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Colorectal Cancer Survival and Mortality, Kingdom of Saudi Arabia, 2011 – 2015

By

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Rami Dafas AlDafas, BSc, Majmaah University (2014)

Thesis Committee Chair: Scott JN McNabb, PhD, MS

An abstract of

a thesis submitted to the Faculty of the

Rollins School of Public Health of Emory University

in partial fulfillment of the requirements for the degree of

Master of Public Health

in Hubert Department of Global Health

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ABSTRACT

Background: Colorectal Cancer (CC) has grown exponentially, particularly in the Kingdom of Saudi Arabia (KSA), to become common among women and men. Surviving CC has become challenging in KSA due to religious and educational reasons, one of which is that screening is not understood and accepted well as a preventive measure. The objective of this study is to assess the survival and mortality rates of CC in KSA during the period 2011 – 2015, especially gender and age-specific survival rates, plus geographic distribution and magnitude.

Methods: Reported CC cases between 2011 and 2015 were analyzed from the Saudi Cancer Registry. Descriptive analyses summarized distributions by gender and Kaplan-Meier curves were generated using SPSS that described survival characteristics. Kaplan-Meier graphs were generated to illustrate differences between stage, location, gender, age, and geographic region. Cox regression was used to identify any relationships between survival time and socio-demographic and pathological factors among reported cases of CC.

Results: The most-affected age group by CC was 45 – 75 year old (69.8% of reported cases). There were significant differences in the status and cancer location of reported cases by age and class. There was a greatest risk of death among those <30 years of age. We found no association between geographic region and survival, but there was a significant relationship between stage of CC and survival time. Notably, the death hazard for a reported female case was 1.07 times that of a male.

Conclusions: CC is one of the most prevalent cancers globally and in KSA. Understanding the survival and mortality indices can influence healthcare policies of screening, diagnosis, and treatment. This study showed that both the young and old are at risk of developing CC. CC has a high hazard ratio and low survival rate. We recommend a change of policy for intensifying the screening of CC among both young and older adults. Risk stratification should be emphasized to identify those with heredity and familial risk of CC.
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I am extremely grateful to my Lord (Allah) for providing me the opportunity to learn and grow on personal and professional levels and for helping to make this thesis possible.

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Chapter 1 – Introduction

Background

One of the most common types of cancer is colorectal cancer (CC). In GLOBOCAN's global statistics from 2012, CC was the second most common cancer in women and third most common in men; the number of new cases reportedly reached 1,400,000 [17]. Developed nations accounted for most cases (55%). Australia and New Zealand reportedly had the highest age-standardized rates, estimated to be 44.8 per 100,000 men and 32.2 per 100,000 women [20]. The lowest prevalence was in western Africa, with age-standardized rates estimated to be 4.5 per 100,000 men and 3.8 per 100,000 women [20]. As with the global prevalence, CC is the third most common and third leading cause of global cancer mortality for men and women. In 2012, CC accounted for > 8.5% of all cancer deaths worldwide; this translates to 694,000 deaths. Perhaps most notable is that the majority of deaths occurred in developing countries despite low prevalence in this context [20].

In the Kingdom of Saudi Arabia (KSA), the incidence of CC has increased significantly since the first reported case in the Saudi Cancer Registry (SCR) in 1994 [6]. According to Alharbi [3], the incidence of CC in KSA is akin to that of developed countries; it is the third most common cancer type among women and the most common among men [3]. In 2013 alone, statistics from the cancer incidence report revealed that CC accounted for 11.9% of all cancer cases in the people surveyed [3]; 46.9% women and 53.1% men. In addition, CC is the second most prevalent cancer type in KSA when standardizing population age; the age-standardized KSA rate for CC for women was 10.1 per 100,000 and 11.7 per 100,000 for men [3]. It is also interesting to note that most at risk for CC are older people. Geographical location is also a risk factor for CC in KSA, as evidenced by the variation in the age-standardized rate [3].

Given the significance of CC for public health, policies relating to CC screening are needed. In examining the screening policy for CC in KSA, Aljumah and Aljebreen [5] noted that all countries should develop and implement control programs per recommendations of the World Health Assembly and the World Health Organization. Among other requirements, such policies should be given in writing to facilitate review and consultation with a wide range of stakeholders. It closely follows that the Ministry of Health's (MoH) proper endorsement is necessary to ensure that there is sufficient political input in terms of resource allocation. The involvement of the MoH could also ensure that the prevention and treatment of CC are high-priority actions as the recommending bodies suggest [5].

Considering the rise in the incidence of CC in KSA and the global emphasis for a national CC in the world, this paper aims to investigate the survival and mortality of reported cases of CC in KSA from 2011 – 2015. This investigation is part of a broader aim to increase awareness of the disease and influence policy interventions.

Problem Statement

KSA continues to witness unprecedented changes amid the socioeconomic improvements attributable to oil-driven wealth. These noteworthy lifestyle dynamics vis-à-vis nutritional and epidemiologic changes necessitate inquiry into CC, with a focus on recent epidemiologic findings that help illuminate the patterns and health burden associated with CC. CC is a source of concern in KSA, as in other parts of the world. Aljumah and Aljebreen [5] observed that the KSA MoH has yet to adopt relevant policies for CC screening. It is likely that these issues will significantly influence the survival and mortality rates associated with CC on a collective or individual basis. Therefore, it is not only necessary but also a timely issue to examine this in KSA. Perhaps such data can serve as a crucial first step in determining whether these issues influence the outcomes of the disease.

Significance of the Problem

This study will be invaluable for both policy and practice. By understanding the survival and mortality related to CC, policymakers can find appropriate screening interventions. In addition, this study can influence the KSA healthcare settings and practitioners; it can prompt administrators to implement appropriate treatment interventions. It would also be incumbent on these institutions to invest in the most effective technologies and personnel for improving their patients' health outcomes. Overall, the data obtained from this study will go a long way toward bridging the gap between knowledge and awareness.

Purpose

The main objective of this study is to assess the survival and mortality rates of CC in KSA during the period 2011 – 2015. In addition, the following specific objectives are to …

- estimate the gender- and age-specific survival rates and mortality from 2011 –2015
- estimate the distribution and magnitude of colorectal cancer from 2011 – 2015

Chapter 2 – Literature Review

Countries experiencing rapid socioeconomic changes are witnessing a significant rise in lifestyle-related health outcomes amid a decline in infectious-related ones [22]. The World Cancer Research Fund [22] notes that colorectal cancer (CC) constitutes one the clearest marker of the nutritional and epidemiologic transition accompanying these changes. The rising incidence in the world -- becoming the third most common cancer globally -- underscores the need for research [13,22]. As the KSA experiences significant transformation (associated with oil-driven wealth) discernible lifestyle changes with nutritional and epidemiologic changes require research on CC, helping to illuminate preventable interventions and the health burden.

Therefore, we review CC in KSA plus provided an analytic assessment to juxtapose the global and regional burdens and discussed risk factors: demographic; geographic; clinical determinants; plus protective interventions to improve survival rates.

Colorectal Cancer

CC is a carcinoma of the large intestine; one originating and affecting the colon or rectum [18]. Cancers affecting the colon or rectum are grouped under the umbrella of CC because of many shared features. CC starts as growth on the colon or rectum's inner lining, producing polyps. However, not all polyps become cancerous, with adenomatous polyps sometimes changing into cancer while the more common hyperplastic and inflammatory polyps are not pre-cancerous [7].

Cancers forming in a polyp may grow over time from the innermost lining into the wall of the colon or rectum. The cancer cells can then grow into blood vessels and lymph vessels, allowing them to travel to proximal lymph nodes or distant body parts. The stage of CC refers to the extent of spread of the cancer, translating to the depth of growth into the wall as well as spread beyond the colon or rectum [7].

Colorectal adenocarcinoma is by far the most common type, with others being less common or even rare. Adenocarcinomas, constituting 95% of colorectal cancers, grow in epithelial cells of the colon or rectum and may be mucinous or signet ring cell adenocarcinomas depending on constitution or appearance [12]. Carcinoid tumors (associated with intestinal hormone-making cells), gastrointestinal stromal tumors (starting from the interstitial cells of Cajal), lymphomas (affecting immune system cells), and sarcomas (starting in blood vessels, muscle layers, and other connective tissues) are less common types of CC [7].

Global Burden

CC is a leading cause of mortality and morbidity worldwide; it ranks third most commonly diagnosed cancer among males and the second among females while accounting for 9% of all cancer cases globally [14]. CC is the fourth leading cause of cancer death globally, accounting for 1.4 million new cancer cases and 700,000 deaths annually. This represents 8% of all cancer deaths [9,14]. Projections based on temporal profiles and demographics demonstrate that the global burden of CC may increase, rising by 60% to more than 2.2 million new cases of CC alongside 1.1 million deaths by 2030 [9].

The burden of CC varies around the world; > 2/3 of the incidence and 60% of its mortality are in countries with a high or very high human development index [9]. However, incidence has been rising in the developing world, associated with changes in lifestyle and nutrition [14]. At the same time, incidence around the world varies by gender, being substantially greater among men. This gender variability remains concerning, with commentators citing complex interactions between sex-specific risk factor exposures, protective effects associated with endogenous and exogenous hormones, and gender-specific differences found in screening practices [14]. Ultimately, global review reveals CC as a significant health burden with geographic and gender differences. Research will inform urgent interventions and determine the design and implementation of interventions.

Colorectal Cancer in the Middle East

The global burden of CC has wide regional variations. In the Middle East, the data reported for incidence and mortality are lower than those for developed countries (Fig 1). The incidence has increased significantly over the past decade [8]. However, while an increase in the CC incidence rate was observed in the Middle East, the trends vary among different countries in the region. Alhurry [4] reported worrying surges in the incidence rates in Kuwait, as well as the Jordan River and Gaza Strip, followed by Syria, Turkey, and Lebanon. Meanwhile, the rest of the Middle Eastern countries were characterized as having low to mild risk of CC, with the southern countries in the Middle East, such as Oman and Yemen, having some of the lowest risks in the world. In a similar fashion to the global gender variability, a male preponderance was observed in the burden of CC in most countries in the Middle East, with reports indicating a higher proportion of men to women with CC [4].

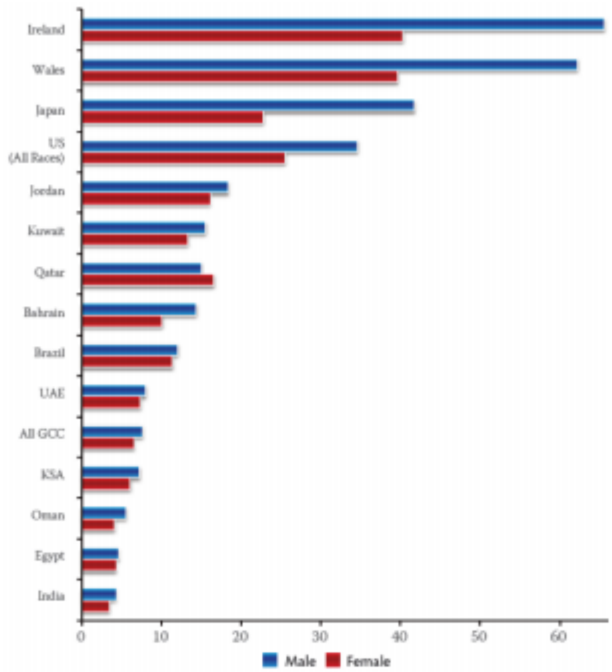

Figure 1: Comparison of CC incidence rates in a number of Middle Eastern countries, juxtaposed against some developed countries [8]

Scholars have explored explanations for the aforementioned rise in CC in the Middle East. Arafa and Farhat [8] cited a number of drivers, including lifestyle changes, food consumption trends, and obesity amid the replacement of the consumption of traditional foods with Western-style foods and ready-made preparations. At the same time, while many high-income countries have rolled out population-based screening programs that help address incidence and mortality, such programs were found to be absent in many countries in the Middle East. Arafa and Farhat [8] suggested that the lack of screening programs may be driven by cultural and religious barriers alongside a lack of higher education or familiarity with the disease.

Colorectal Cancer in KSA

Bazarbashi, Al Eid, and Mingue [10] clarified that the SCR provides population-based cancer statistics in KSA, publishing epidemiologic data on cancers in the country covering the period of 1994 to the present. Based on the SCR data for 2014, the incidence data revealed that CC accounted for 11.5% of all newly diagnosed cancer cases among KSA nationals, ranking first among men (10.6/100,000) and third among women (8.2/100,000) [19]. Earlier data from 2012 showed similar patterns, with CC ranking first in incidence among men, at 13.3%, and third among women, at 9.3% [10]. Beyond the incidence, the overall 5-year survival rate for CC was 44.6% for the period 1994-2004, with more recent data lacking; the researchers explained the low survival rate as being associated with the lack of screening and specialized care outside major cities, among other factors [6]. The incidence of CC in KSA is significantly lower than the incidences of the developed countries in the West; lower than some Middle Eastern countries, such as Jordan; and higher than Middle Eastern countries, such as Oman (Fig 2).

Another crucial observation regarding CC in KSA was the age at the time of diagnosis, which Alamri, Saeedi, and Kassim [2] found to be low compared with reports from developed countries. Meanwhile, the median age at presentation for CC in KSA remained stable, at about 60 years for men and 55 years for women [6]. Considering that CC presents at a significantly younger age among Saudis, especially in women, decisions regarding the threshold age for screening should consider the age of presentation [6].

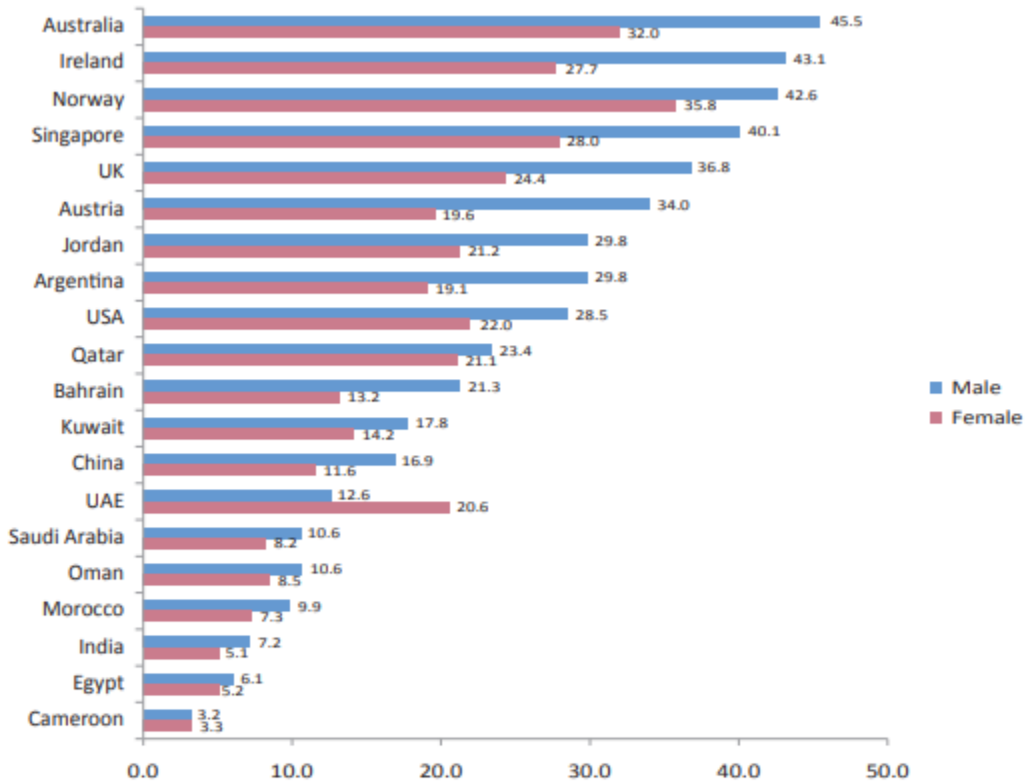

Figure 2: Comparison of the age-standardized rates of CC in KSA and selected countries [19]

Etiology and Risk Factors for Colorectal Cancer in KSA

The implementation of effective public health interventions against CC depends on understanding the underlying drivers and risk factors for the disease, which calls for attention to nutrition, physical activity, and lifestyle changes; genetics and family history; medical conditions and drugs; and demographic factors. In terms of nutrition and lifestyle changes, scholars have pointed to the discernible Westernization of the KSA diet as one of the drivers [21]. Alamri, Saeedi, and Kassim [2] agreed with this assertion, observing that long-term behavior modifications in aspects like food choices, dietary patterns, and physical activity are crucial in addressing CC in KSA.

Genetics and family history are also good predictors of the likelihood of developing CC in KSA. Al Wutayd [1] observed that first-degree relatives of patients with CC have double the risk, while siblings of subjects with advanced neoplasm have four times the risk of also being diagnosed with advanced neoplasm. Sibiani [21] agreed with this claim, observing that genetic predispositions have been linked to CC for many years, as exemplified by the K-RAS mutation. Beyond genetic factors, other risk factors include smoking, non-alcoholic fatty liver disease, metabolic syndrome, and use of non-steroidal anti-inflammatory drugs. [1,2]

Demographic Factors

Beyond risks and drivers, demographic factors like age and gender also contribute to the CC burden borne in KSA, and it is important to consider these issues for establishing effective interventions. In terms of age, Al Wutayd *et* al. [1] noted that one of the major risk factors for CC is the patient's age, which has led to many guidelines recommending colorectal cancer screening for individuals aged 50 years and older. The risk of developing CC increases with age, with the median age at diagnosis being 60 years among men (range: 17 – 110 years) and 57 years among women (range: 14 – 100 years). (Fig 3)

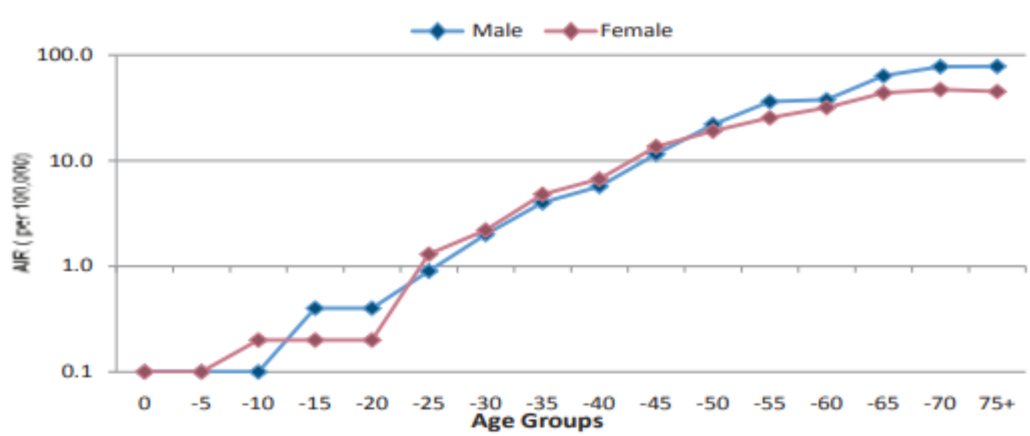

Figure 3: Age-specific incidence rate for CC in KSA [19]

In addition to age, gender constitutes a crucial demographic factor relevant to CC in KSA, as demonstrated by the age standardized rate of 10.6/100,000 for men and 8.2/100,000 for women [19]. Sibiani *et* al. [21] ranked CC first among males and third among females in terms of the incidence of all cancers in KSA. Gender disparities have also been found in terms of survival rates, whereby the 5-year survival rate for KSA men, at 41%, is significantly lower than that for KSA women, at 50.6%. (Fig 4) The explanation for the aforementioned difference in survival rates may lie in KSA women's potentially having a lower threshold for seeking medical attention compared with men, which would translate into KSA women presenting earlier in the course of cancer than their male counterparts.

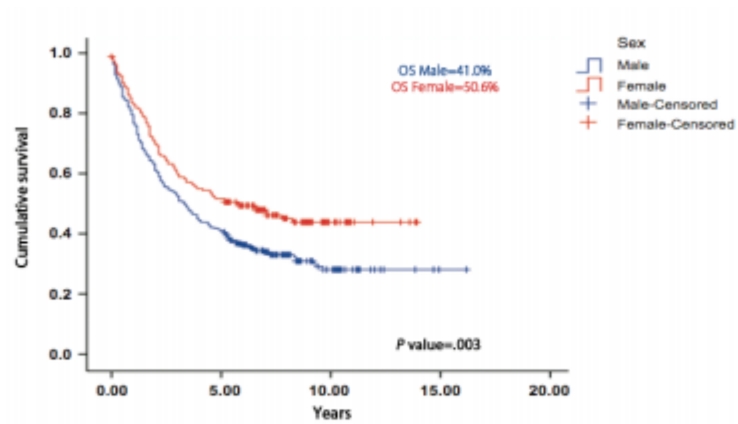

Figure 4: Survival curve for CC in KSA, stratified by gender [6]

Geographic Variation

The epidemiology of CC varies geographically in KSA, continuing the theme of the global health burden varying by world regions and the burden in the Middle East varying across nations. The regions bearing the highest age-standardized incidence rates include the Eastern region (13.6/100,000), Riyadh (13.1/100,000), Makkah (11.7/100,000), Qassim (10.8/100,000), and Tabuk (10/100,000) among males [19]. Among females, the regions with the highest incidence includes Riyadh (14.5/100,000), the Eastern region (10.2/100,000), the northern border region (8.7/100,000), Makkah (7.9/100,000), and Qassim (6.9/100,000). Meanwhile, Baha, Jouf, and Jazan have the lowest age-standardized rates. (Fig 5) Such geographic variation constitutes another pertinent consideration for the development, implementation, and distribution of interventions, such as screening and public health campaigns for colorectal cancer in KSA.

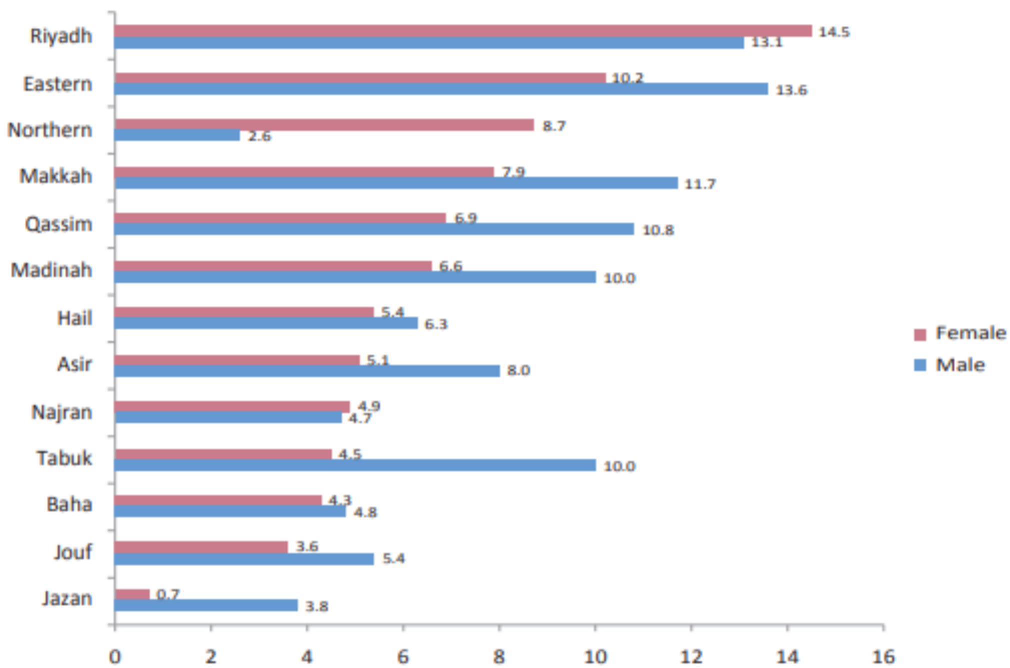

Figure 5: Geographic variation of CC in KSA [19]

Clinical Factors

Clinical factors are relevant in the context of management and treatment outcomes and access to services. Aljumah and Aljebreen [5] provided an overview of various relevant clinical considerations for CC, beginning with the observation that the recent publication of clinical practice guidelines for CC in KSA constitutes a major step in managing the disease. However, policies, which are stricter high-level statements supported by a higher degree of consensus than guidelines are, may foster the positive influence of clinical guidelines in improving the management of CC. At the same time, the two scholars observed that the clinicopathological patterns of CC in the KSA context reveal that advanced-stage disease and a high incidence of adverse prognostic factors are substantially more common presentations among young patients. Indeed, young people seem to exhibit worse survival than their older Saudi counterparts do. Zubaidi *et* al. [25] agreed with this finding, observing that CC survival closely relates to the clinical and pathological stage at diagnosis, with young age being associated with more severe disease and higher mortality in the KSA population.

Another important consideration pertains to the availability of modern technological innovations in the diagnosis and management of CC, which may also play a crucial role in determining outcomes [16]. In vivo cytological examinations through tools like confocal laser endomicroscopy, optical coherence tomography, and endoscopic ultrasound are accessible in Saud Arabia. Guraya [16] observed that endoscopic ultrasound is proving highly valuable as a clinical adjunct in the management of CC. The knowledge that technological innovations have crucial management implications for CC may inform expenditure in relation to the disease, as well as the distribution of resources, considering that some regions may have higher access to the best clinical equipment in ways that skew the outcomes.

Interventions for Improved Colorectal Cancer Survival Rates

A number of factors play a role in determining CC survival rates, and they have been explored in the KSA context. These factors relate to the personal or individual and societal levels, translating into crucial public health implications. At the individual level, issues like nutrition (food choices and dietary patterns) and physical activity are crucial in the management of CC in KSA [2]. At the societal level, screening constitutes one of the factors that may improve survival rates among those with colorectal cancer. Aljumah and Aljebreen [5] reported that screening through approaches like sigmoidoscopy and colonoscopy has the capacity to prevent most deaths from distal CC. International case studies have demonstrated the usefulness of screening in improving survival rates for the disease [5]. However, gaps in screening exist in KSA, both in terms of the availability of screening services and public awareness. Guraya [16] noted the lack of nation-wide screening programs, which may be driven by cultural–religious barriers alongside the absence of public awareness campaigns. The latter issue of public awareness related to CC constitutes the next societal factor that may determine improved survival rates. Public awareness would lead to improved survival through screening, earlier intervention, and behavioral modifications in terms of nutrition, physical activity, and lifestyles. However, Aljumah and Aljebreen [5] noted the lack of sufficient awareness of screening, polyps as a risk factor for CC, and family history among both the public and practitioners. Bridging the knowledge and awareness gap in these areas may help improve survival rates.

Chapter 3 – Manuscript

Introduction

One of the most common types of cancer is colorectal cancer (CC). In GLOBOCAN's global statistics from 2012, CC was the second most common cancer in women and third most common in men; the number of new cases reported reached 1,400,000 [17]. Developed nations accounted for most cases (55%). Australia and New Zealand reportedly had the highest age-standardized rates, estimated to be 44.8 per 100,000 men and 32.2 per 100,000 women [20]. The lowest prevalence was in western Africa, with age-standardized rates estimated to be 4.5 per 100,000 men and 3.8 per 100,000 women [20]. As with the global prevalence, CC is the third most common and third leading cause of global cancer mortality for men and women. In 2012, CC accounted for > 8.5% of all cancer deaths worldwide. This translates to 694,000 deaths. Perhaps most notable is that the majority of deaths occurred in developing countries despite low prevalence in this context [20].

In the Kingdom of Saudi Arabia (KSA), the incidence of CC has increased significantly since the first reported case in the Saudi Cancer Registry (SCR) in 1994 [6]. According to Alharbi [3], the incidence of CC in KSA is akin to that of developed countries; it is the third most common cancer type among women and the most common among men [3]. In 2013 alone, statistics from the cancer incidence report revealed that CC accounted for 11.9% of all cancer cases in the people surveyed [3]; 46.9% women and 53.1% men. In addition, CC is the second most prevalent cancer type in KSA when standardizing population age; the age-standardized KSA rate for CC for women was 10.1 per 100,000 and 11.7 per 100,000 for men [3]. It is also interesting to note that most at risk for CC are older people. Geographical location is also a risk factor for CC in KSA, as evidenced by the variation in the age-standardized rate [3].

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Considering the rise in the incidence of CC in KSA and the global emphasis for a national CC in the world, this paper aims to investigate the survival and mortality of reported cases of CC in KSA from 2011 – 2015. This investigation is part of a broader aim to increase awareness of the disease and influence policy interventions.

Problem Statement

KSA continues to witness unprecedented changes amid the socioeconomic improvements attributable to oil-driven wealth. These noteworthy lifestyle dynamics vis-à-vis nutritional and epidemiologic changes necessitate inquiry into CC, with a focus on recent epidemiologic findings that help illuminate the patterns and health burden associated with CC. CC is a source of concern in KSA, as in other parts of the world. Aljumah and Aljebreen [5] observed that the KSA Ministry of Health has yet to adopt relevant policies for CC screening. It is likely that these issues will significantly influence the survival and mortality rates associated with CC on a collective or individual basis. Therefore, it is not only necessary but also a timely issue to examine this in KSA.

Perhaps such data can serve as a crucial first step in determining whether these issues influence the outcomes of the disease.

Significance of the Problem

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Purpose

The main objective of this study is to assess the survival and mortality rates of CC in KSA during the period 2011 – 2015. In addition, the following specific objectives are to …

- estimate the gender- and age-specific survival rates and mortality from 2011 –2015.
- estimate the distribution and magnitude of colorectal cancer from 2011 – 2015.

Methods

Data Source

These data were obtained from the Saudi Cancer Registry (SCR), a population-based registry established by the Ministry of Health (MoH) in KSA in 1994 to record all newly diagnosed cases of cancer, with information on site and histology. The SCR collected data from healthcare facilities across all 13 administrative regions of KSA.

Study Design

This is a retrospective, descriptive epidemiologic analyses of all recorded cases of CC in the Saudi Cancer Registry (SCR) from 2011 to 2015. Statistical analyses were conducted with descriptive statistics, Kaplan and Meier graphs, and Cox regression. For data analysis, SPSS was used to perform all analyses.

Study Variables

Independent variables were region and clinical factors (i.e., stage, location). The dependent variables were mortality and survival. Control variables were age group and gender. All variables were categorical. The geographic region variable was originally divided into six: Central, Eastern, Northern, Western, Southern, and Unknown (other regions). Central (Qaseem and Riyadh), Eastern (Dammam and Al-Qatif, Al-Hassa, and Al-jubil), Northern (Al-Jawf, Northern borders, Ha'il), Southern (Al-Bahah, Jizan, Aseer, and Najran), and Western (Jeddah, Madinah, Makkah). The age group was coded into six: < 30 years of age; from 30 to 45 years of age; from 45 - 55 years of age; 55-56 years of age; 65-75 years of age, and from 75 to 122 years of age. Location of cancer was subdivided into three: colon; rectosigmoid; and rectum, and stage was subdivided into four: distant metastasis, localized, regional, and unknown.

Ethics

The study was based on secondary data without any identifiers; it did not meet the category of human subject's research and thus was not subject to review by the Emory University Institutional Review Board (IRB).

Statistical Analyses

From 2011 to 2015, there were 6,876 case reports in KSA registered in the Saudi Cancer Registry database (Table 1); 6,875 patients were Saudi and one was non-Saudi, whose data were removed. All 6,875 patients were followed from 2011 and 2015; the last reported case was Nov 2, 2018. The output considered in our analyses was survival. Variables were divided into two groups: demographic (gender, age, and geographic region) and clinical/pathological factors (stage and tumor location).

We noted that there were missing values for some variables. So, we cleaned the dataset to find and eliminate errors. In first step, we keep all missing points in the descriptive analysis, in the second step, we delete them from data during Cox regression.

Descriptive analyses summarized characteristics (mean, median for quantitative variable, and mode for categorical variables). A nonparametric test Wilcoxon–Mann–Whitney was done to test of the null hypotheses that equally likely a randomly selected value from one group would be different to a randomly selected value from a second group (male and female). But, the Mann-Whitney test could not be done to compare between more than two independent groups. So, a rank-based nonparametric test, the Kruskal-Wallis test (one-way ANOVA on ranks) determined if there were statistically significant differences between two or more groups of an independent variable on an ordinal dependent one (age classes, region groups, stage groups, location groups).

We performed survival analysis and generated a Kaplan-Meier survival plot using SPSS. We were interested in the time until death occurred. So, we created a median of life table and the Kaplan-Meier curve, to describe survival characteristics for our sample. Kaplan-Meier is the most common method to graphically present the data showing the proportion of patients who were alive at each time point that a death was observed. Log-rank test is a commonly used method to comparing survival outcomes between groups. The median survival is the smallest time at which the survival probability drops to 50% or below. The median survival time are reported with their 95% confidence interval (CI).

Kaplan-Meier tests were done to illustrate the difference between, stage, location, gender, age, and geographic regions. But, analyzing data with Kaplan-Meier can only describe the survival according to one factor under investigation and ignores the impact of others. So, we completed our analysis by Cox regression. To investigate the effect of variables upon the time a death, a Cox regression is the proper method. Cox regression was done for investigating the association between the survival time of reported cases and the predictor variables, sociodemographic, and pathological factors. The survival model related the time that passes before death occurred, to covariates that may be associated with that quantity of time. P-values were two-tailed. P-value <0.05 was considered significant. Rates were compared using probability of success ratios and 95% confidence interval (CI).

The survival function was evaluated from the survival times of all patients, regardless of any factor retained in the study, because the associated covariate factors of reported cases of CC should have an impact on survival times. For example, confounders alter the association between risk factors and outcomes; they should be adjusted in the model. The analytic Cox regression analyzed the association between tumor stage, location of cancer, and outcome and was very similar to logistic regression models that we used for binary variables: status=1 if the patient died; and status=2 if the patient survived. Five variables were incorporated into the model: stage, location, gender, age, and region.

Results

1- Descriptive

Male case-patients accounted for 54.7% (3,764) of the records; female case-patients accounted for 45.3% (3,111). Overall, patients ranged from 8 to 122 years old, with a mean age of 58.6. At least 50% of patients are 58 years of age or younger. The most frequent age observed was 57 years. Most reported cases were between 45 and 75 years old (69.8%). (Table 1)

All were Saudi, with a majority 35.4 % (2,431) of case-patients from the Central region. There were 1,978 (28.8%) case-patients were from Western region; 1,263 (18.4%) case-patient were from the Eastern region; 765 (11%) case-patients were from the Southern region; and 387 (5.6%) case-patients were from the Northern region. In terms of the CC stage, 1,895 (27.6 %) reported cases had distant Metastasis; 1,693 (24.6%) had regional stage; 2,679 (39%) patients had localized stage; and 608 (8.8%) had an unknown stage. The majority of case-patients were alive (5,671 [82.5%]); 1,195 (17.4%) had died and 8 (0.1%) were lost to follow-up. (Table 1)

A comparison of subgroups revealed significant differences between two independent groups and using Kruskal-Wallis we compare between more than two independent groups. (Table 1) Using Mann-Whitney, we found non-significance for gender, so the hypothesis of differences between male and female was rejected (P- value = 0.476).

The Kruskal-Wallis testing was significant for age groups; and our hypothesis of differences between patients with different age was accepted (P-value = 0.000). The null hypothesis of equality in status among regions could not be rejected (P-value = 0.203). Also, Kruskal-Wallis analyses results were not significant for the location variable; differences in status between colon, rectosigmoid and rectum could not be accepted at 95% (P-value = 0.066) but the statistical test was significant at 90%. The Kruskal-Wallis test was significant for stage; statistical differences existed between sub groups (P-value = 0.000). There was a significant difference for status and location of the CC among the six classes of age. Plus, there were significant differences in the status and location of CC according to age.

1- **Survival Analysis**

2-1 Kaplan and Meier

There were significant difference in mortality hazards among stages, location of CC, gender, age, and geographic regions, by the log-rank test (P-value = <0.001). The log-rank test evaluated the alternative hypothesis that there might exist any type of relationship between disease time and the factors. We observed that 50% or less of females had a median survival equal or less to 5.9 years (Table 2); this median survival was less than male counterpart median survival (6 years). We observed that females carried a higher risk of death compared to male patient between time 3 and 5 years. Female patients had the same risk of death than male cases between time 0 to 1 and 2 to 3 years. (Figure 1)

We observe less survival, so a higher risk of death among reported cases < 30 years old (Table 2). These findings could be due to late-stage diagnoses. Survival function was greater among those >75 years (Figure 2); we noted that median survival time is equal to 4.3 years for patients > 75 years old (Table 2).

This study (Table 3) found no association between geographic region and survival. Results from survival analysis reported a higher median of survival for those case patients living in the Western region, so less risk of death. The same result was found in the survival analysis of geographic region variable (Figure 3).

A significant relationship exists between stage and survival time; median survival was to 2.9 for distant metastasis and equal to 6 for localized (Table 2). This result was shown by Kaplan Meier analyses; patient with distant metastasis had a greater risk of death compared to other reported cases. (Figure 5).

2-2 Cox regression

Results showed that the more covariates that existed in the model, the more robust the model and the fewer errors (-2 Log Likelihood = 17219,07 is greater than -2 Log likelihood =16611,18 under "Block 0: Beginning block" refers to the actual without the explanatory factors). Also, results showed that stage, location, gender and age, all affect patients' survival time.

The quantities exp (beta), called hazard ratios (HR) indicated that as the value of the covariate increased, the event hazard increased and thus the length of survival decreased (Table 4). Hazard Function at mean of covariates was ascending, showing that risk increased over time, the same result was validated by the survival function at mean of covariates. A value of beta greater than zero or equivalent l means a hazard ratio (HR) >1 indicates the factor was associated with a bad prognosis.

Depending on the results, the HR for females meant that the death hazard for a female was 1.07 times that of a male, but the coefficient beta was not significant. From hazard ratio, female patients were more likely than males to be at risk. In fact, the CI for HR included 1. So, being male was associated with a good prognostic. The HR = 1.07, with a 95% CI of 0.95 – 1.21 (Table 3). These results indicated that gender made a smaller contribution to the difference in the HR after adjusting for covariates.

Patients with age > 75 were about 3 times more likely to be at risk compared to others. The risk of dying was less for reported cases between 30 – 45 compared to all reported cases. Those aged > 75 had the greatest hazard function, and those between 30 – 65 had the lowest risk. The risk of death increased with age, except for those < 30 years.

Living in the Western, Central, or Northern regions was associated with a good prognosis.. There was very small difference in the risk of death among reported cases from the Western, Central, or Northern regions. The risk of death was greater for reported cases from the Eastern region compared to those from the Southern region (HR=1.08 and CI included 1; Table 3).

Patients with CC were more likely to be at risk than those with rectum cancer; the event hazard increased and the length of survival decreased (90% p-value =0.07). The risk of dying was greater for patients with recto-sigmoid than those with rectum, but the CI included 1.

Coefficient equal to 1.60 is the estimated logarithm of the HR for distant metastasis stage versus regional. In fact, depending on the model, a HR of 4.95 corresponded to 83.19% (=4,95\[1+4,95]) of early death (P-value = 0) for patients with distant metastasis. At any particular time, 1.05 times as many patients in the localized sub-group experienced death compared to the regional sub-group (Table 3).

From the P-value, we conclude that stage and location were bad prognostic factors. Being female was a bad prognostic factor, therefore age and Central, Northern, and Western regions are a good prognostic factors because the event hazard decreased and the length of survival increased.

Having fit a Cox model to these data, we visualized the predicted survival proportion between 0 and 6 periods for each risk group. Any point on the survival curve showed the probability that a reported case of a given gender will live past that time. Males have the highest survival curves and the lowest hazard curves (Figure 1). This confirms the result shown by the Kaplan Meier analyses. Reported cases aged >= 65 had the lowest survival curves; reported cases aged between 30 and 55 had higher curves than whose aged < 30 (Figure 2).

Survival and hazard function showed that the risk of dying was higher for patients from Eastern and Southern regions. In fact, those living in Central, Western, and North regions had the highest survival. (Figure 3) Survival and hazard function also showed that reported cases with CC had a higher risk than those with rectum and rectosigmoid cancer and confirmed that the risk of dying was greater for those with recto sigmoid than with rectum locations. (Figure 4) Survival and hazard function confirm the result found in Coz regression; those with distant metastasis had a higher risk than those with regional or localized stages. Those with a regional stage had a greater risk than those with a localized sub-group. (Figure 5)

Discussion

This study assessed the survival and mortality rates of reported cases of CC. We investigated how survival and mortality differed across gender and age spectra. More males than females (54.7% vs 45.3%) developed CC, although the difference was not statistically significant. The median age most affected by CC was 58 years. Most reported cases (39%) had a localized tumor, followed by distant metastasis in 27.6% and regional tumors in 24.6%. The results also showed that CC most commonly affects the colon followed by the rectum and rectosigmoid. Regarding survival, the median survival age was 5.9 years for women and 6 years for men. The age group with the lowest survival rate was < 30 years at 3.8 years, followed by individuals aged > 75 years at 4.3 years. Notably, the HR was greatest in the age group of 65–75 years, at 0.68 and lowest in patients aged 30–45 years, at 0.40. Another significant finding is the difference in survival based on the stage of the tumor, with distant metastasis having a survival rate of 2.9 years; this was lower than the rates for regional tumors, at 5 years, and localized tumors, at 6 years. This difference in survival rates can be explained by the high HR of 4.95 for distant metastasis and low HR of 1.30 for localized tumors.

The burden of CC in the KSA population is highly affected by age and severity, as indicated by the survival rate and HR based on the stage of cancer. Late diagnosis was associated with quick disease progression, and clinical interventions may not be effective in cases of distant metastasis. A localized tumor can be excised, leading to complete recovery. The scientific literature also shows an association between young age of diagnosis and low survival rate. According to Gabriel et al. [15], case-patients aged 50 years and below often present with advanced stages (stages III and IV) of CC, characterized by distant metastasis and the prevalence of CC is higher than that of rectal cancer. The authors found relatively high hazard ratios in patients from the low income and education brackets, and this association could be due to a poor access to healthcare for screening purposes. In another retrospective study in KSA covering the period of 1994 – 2010, the median age at presentation of rectal cancer was 55 and 60 years for women and men, respectively [6]. Over this period, the highest proportion of individuals with distant metastasis was 29.2%, which is close to the finding of the current study, at 27.6%. Alsanea *et* al. [6] relied on information from the cancer registry, which showed a low burden of localized tumors of 9.4%; this is remarkably lower than the current value of 39%. The discrepancy indicates that the period earlier than 2004 was characterized by poor screening and diagnosis of CC.

A study by van Eeghen, Bakker, van Bochove, and Loffeld [23] found similar survival rates among colorectal cancer patients in the Netherlands. Colon and rectal cancers were associated with survival rates of 5.13 and 4.67 years, respectively. In this study, age and tumor progression were significant predictors of the patients' death. The authors indicated that comorbidity was also a positive predictor of mortality, as it raised the hazard ratios. Elderly age is associated with more comorbid conditions and severe cases of metastasis; hence, high mortality is recorded in this age group. Notably, the current study should trigger the attention of healthcare stakeholders to focus on young adults, who have shown a high burden of CC and low survival rates.

The findings in this study were limited by a poor record system that did not provide some variables of interest (e.g., region, staging, and mortality). Another limitation was the failure to consider the comorbid conditions that affect patient survival. The assumption that CC was the exclusive cause of death was inaccurate. Other chronic diseases increase the risk of death, especially among the elderly. In addition, the retrospective design in this study means that the researchers did not have control over the original data collection mechanism. In effect, any errors in the original studies have been transferred to the current research.

Chapter 4 – Conclusion and Recommendations

CC is one of the most prevalent cancers globally and in KSA. Understanding the survival and mortality indices can influence healthcare policies regarding screening, diagnosis, and treatment. This study shows that CC is not a disease only of older adults, as young adults also have an increased risk of developing the disease. Our findings also indicate that CC in young adults was detected mostly at an advanced stage (stage III and IV), when it has already metastasized. In effect, the disease had a high HR and low survival rate.

Based on these findings, we recommend a change of policy for intensifying the screening of CC in both young and older adults. The disease dynamics are changing, and CC does not only affect older adults. Risk stratification should be emphasized to identify people with heredity and familial risk of CC, which influences the cancer demographics [24]. The aim is to diagnose the tumor early, when it is still localized, as this is associated with a higher survival rate than when it has metastasized. Notably, the research results will be shared with public health stakeholders in KSA for further dissemination to the public. People need to understand the risk and survival rates of cancer in certain age groups; this health information can then guide them in making healthcare decisions [11].

In the future, research should evaluate the spread of the cancer cells and determine the most affected organs and the hazard involved. In addition, there is a need to assess the effect of treatment, such as chemotherapy and radiotherapy, on the survival rates. The results also underscore the need to identify the reasons for delays in early cancer diagnosis or complacency in screening.

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Table 1. Characteristics of Reported Cases of Colorectal Cancer, Kingdom of Saudi Arabia, 2011 – 2015

Variable		N (%)	P-value
Gender	Female	3111 (45.3)	0.476 *
	Male	3764 (54.7)	
Age Distribution	0-30	188 (2.7)	
	31-45	950 (13.8)	
	46-55	1550 (22.5)	0.000 #
	56-65	1788 (26)	
	66-75	1439 (21)	
	76-122	960 (14)	
Geographic Region ✤	Central	2431 (35.4)	
	Eastern	1263 (18.4)	
	Northern	387 (5.6)	
	Western	1978 (28.8)	0.203 #
	Southern	765 (11.1)	
	Unknown	51 (0.7)	
Location	Colon	4173 (60.7)	
	Rectosigmoid	1077 (15.7)	0.066 #
	Rectum	1625 (23.6)	
Stage	Distant Metastasis	1895 (27.6)	
	Localized	2679 (39)	0.000 #
	Regional	1693 (24.6)	
	Unknown	608 (8.8)	
Status	Alive	5672 (82.5)	
	Dead	1195 (17.4)	
	Unknown	8 (0.1)	

* Mann-Whitney # Kruskal-Wallis ✤ Central (Qaseem and Riyadh cities), Eastern (Dammam , Al-Qatif ,Al-Hassa, Al-Jubil cities), Northern (Al-Jawf, Northern borders, Ha'il cities), Southern (Al-Bahah, Jizan, Aseer, and Najran cities), and Western (Jeddah, Madinah, Makkah cities)

Table 2. Reported Cases of Colorectal Cancer, by Survival Time, Kingdom of Saudi Arabia, 2011 – 2015

Variable		Median Survival Time
Gender	Female	5.9
	Male	6
Age Distribution	0-30	3.8
	31-45	5
	46-55	6
	56-65	5
	66-75	5
	76-122	4.3
Geographic Region ✤	Central	5
	Eastern	5
	Northern	5
	Western	6
	Southern	5
Location	Colon	6
	Rectosigmoid	5.9
	Rectum	6
Stage	Distant Metastasis	2.9
	Localized	5
	Regional	6

✤ Central (Qaseem and Riyadh cities), Eastern (Dammam , Al-Qatif ,Al-Hassa, Al-Jubil cities), Northern (Al-Jawf, Northern borders, Ha'il cities), Southern (Al-Bahah, Jizan, Aseer, and Najran cities), and Western (Jeddah, Madinah, Makkah cities)

Table 3. Reported Cases of Colorectal Cancer Mortality, Kingdom of Saudi Arabia, 2011–2015

Variable	Beta	P-value	Hazards Ratio	95% CI	
				Lower	Upper
Gender	0.07	0.29	1.07	0.95	1.21
Age Distribution		0.00			
0-30	-0.41	0.03	0.66	0.45	0.97
31-45	-0.91	0.00	0.40	0.32	0.51
46-55	-0.84	0.00	0.43	0.36	0.53
56-65	-0.78	0.00	0.46	0.38	0.56
66-75	-0.39	0.00	0.68	0.56	0.82
Geographic Region✤		0.30			
Central	-0.08	0.45	0.92	0.75	1.14
Eastern	0.08	0.50	1.08	0.86	1.36
Northern	-0.06	0.69	0.94	0.69	1.28
Western	-0.10	0.36	0.90	0.72	1.12
Location		0.15			
Colon	0.14	0.07	1.15	0.99	1.34
Rectosigmoid	0.04	0.69	1.04	0.85	1.27
Stage		0.00			
Distant Metastasis	1.60	0.00	4.95	4.08	6.00
Localized	0.26	0.02	1.30	1.05	1.60

✤ Central (Qaseem and Riyadh cities), Eastern (Dammam , Al-Qatif ,Al-Hassa, Al-Jubil cities), Northern (Al-Jawf, Northern borders, Ha'il cities), Southern (Al-Bahah, Jizan, Aseer, and Najran cities), and Western (Jeddah, Madinah, Makkah cities)

Figures

Figure 1. Reported Cases of Colorectal Cancer, by Gender, Kingdom of Saudi Arabia, 2011 – 2015

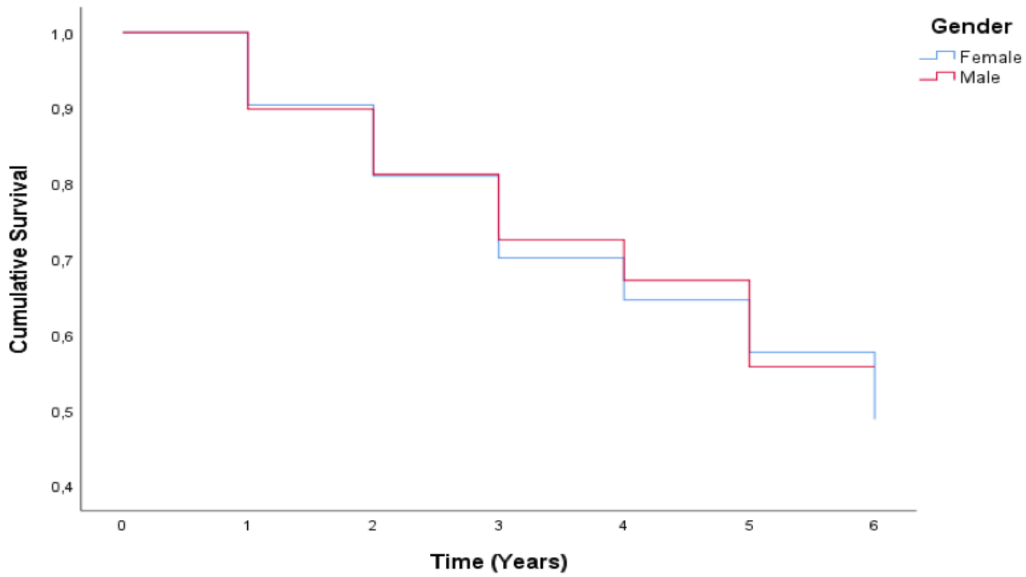

Figure 2. Reported Cases of Colorectal Cancer, by Age Distribution, Kingdom of Saudi Arabia, 2011 – 2015

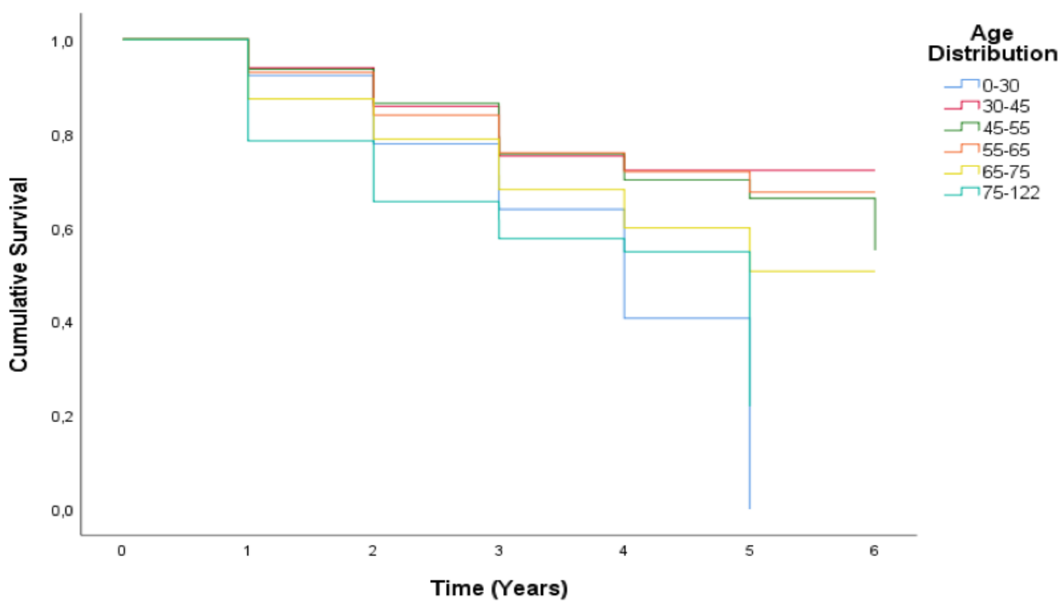

Figure 3. Reported Cases of Colorectal Cancer, by Geographic Region, Kingdom of Saudi Arabia, 2011 – 2015

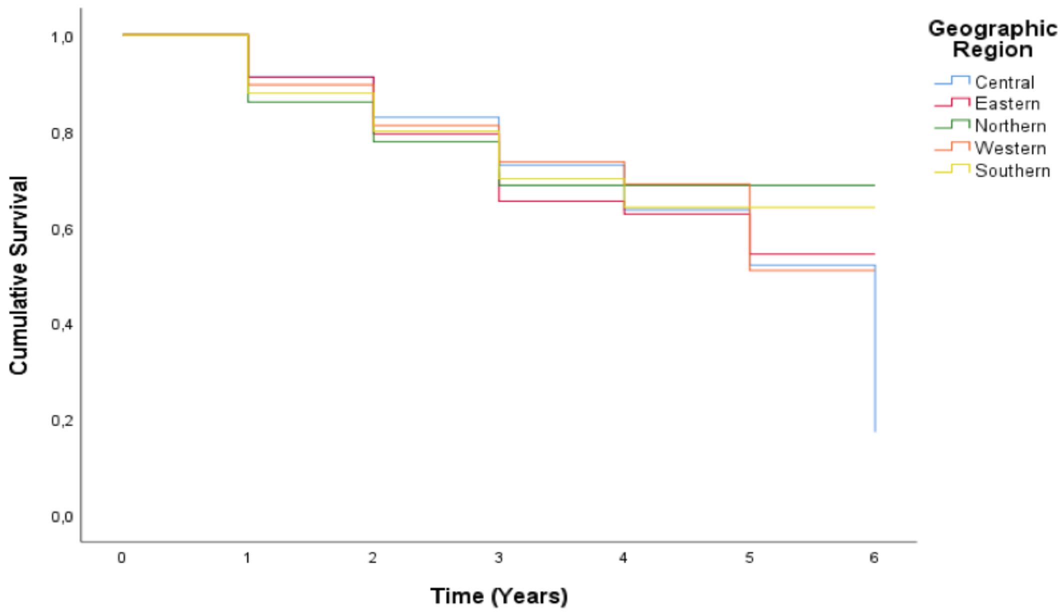

Figure 4. Reported Cases of Colorectal Cancer, by Location, Kingdom of Saudi Arabia, 2011 – 2015

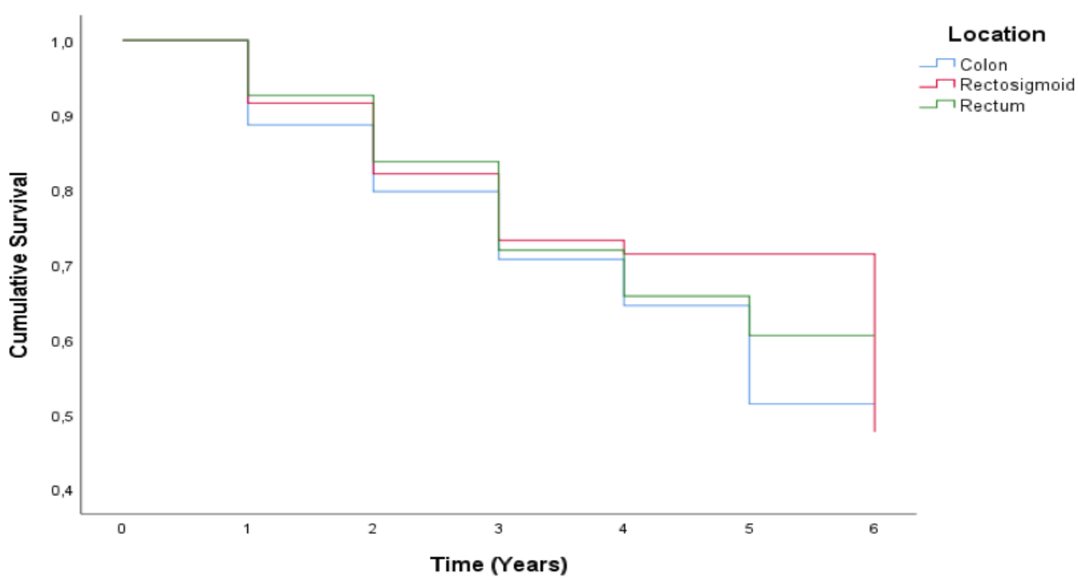

Figure 5. Reported Cases of Colorectal Cancer, by Stage, Kingdom of Saudi Arabia, 2011 – 2015