------

Duration:-----------------------------

Radiotherapy:

Date of starting radiotherapy: DD/MM/YYYY

Frequency:------------------------------

Duration:---------------------------------

3. **Histopathology report:**

Laboratory name:

Record serial number:

Referral side:

Case summary: ………………………………………………….

Tumor size at histological examination   1 - (<2 cm)   2 - (≥2 cm) Lymph nodes

  1- None   2-one   3 – (2-3)   4- (>3)

 Receptors status (carcinoembryonic antigen (CEA) and CA 19-9

  1- Positive   2- Negative   3 – Unknown

Time passed (months) from the date of diagnosis and the last visit: DD/MM/YYYY

ANNEX 2: PERMISSIONS AND ETHICAL APPROVALS

University of Glasgow | College of Medical, Veterinary & Life Sciences

Dear Mr Al-Nsour

Project Title: Colorectal cancer survival in Jordan (2003-2007).
Project No: FM 00310

The College Ethics Committee has reviewed your application and has agreed that there is no objection on ethical grounds to the proposed study. They are happy therefore to approve the project, subject to the following conditions

The research should be carried out only on the sites, and/or with the groups defined in the application.

Any proposed changes in the protocol should be submitted for reassessment, except when it is necessary to change the protocol to eliminate hazard to the subjects or where the change involves only the administrative aspects of the project. The Ethics Committee should be informed of any such changes.

- If the study does not start within three years of the date of this letter, the project should be resubmitted.
- You should submit a short end of study report to the Ethics Committee within 3 months of completion.

Yours sincerely

Professor William Martin
College Ethics Officer

International Agency for Research on Cancer

World Health Organization

150 cours Albert Thomas
69372 Lyon cedex 08, France

IARC Ethics Committee (IEC) Tel.: +33 4 72 73 85 43
Fax: +33 4 72 73 85 64 E-mail: iec@iarc.fr http://ethics.iarc.fr/

Ref.: IEC 12-07   **28th March 2012**

You submitted the following project for review by the IARC Ethics Committee (IEC):

Project No. 12-07

Colorectal cancer survival in Jordan 2003-2007

Dr M. Nsour
Cancer Information Section (CIN)
IARC

28th March 2012

UNIVERSITY OF GLASGOW

FACULTY OF MEDICINE ETHICS COMMITTEE FOR NON CLINICAL RESEARCH INVOLVING HUMAN SUBJECTS

APPLICATION FORM FOR ETHICAL APPROVAL

NOTES:

THIS APPLICATION FORM SHOULD BE TYPED NOT HAND WRITTEN.

ALL QUESTIONS MUST BE ANSWERED.
"NOT APPLICABLE" IS A SATISFACTORY ANSWER WHERE APPROPRIATE.

FACULTY PROJECT CODE:

Project Title

Colorectal cancer survival in Jordan (2003-2007).

Date of submission: *17 August 2010.*

Name of all person(s) submitting research proposal: *Mohannad Al Nsour*

Position(s) held: **PhD student**

Department/Group/Institute/Centre:
University of Glasgow. College of Medical, Veterinary and Life Sciences. Public Health and Health Policy.

International Agency for Research on cancer (IARC). Cancer Information Section

Address for correspondence relating to this submission

Mohannad Al- Nsour
P.O.BOX:963709.
Postal code: 11196, Amman, Jordan.
Mobile: +962 (0) 777763519.
E-mail: mohannadnsour973@yahoo.com

Name of Principal Researcher (if different from above e.g., Student's Supervisor)

Position held :
Undergraduate student project   Yes/<u>No</u>
Postgraduate student project   <u>Yes</u>/No

If yes, please state degree being undertaken: PhD

1. Describe the purposes of the research proposed. Please include the background and scientific justification for the research. Why is this an area of importance?

Jordan, as other Eastern Mediterranean countries, still suffers from scarcity of local research that investigate the incidence, survival, prevalence and the other different aspects of cancer in these countries. Recently, Jordan, in cooperation with World Health organization (WHO), launched the National Health Research Priorities (2009-2012). Colorectal cancer was at the top of these priorities.

In Jordan, colorectal cancer is the second leading incidence rate in both males (after lung cancer) and females (after breast cancer) where it affected (12.1percent), and (8.9percent) respectively. Furthermore, colorectal cancer is considered the second prevalent cause of death among cancer deaths.

Few survival studies were conducted in developing countries. In Jordan, to best of our knowledge no information is available about the survival statistics of colorectal cancer. Survival statistics are means of quantifying the effectiveness of early detection strategies and treatment regimes at the population level [15, 24]. They are useful as comparative measures between different populations. Information about the survival rates will help us take further preventive and control measures in order to improve the quality of cancer care they receive. Survival data is an important tool to evaluate the effectiveness and efficiency of cancer health services.

2. Describe the design of the study and methods to be used. Include sample size and the calculation used to determine this. Statistical advice should be obtained if in doubt.

The design for this project will be a descriptive study using data from the Jordan cancer registry (JCR). All Jordanian colorectal patients who were diagnosed with Colorectal cancer during the period 2003 (January 1st- 2007 (December 31st) and registered in Jordan cancer registry will be enrolled in this project. No sample size will be drowning. Colorectal cancer information patients will be officially collected from the Jordan cancer registry. Identifying the vital status of the patients will be ascertained from Civil registration Bureau through unique National Identification number (ID) of the patients. ID number will be used for verifying the duplication. Active strategies for completing the missing information will be followed: Reviewing medical records of the hospitals and reviewing the pathological laboratory reports to obtain the missing information related to the site, stage, and grade of the cancer. Patients not traced after these efforts, they will be considered as a lost of follow cases. No home visits or phone calls to the patients.

3. Describe the research procedures as they affect the research subject and any other parties involved.
It should be clear exactly what will happen to the research participant, how many times and in what order.

Not applicable.

4. How will potential participants in the study be (i) identified, (ii) approached and (iii) recruited?
Give details for cases and controls separately if appropriate:

The subjects of this study will the Jordanian population, aged 15 years and over, who were diagnosed with a primary colon (International Classification of Diseases-10 C-18) or rectum (ICD-10 C19 and C20) cancer during the period 2003 (January 1st- 2007 (December 31st) and registered in Jordan cancer registry verified by histopathology report. Non-Jordanian nationalities, any case with no histological report and prevalent and/or recurrent cases will be excluded from the study.

5. What are the ethical considerations involved in this proposal? (You may wish for example to comment on issues to do with consent, confidentiality, risk to subjects, etc.)

Data will be handled in compliance with the Data Protection Act 1988; information will be treated with utmost confidentially: At the analysis stage, computer generated numbers replace subjects. Identifying information and the results published with no reference to names of studied subjects. Results obtained from data collection and analysis stayed confidential and not used for purposes other than those mentioned in the proposal.

6. Outline the reasons why the possible benefits, to be gained from the project, justify any risks or discomforts involved.
There is no direct contact with patients. No any risks or discomforts can be caused.

7. Who are the investigators (including assistants) who will conduct the research? What are their qualifications and experience? This research will be contacted by me (Mohannad Al-Nsour). Iam a holder Bachelor of Medicine, Bachelor of Surgery (MB, BSc.), MSc. In Epidemiology, and Board in Community Medicine/Epidemiology. Currently Iam PhD fellow at International Agency for research on cancer & Glasgow university (Joint program). Iam working in this project under supervision of : Dr.David Forman, International Agency for Research on Cancer (IARC). Head, Descriptive Epidemiology Production Group.
Dr. David S Morrison, University of Glasgow. Director, West of Scotland Cancer Surveillance Unit.

8. Are arrangements for the provision of clinical facilities to handle emergencies necessary? If so, briefly describe the arrangements made.

Not Applicable. There is no direct contact with study subjects

9. In cases where subjects will be identified from information held by another party (for example, a doctor or hospital), describe how you intend to get this information. Include, where appropriate, which Multi Centre Research Ethics Committee or Local Research Ethics Committee will be applied to.

Official approval of Jordan cancer registry to utilize available colorectal cancer data was obtained. Official approval from the ethical committee at the Jordan ministry of health was obtained. Furthermore, official approvals from different sectors will be obtained according to the project needs.

10. Specify whether subjects will include students or others in a dependent relationship.

Not Applicable. There is no direct contact with study subjects

11. Specify whether the research will include children or people with mental illness, disability or handicap. If so, please explain the necessity of involving these individuals as research subjects, and include documentation of the suitability of those researchers who will be in contact with children (eg Disclosure Scotland).
No children or people with mental illness, disability or handicap will be including in thee project.

12. Will payment or any other incentive, such as a gift or free services, be made to any research subject? If so, please specify and state the level of payment to be made and/or the source of the funds/gift/free service to be used. Please explain the justification for offering an incentive.

There is no any type of incentive will be made to any research subject

13. Please give details of how consent is to bee obtained. A copy of the proposed consent form, along with a separate information sheet, written in simple, non-technical language MUST ACCOMPANY THIS PROPOSAL FORM.

A special form (appendix 1) was developed to collect the requested information. This information includes: 1. Socio-demographic data: ID number, name, sex, age, date of birth, address, (Governorate), main source of medical services, having health insurance, the type of health insurance, and date of diagnosis. 2. Clinical data: site, grade, stage, and morphology. 3. Type of treatment collected from medical records form main hospitals and pathological laboratories. 4. Vital status data: if the patient alive or dead. The starting point is the date of diagnosis of the patients, which was reported in files from 2003-2007. No any other forms will be used during project implementation.

14. Comment on any cultural, social or gender-based characteristics of the subject, which have affected the design of the project or may affect its conduct.

Not applicable.

15. Please state who will have access to the data and what measures will be adopted to maintain the confidentiality of the research subject and to comply with data protection requirements e.g. will the data be anonymised, how will it be stored, how will access be restricted, and for how long will it be retained?

Information will be treated with utmost confidentially: At the analysis stage, computer generated numbers replace subjects. Identifying information and the results published with no reference to names of studied subjects. Results obtained from data collection and analysis stayed confidential and not used for purposes other than those mentioned in the proposal.

16. Will the intended group of research subjects, to your knowledge, be involved in other research? If so, please justify.

Not applicable.

17. Proposed starting date : 01/05/2009.

   Expected completion date: 01/05/2012.

---

18. Please state location(s) where the project will be carried out.

Jordan cancer registry, government and private hospitals, and Pathology laboratories, and Civil Registration Bureau.

---

19. Please state briefly any precautions being taken to protect the health and safety of researchers and others associated with the project (as distinct from the research subjects) e.g. where blood samples are being taken

Not applicable.

---

20. Please state all relevant sources of funding or support for this study

There is no fund for the Project.

---

21 a). Are there any conflicts of interest related to this project for any member of the research team? This includes, but is not restricted to, financial or commercial interests in the findings. If so, please explain these in detail and justify the role of the research team. For each member of the research team please complete a declaration of conflicts of interest below.

<div align="center">No conflict of interest.</div>

Researcher:
Name: _____conflict of interest Yes / No
If yes, please detail below
Researcher:
Name: _____conflict of interest Yes / No
If yes, please detail below
Researcher:
Name: _____conflict of interest Yes / No
If yes, please detail below
Researcher:
Name: _____conflict of interest Yes / No
If yes, please detail below

21 b). If there are any conflicts of interest, please describe these in detail and justify conducting the proposed study.

None.

---

22. How do you $\checkmark$ **intend to disseminate the findings of this research?**

I intend to disseminate the findings of this research through presentations, publications, and sharing my results with technical persons and policy makers who are working in cancer field in Jordan.

I confirm that have read the University of Glasgow's Data Protection Policy
[http://www.gla.ac.uk/services/dpfoioffice/policiesandprocedures/dpa-policy/]

Please check initial box

Signed __Mohannad Al-Nsour   **Date:** 17 August 2010
(Proposer of research)

For student projects

I confirm that I have read and contributed to this submission and believe that the methods proposed and ethical issues discussed are appropriate.

I confirm that the student will have the time and resources to complete this project.

Signed __Mohannad Al-Nsour _____   **Date** _17 August 2010
(Supervisor of student)

Send completed _signed_ form to

Sarah Torbet
Medical Faculty Office
Wolfson Medical School Building
University Avenue
Glasgow

G12 8QQ
Tel: 0141 330 5921
Fax: 0141 330 5440

Please also send electronic versions of completed form and all other paperwork to
s.torbet@clinmed.gla.ac.uk

CENTRE INTERNATIONAL DE RECHERCHE SUR LE CANCER
INTERNATIONAL AGENCY FOR RESEARCH ON CANCER

IARC ETHICS QUESTIONNAIRE

This form should be completed by the Principal Investigator for all applications. Please answer all questions carefully. If you consider some of these are not relevant to your study, answer N/A. The IRB/ERC will decide.

1. Title of Research:

Full title

Colorectal cancer survival in Jordan 2003-2007

Acronym

Type of project *(please circle)*:
  i.   Studies based on grouped data (pooled and previously collected material)
  ii.   Descriptive epidemiological studies (record linkage and population surveys)
  iii.   Analytical epidemiological studies (case-control and cohort)
  iv.   Randomized population studies
  v.   Other

If other, give details:

Please indicate whether project funded on external funds: Yes   No   X

OR on the regular budget. Please provide Project Abstract Sheet reference:

2. IARC Principal Investigator:

Title: **Student**   First Name/Initials: **Mohannad**   Last Name: **AlNsour**

IARC Cluster/Group/Team: **Cancer Information Section**

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3. Proposed study dates and duration:

Start date:

| 01/05/2009 | 01/05/2012 |

Duration: Years:

| Three |

Months:

| - |

4. What is the principal research question / objectives? (Must be in language comprehensible to a lay person – up to 250 words)

Research questions:

1. What are the Observed and relative 5 years Survival rate of colorectal cancer in Jordan in patients diagnosed in 2003-2007?
2. Does survival from colorectal cancer differ between Jordan and other comparable countries, and if so, can these be explained by differences in patient factors, disease characteristics, or treatment?".
3. Are there survival differences between treatment cites *within* Jordan and how might they be explained?".

Objectives:

1. To produce estimates of observed survivals 1, 3, and 5 years for colorectal cancer Jordanian patients.
2. To report the influence on survival rates of patient's age, and the morphology, anatomical sub-site of the tumour, age at diagnosis, and type of treatment). Moreover, to determine the net effect of each of these different variables on the risk of survival rates of colorectal cancer patients.
3. To produce estimates of 5 years relative survivals for colorectal cancer Jordanian patients with their corresponding age-standard relative survivals.

5. What is the rationale and justification for the research? (Must be in language comprehensible to a lay person – up to 250 words)

Survival statistics are means of quantifying the effectiveness of early detection strategies and treatment regimes at the population level. They are useful as comparative measures between different populations. It is these comparisons that help us to identify possible reasons for the differences and suggest targets for improvement and a means of monitoring progress toward them. Nowadays cancer registry role has developed beyond providing cancer counts and incidence; cancer registry is plying a major role in monitoring and evaluation of screening programs, and following-up of cancer patients to examine the quality of cancer services they receive.

6. Provide practical details of the research to be conducted. It should be clear what happens to each research participant, how many times and in what order (up to 250 words)

In Jordan, there are two main referral centres provide treatment for patients with cancer; AL-Basheer hospital which belongs to ministry of health and King Hussein Cancer Center. The name of the center to honor the late King Hussein, who died of cancer, implied full Royal support for this project. These two centres are located in Amman the capital city of Jordan and they receive cancer patients from different governorates in the country. Furthermore, the two major histology laboratories are located in these two centres. All Jordanian colorectal cancer patients who diagnosed in 2003 (January 1st) – 2007 (December 31st) will be included in the study.

1. Colorectal cancer information patients will be officially collected from the Jordan cancer registry.
2. Identifying the vital status of the patients will be ascertained from Civil registration Bureau through unique National Identification number (ID) of the patients. ID number will be used for verifying the duplication.
3. Active strategies for completing the missing information will be followed :
   - Reviewing medical records of the hospitals.
   - Reviewing the pathological laboratory reports to obtain the missing information related to the site, stage, and grade of the cancer.
4. Patients not traced after these efforts, they will be considered as a lost of follow cases. No home visits or phone calls to the patients.

Written permissions to the Ministry of Health, King Hussein Cancer Center, Royal Medical Services Hospitals, private hospitals and labaratories, civil registration Beuro (Ministry of interior), and department of Health Statistics will be requested. Furthermore, a copy of the proposal should also be submitted.

7. Please list all partner institutions where the research will take place and indicate their tasks. Give details of the main investigator in each centre. For new partners, please provide their website address:

Name and address of institution	Main investigator
Ministry of Health	**Mohannad Al Nsour**
King Hussein Cancer Centre	**Mohannad Al Nsour**

8. Has local ethics approval been requested from all the partner institutions listed in question 7? If yes, what was the outcome? (Attach copies) If no, please indicate if it will be requested and if not, explain why.

Yes. Local ethics approvals have been requested from all the partner institutions listed in question 7.

9. Will the research participants receive any clinical intervention or procedure including taking samples of human biological material over and above that which would normally be considered a part of routine clinical care?

YES ☐   NO ☒ X

Additional intervention	Average number per patient		Average time taken (mins/hrs/days)	Details of additional intervention or procedure, who will undertake it and what training they have received
	Routine care	Research		

Add more details on a separate sheet if necessary.

10. Will research participants be subject to any non-clinical research-related interventions or procedures (for example, administration of questionnaires)?

YES ☐   NO ☒

Additional intervention	Average number per patient	Average time taken (mins/hrs/days)	Details of additional intervention or procedure, who will undertake it and what training they have received
	Research		

Add more details on a separate sheet if necessary.

11. Will interviews discuss any topics or issues that might be sensitive, embarrassing or upsetting?

YES ☐   NO ☒

If yes, give details of procedures in place to deal with these issues:

12. What are the potential adverse effects, risks or hazards for research participants either from giving or withholding medications, medical devices, ionizing radiation or from other interventions including non-clinical:

None

13. What is the potential for pain, discomfort, distress, inconvenience or changes to lifestyle for research participants:

None

14. What is the potential for benefit for research participants and the community as a whole?

Information about the survival rates will help us take further preventive and control measures in order to improve the quality of cancer care they receive. Survival data is an important tool to evaluate the effectiveness and efficiency of cancer health services.

15. What is the potential for adverse effects, risks, discomfort, distress or inconvenience to the researchers, technicians and nurses involved?

None

16. How will potential research participants in the study be (i) identified, (ii) approached and (iii) recruited? What are the principal inclusion and exclusion criteria?

Give details for controls separately if appropriate.

All Jordanian colorectal cancer patients who diagnosed in 2003 (January 1st) – 2007 (December 31st) will be included in the study. No sample size will be drowning. The outcome of interest is colorectal cancer cases is either alive or dead or unknown.

Inclusion criteria: All Jordanian colorectal patients (aged 15 years and above) who were diagnosed with invasive primary Colorectal cancer (C18-C20.9) during the period 2003 (January 1st- 2007 (December 31st) and registered in Jordan cancer registry verified by histopathology report.

Exclusion criteria: Non-Jordanian nationalities, any case with no histological report and prevalent and/or recurrent cases will be excluded from the study

17. Will any research participants be recruited who are involved in existing research or have recently been involved in any research prior to recruitment?

YES ☐   NO ☒   NOT KNOWN ☐

Give details and justify their inclusion:

```
```

18. Has any responsibility for the research been delegated to a subcontractor?

<div align="right">

YES ☐   **NO** ☒

</div>

Give details including name of research contract organization/site management organization and summary of delegated responsibility

```
```

19. Will informed consent be obtained from research participants?

<div align="right">

YES ☐   **NO** ☒

</div>

Give details of how it will be done and who will do it. Also provide the information sheet:

```
```

20. Describe and justify the inclusion of vulnerable groups: children, the elderly, those unable to consent because of mental incapacity.

```
Not applicable
```

21. Will a signed record of consent be obtained?

<div align="right">

YES ☐   **NO** ☒

</div>

If answer is YES, please provide copies. If answer is NO, please justify:

```
```

22. How long will the participants have to decide whether to take part in the research?

Not applicable.

23. What arrangements have been made for participants who might not adequately understand verbal or written information in the local language? *(e.g. translation, use of interpreters, etc.)*

Not applicable.

24. Will individual research participants receive any *payments* for taking part in this research?

YES ☐   NO ☒

Indicate how much and on what basis this has been decided:

25. Will individual research participants receive *reimbursement of expenses* or any other *incentives or benefits* for taking part in this research?

YES ☐   NO ☒

Indicate how much and on what basis this has been decided:

26. What arrangements have been made to provide indemnity and/or compensation in the event of a claim by, or on behalf of, participants for _non-negligent_ harm?

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```

27. How is it intended the results of the study will be reported and disseminated?

|_X_| Peer reviewed scientific journals
|X__| Internal report
|_X_| Conference presentation
|_X_| Other publication
|_X_| Submission to regulatory authorities
|__| Access to raw data and right to publish freely by all investigators in study or by Independent Steering Committee on behalf of all investigators
|__| Written feedback to research participants
|__| Presentation to participants or relevant community groups
|__| Other/None

If other/none of the above, give details and justify:

```
```

28. Will the research involve any of the following activities at any stage (including identification of potential research participants)?

YES [ ]   NO [X]

If yes, tick as appropriate:

|__| Examination of medical records by those who would not normally have access
|__| Electronic transfer by magnetic or optical media, e-mail or computer networks
|__| Sharing of data with other organizations
|__| Export of data
|__| Use of personal addresses, postcodes, faxes, e-mails or telephone numbers
|__| Publication of direct quotations from respondents
|__| Publication of data that might allow identification of individuals
|__| Use of audio/visual recording devices
|__| Storage of personal data which allows identification on any of the following:

|__| Manual files including X-rays
|__| Local study centre
|__| IARC computer

Further details:

>

29. What measures will be put in place to ensure confidentiality of personal data? Give details of whether any encryption or other anonymisation procedures will be used, and at what stage:

> Data will be handled in compliance with the Data Protection Act 1988. Information will be treated with utmost confidentially: At the analysis stage, computer generated numbers replace subjects. Identifying information and the results published with no reference to names of studied subjects. Results obtained from data collection and analysis stayed confidential and not used for purposes other than those mentioned in the proposal.

30. Where will the analysis of the data from the study take place and by whom will it be undertaken?

> The data analysis will take part at IARC setting. Section of information. The analysis will contacted by the main researcher under supervision of Dr.Forman head, section of cancer information and Dr.Morrison, Glasgow University.

31. Who will have control of, and act as the custodian for, the data generated by the study?

> The analysis will contacted by the main researcher under supervision of Dr.Foreman head, section of cancer information and Dr.Morrison, Glasgow University.

32. Who will have access to the data generated by the study?

The main researcher.

33. For how long will the data be stored? | 5 | **Months** | |

Give details of where they will be stored, who will have access, and of the custodial arrangements for the data:

Data files will be maintained on a single password protected computer. The main

researcher will control access to the computer.

34. Explain measures for specimen storage, transport and processing.

Include details of (i) where will the specimens be stored and for how long, (ii) who will have access to these samples, (iii) will identification of individuals be feasible.

Not applicable.

35. How has the scientific quality of the research been assessed? *(Tick as appropriate)*

|__| Independent external review
|__| Review within a multi-centre research group
|_X_| Internal review (e.g. involving colleagues, academic supervisor)
|__| None external to the investigator
|__| Other, e.g. methodological guidelines

If other, give details

If you are not in possession of any referees' or other scientific critique reports relevant to your proposed study, justify and describe the review process and outcome. If review has been undertaken but not seen by the researcher, give the details of the body which has undertaken the review:

A copy of any referees' comments or other scientific critique reports relevant to the proposed research must be enclosed with the application form.

36. What arrangements are in place for monitoring and auditing the conduct of the research?

37. Has funding for the research been secured?   YES ☐   NO [X]

Give details of funding organization(s), amount secured and duration of funding:

Organisation	
Address	
Postcode	
IARC contact	
Telephone	
e-mail	
Fax	
Amount €	
Duration (months)	

Organisation	
Address	
Postcode	
IARC contact	
Telephone	
e-mail	
Fax	
Amount €	
Duration (months)	

38. Will individual researchers, other than IARC staff, receive any personal payment over and above normal salary for undertaking this research?

YES ☐ NO ☒ X

Indicate how much and on what basis this has been decided:

---

39. Will the host organisation or the researcher's department(s) or institution(s) receive any payment or benefits in excess of the costs of undertaking the research?

YES ☐ NO ☒ x

Give details:

---

40. What do you consider to be the main ethical issues or problems which may arise with the proposed study, and what steps will be taken to address these?

1. Official approval of Jordan cancer registry to utilize available colorectal cancer data. Furthermore, official approval from the ethical committee at the Jordan ministry of health, King Hussein Cancer Center, Royal medical services, Department of Health statistics, and some of the private sector hospitals are needed to be obtained in advance.
2. Data will be handled in compliance with the Data Protection Act 1988
   - Information will be treated with utmost confidentially: At the analysis stage, computer generated numbers replace subjects.
   - Identifying information and the results published with no reference to names of studied subjects.
   - Results obtained from data collection and analysis stayed confidential and not used for purposes other than those mentioned in the proposal.

Please attach:
- **The participant information sheet**
- **The consent form**
- **The questionnaire**

- **The protocol**
- **Any advertising material**
- **Any other relevant documents**

(as appropriate)

Date 01/08/2010

Signature of Principal Investigator : Mohannad Al-Nsour

Signature of Group Head ………………………………………………………………..

Signature of Cluster Coordinator ……………………………………………………….

Confidentiality Form

I the undersigned: ……………………………………………………………

Agree not to disclose any information related to cancer patients that are registered at the

Jordan Cancer Registry.

I hereby sign, holding all responsibility to the above.

Full Name: --

Signature: --

Certified by Non_Communicable Disease Directorate

Certified by the Jordan Cancer Registry

Ministry of Health – NCDD

Jordan Cancer Registry

Amman-Ph.962 6 5662067

Request for Data from the National Jordan cancer Registry (JCR).

Date Submitted : ....

Name : ....

Department : ....

Institution : ....

Phone No : .... Fax No : .... Email :..

Information Requested :

(Specify ,Time Period ,Site,Histology,Region,etc.)

Purpose of Data Request:

(Presentation / conference/assembly /publication/clinical,epidemiological study,etc.)

Collaborators and Co-authors:

Requester's affirmation statement:

I hereby, supplicant of the above data affirm that the data given to me from the National Jordan Cancer Registry- JCR- will be treated with utmost confidentiality concerning patient's identity, I also confirm that the data given to me will not be presented or published by me or any of my collaborators as an original work but rather can be cited in my presentation and/or publication with acknowledgement to the JCR .also confirm to provide copy of my work and feed-back to the JCR.

Requester's Signature:.................................. Date:...

For administrative use only :

Request:/ Approved : ……………………….Not Approved…………………………………………………….

Director of Jordan Cancer Registry………………………………Sign…………………………………………

Director of Non-Communicable Disease Directorate…………………………….Sign………………………….

Date:…………………………….

<table>
<tr><td colspan="2" align="center">**FORM A : Exempt IRB Review**</td></tr>
<tr><td>**Version**</td><td>1.1</td></tr>
<tr><td>**Date Approved**</td><td>February 2010</td></tr>
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<tr><td align="center">**IRB Number**</td><td></td></tr>
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<tr><td>**Principal Investigator**</td><td>Dr.Mohannad Al Nsour</td></tr>
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Check list for a complete submission

A. The following documents **must** be submitted for the **Exempt Review** so that the application will be considered as complete and an IRB number will be then generated:

☐ CV(s) of Principal Investigator(s).
☐ Confidentiality Agreement for "Chart Reviewer(s)" only.
☐ Grant Application (if any)
☐ Consent Form (if any) or Request for Waiver of Consent Form. (Only for questionnaire/survey)
☐ Questionnaire or Survey (if any)
☐ Data Collection Sheet (if any)
☐ Other study related documents such as Investigator's Brochure, other Institutional IRB Approvals, Flyers, Advertisement... etc (if any). This should be identified by version and issue date.

B. Please **NOTE** the followings:

- You must use the most updated IRB-form version.
- The IRB form is to be electronically completed (it cannot be hand written).
- The IRB form must be signed by ALL investigators and co-investigators properly.
- Upon completion of the submission process, the study will be assigned an **IRB-proposal number**, without this number, the study will not undergo any review from the IRB.

For more help, please contact the IRB office on:
   Tel   : (+9626) 5300460 Ext 1669
   Email: irboffice@khcc.jo

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(1) Study team

1.1 Principal Investigator(s):

Principal Investigator from KHCC: Mr.Wael Shilbayah	**Department:** CTR-CRRO
Telephone Number:	**Fax Number:**
E-mail address: wshilbayah@khcc.jo	
By signing, the PI assures that he/she will protect the privacy and the rights and welfare of human research subjects to the best of his/her ability.	
Signature of the KHCC PI:	**Date:**
KHCC Department Chairman Name:	**Signature:**	**Date:**

Principal Investigator from outside KHCC: DR.Mohannad Alnsour	**Signature:**

1.2 Co-Investigator(s)

Co-Investigator	Department	Telephone	E-mail	Signature	Date
Mr.Wael Shilbayah					
Dr.kamal Arqoob					

Signature of all Co-investigators acknowledges that they are thoroughly familiar with the contents of this research and pledge to assist the PI in protecting the privacy and the rights and welfare of human research subjects.

1.2.1 Chart Reviewer(s):

The PI must define a chart reviewer. He /she will be responsible for collecting patients' data from the medical records.

Chart-Reviewer: Mr.Wael Shilbayah   **Signature:**
Chart-Reviewer: Dr.kamal Arqoob   **Signature:**
Chart-Reviewer: **Signature:**
Chart-Reviewer: **Signature:**
Chart-Reviewer: **Signature:**
Chart-Reviewer: **Signature:**

1.3 Research Office: *Information about Research Staff is intended to facilitate communication.*

Clinical Research Coordinator CRC:	Telephone Number:
	E-mail address:
Biostatistician:	Telephone Number:
	E-mail address:

(2) Exempt from IRB review?

2.1 Does the protocol include?

      2.1.1 - Children (Only for Interviews/Surveys)   ☐Yes   ☒ No

      2.1.2 - Fetuses, pregnant women, or human in vitro fertilization   ☐Yes   ☒ No

      2.1.3 - Cognitively impaired   ☐Yes   ☒ No

      2.1.4 - Deception of subjects   ☐Yes   ☒ No

If any one of the answers is **Yes**, then the protocol is **NOT exempt,** you need to **complete Form-B**

2.2 Assessment of risk level of your project;

      Above than minimal risk   ☐Yes   ☐ No

      At the level of minimal risk   ☐Yes   ☐ No

      Lower than minimal risk   ☒Yes   ☐ No

If it qualifies at "level of" OR "more than" minimal risk, then the protocol is NOT exempt, you need to complete Form-B

2.3 The protocol must qualify under one of the following categories:

    2.3.1 ☐ **Surveys/ Interviews/ standardized educational tests/ observation of public behavior.**

Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures or observation of public behavior if: (1) information obtained is recorded in such a manner that human subjects cannot be identified, directly or through identifiers linked to the subjects; or (2) and disclosure of human subjects' responses outside research would not reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability or reputation; AND children are not involved.

  **Observation of public behavior in children may be exempt if the investigator does not participate in the activities being observed.*

    2.3.2 ☒ **Secondary use of pre-existing data.**

Research involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens (1) if these sources are publicly available, OR (2) if the information is recorded by the investigator in such a manner that subjects cannot be identified directly. "Existing data" means that the information or materials must already exist at the time of the research proposal, i.e. no on-going collection. If any of the above mentioned points (1 or 2) is not meet, then the project can not be exempt. It might be reviewed under expedited review.

    2.3.3 ☐**Research involving materials to be collected solely for non-research purposes.**

Research involving materials (data, documents, records, or surplus specimens) that will be collected solely for non-research purposes (such as medical treatment or diagnosis). Some of these might be reviewed under expedited review.

2.3.4 ☐ Taste and food quality evaluation.

Taste and food quality evaluation and consumer acceptance studies: (1) if wholesome foods without additives are consumed; or (2) if food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural chemical or environment contaminant at or below the level found to be safe, by the JFDA or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the Jordanian Ministry of Agriculture.

4.3.5 ☐ Contract laboratory for de-identified sample analysis.

Analyzing de-identified samples in a specialty laboratory or reading center if: (1) the investigator will never have access to the subject identifiers, and (2) the investigator is not a consultant, co-investigator, or author in the study, and (3) the investigator did not contribute to the protocol other than related to the assay or service provided by his/her laboratory. [Examples: serving as the ECG reading center or measuring plasma vasopressin on de-identified samples for a national trial with no other involvement in the trial.]

(3) Research Summary

3.1 Research Title:

Colorectal cancer survival in Jordan 2003-2007
3.2 Purpose of the Study:
☐ Poster/ Oral Presentation at Conference.
☐ Research Paper for Publication.
☐ Master Degree
☒ Ph.D. Degree
☐ Others

3.3 Study Design

Aims

Explore observed and relative 5 years Survival rate of colorectal cancer in Jordan in patients diagnosed in 2003-2007

Identify the determinants (age, sex, site, grad, stage, treatment) of the Observed 5 years Survival rate of colorectal cancer in Jordan in patients diagnosed in 2003-2007

Rational/Hypothesis:

Our hypothesis is that there are differences in survival between Jordanian colorectal patients compared to colorectal patients in the developed countries; in addition to differences in survival between patients treated at different hospital services in Jordan (public health, teaching, and military hospitals) and that these differences could be explained by differences in patients' management.

Our study will take place at national level including all Jordanian colorectal patients (aged 15 years and above) who were diagnosed with invasive primary Colorectal cancer (C18-C20.9) during the period 2003 (January 1st- 2007 (December 31st) and registered in Jordan cancer registry verified by histopathology report.

The outcome of interest is the status of colorectal cancer cases (live, dead). The time at risk for each case will be measured by months from date of diagnosis to the last contact date. A special form was developed to collect the requested information. This information include

1. **Sociodemographic data**: ID number, name, sex, age, date of birth, address (Governorate), main source of medical services, having health insurance, the type of health insurance, and date of diagnosis.

 2. **Clinical data**: site, grade, stage, and morphology.

3. **Type of treatment** collected from medical records from main hospitals and pathological laboratories.

4. **Vital status data:** if the patient alive or dead. The starting point is the date of patients' diagnosis, as reported in files from 2003-2007.

Proposed Sample Size:

The overall sample size for this study is 2,000 cases from different sites. The estimated sample size from King Hussein cancer center is 400.

Statistical Consideration:

Data collected will be analyzed in the following manner:

1. Descriptive analysis (frequencies, and percentages and cross-tabulation) of the baseline characteristics.
2. Kaplan Maier method will be used to determine the observed survival probability over the time.
3. The effect of different predictors on survival rate (age at diagnosis, sex, stage, site, grade, and type of treatment) will be observed through survival graphs and using log rank test.
4. Cox proportional hazard regression will be used to assess the net effect of each variable after simultaneously controlling the effects of potential confounders.

5. Life table for Jordanian population will be used to produce relative survivals (there is no available information on cause-specific mortality during the study time period, thus the calculation of cause-specific survival is not applicable).
6. To compare the result with other countries, age-standardized relative survival will be calculated.
7. Data will be analyzed using STATA (version 10).

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3.4 Other sites where the research will be performed:

The research will be also performed at the AL-Basheer Hospital

3.5 Source of Funding:

The source of funding will be the International Agency for Research on Cancer (IARC) which is part of the World Health Organization