original article

Demographic features of patients with colorectal carcinoma based on 14 years of experience at Jordan University Hospital

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BACKGROUND: Colorectal cancer (CRC) is the third most common cancer worldwide. In the West, the incidence has stabilized or decreased. There are only occasional published studies that describe the epidemiology of CRC and its changing trends in Jordan and other Middle Eastern countries.

OBJECTIVES: Describe the epidemiological features of CRC, predict future trends and compare the results with those from other Arab and Middle Eastern countries and the West.

DESIGN: Retrospective epidemiologic study.

SETTING: Tertiary center, teaching hospital.

PATIENTS AND METHODS: A retrospective study covering 14 years (2003 to 2016). All cases of CRC were retrieved from the computerized system. Demographic data were recorded and analyzed using Mathematica 11.2 and IBM SPSS version 23 software. Mathematical grey forecasting models were used to predict future trends.

MAIN OUTCOME MEASURES: Number of cases and accumulated average over time, percentages of demographic variables and results of mathematical forecasting models.

SAMPLE SIZE: 970.

RESULTS: The male-to-female ratio was 1.5:1 and 97.4% were adenocarcinomas. The accumulated mean number of diagnosed cases doubled from 44.8 between 2003 and 2007 to 82.9 from 2008 to 2016. The accumulated annual average increased beginning in 2008. The forecasting models predicted a further increase in CRC. The mean age was 60.5 years and the median 62.0. Half of the cases presented at an advanced stage (TNM stage III or IV).

CONCLUSION: CRC is increasing and is expected to increase further. Better health care planning that includes education and screening is needed to reverse these rising trends and to improve early detection.

LIMITATIONS: Single institution study.

CONFLICT OF INTEREST: None.

Cancer is an imposing health care problem. The incidence is increasing and cancer-related mortality is now the second most common cause of death globally.[1] In 2015, there were 17.5 million newly diagnosed cancer cases and 8.7 million cancer related deaths worldwide. Colorectal cancer (CRC) is one of the commonest cancers; globally it is the third most common cancer, with 1.7 million new cases and 832,000 deaths according to the 2015 estimates.[1] In Jordan, CRC is the second most common cancer in Jordan after breast cancer.[2]

The first step in understanding cancer is to evaluate its local epidemiology. Studies of the epidemiology of cancer in Jordan and the neighboring Arab countries are scarce. This study, which covers a 14-year period and includes 970 cases, is the largest study performed to date in Jordan. Jordan had a population of 9 531 712 according to the last national census.[3] The Jordan Cancer Registry (JCR) was established in 1996. It describes the overall cancer burden in Jordan, but detailed information about individual tumor types still needs investigation. Jordan University Hospital (JUH), where the study was conducted, is a tertiary referring center in Amman, Jordan, and an academic institution connected to the University of Jordan. The hospital was established in 1971 and currently serves more than 500 000 patients annually.[4] The aim of this study was to explore the trends and epidemiological characteristics of CRC among JUH patients and to predict future incidence trends. We also compared these epidemiological characteristics with those obtained from studies from Arab and Middle Eastern countries and from the West.

PATIENTS AND METHODS

This retrospective epidemiological study covered a 14-year period from the 1 January 2003 to 31 December 2016. All CRC patients (970 cases) who were diagnosed with CRC at JUH throughout that period were included in the study. The computerized system in the histopathology department at JUH was searched for cases of CRC. To minimize the number of missed cases, the system was initially searched for all colonic biopsies received in the histopathology lab within the study period, and these were saved as pdf files and read thoroughly by the research team who documented all the malignant cases. Data were collected from these histopathological reports and key demographic data were recorded including: age, gender, date of first diagnosis, tumor size, site, histological type, type of the specimen, and number of lymph nodes affected. Institutional research board (IRB) ethical approval was obtained from the Ethics Committee of the Faculty of Medicine in the University of Jordan and from JUH.

Tumor stage was assessed using the American Joint Committee on Cancer (AJCC) tumor/node/metastasis (TNM) classification and staging system for colon cancer, 8th edition.[5]

Tumor site was divided according to the anatomical location into caecum, ascending, transverse, descending colon, sigmoid or rectal. Some tumors were defined as recto-sigmoid by the surgical team and recorded as such. For statistical analysis the site was re-categorized to right- or left-sided; with the caecum, ascending and transverse colon regarded as the right side and the descending, sigmoid and rectum considered the left side. For specimens where the patient had a diagnostic biopsy with no subsequent surgery at JUH, the site was commonly recorded as colon without any further qualifications. These were recorded as colonic tumors and excluded from the statistical analyses related to the site.

Histological types were divided into primary adenocarcinoma, which constituted the majority of cases, and others which included carcinoid tumors, lymphomas and gastrointestinal stromal tumors. Where relevant, our results were compared to those obtained from JCR and other published studies from Jordan and other Middle Eastern countries. The 2012 JCR data were used for comparison purposes as these included the most detailed statistical analysis.

Data were processed using Mathematica 11.2 and IBM SPSS version 23 software (IBM, Armonk, NY). Continuous data was expressed as mean, median and standard deviation, while categorical data was expressed as percentages. The t-test or nonparametric Mann-Whitney test for equality of means were used to evaluate the data. A P value was significant if <.05. Confidence intervals (95%) are reported when appropriate. To predict future trends in incidence, an optimized nonlinear grey Bernoulli model (NGBM) was used after comparison with traditional grey and Verhm models. All three models were compared with and without Fourier residual modifications. Model prediction accuracy was judged via the mean absolute percentage error (MAPE). MAPE between 0.20 and 0.50 was considered reasonable. NGBM with Fourier modification was considered the most accurate as it had the least MAPE, as expected as this model is the best to deal with non-linear data.[6]

RESULTS

During the 14-year study period from the 1 January 2003 to 31 December 2016, there were 970 cases of colorectal carcinomas. The mean number of cases diagnosed annually was 69.3, but the number of cases

increased markedly beginning in 2008; the mean number of cases of 44.8 per year from 2003 to 2007 almost doubled to 82.9 per year between 2008 and 2016. There was a statistically significant difference between the number of cases diagnosed in these two time periods (2003 -2007 vs 2008 - 2016, *P*=.005). The increase in the cumulative mean since 2008 (by smoothing) was also statistically significant (**Figure 1**) (one-sided *P*<.001). The rise in CRC cases in these two time periods was also documented in the JCR: 194.5 cases were diagnosed between 2000-2007 vs 273.8 between 2008 and 2012 (two-tailed *P*<.0001). Although CRC increased in incidence, the the age standardized rate (ASR) for CRC among Jordanians according to the JCR 2012 was relatively low (16.3/100 000)[2] in comparison with the ASR between 2010 and 2014 in the United States, which was 39.8/1 000 000.[7] The male to female ratio among the study population was 1.5:1. Forty percent (n=388) patients were females accounting for 40% of cases (**Figure 2**).

Table 1 shows the number of cases per age group by gender. There was a male predominance in the age group 61-80, whereas there was minimal difference between the other age groups (**Figure 3**). This difference was not statistically significant, (one sided *P*=.495). Patients ranged in age from 12-97 years with a mean (SD) age of 60.5 (13.8) years. The age range in females was 12-89 years, with a mean of 57.7 (14.4) years and a median of 62 years, whereas the age range in males was 21-97 with a mean of 62.4 years, and a median 60 years. Only 9% of patients were 40 years old or younger (85 out of the 949 patients where age was recorded) and 25.0% of the patients were 50 years old or younger (237 patients out of 949). Although seemingly a large number of cases at a young age, the age standardized rate of the age groups 20-24 and 25-29 are the same as those in the United States (0.6 and 1.2, respectively). There was no statistically significant difference between the Jordan ASR and the United States ASR for the different age groups as compared by chi-square test (*P*=.333).

Regarding tumor type, 945 cases (97.4%) were diagnosed as colonic adenocarcinomas; of these 17 were the mucinous type (1.8% of the adenocarcinoma cases) and 5 were the signet ring type, accounting for 0.5% of the adenocarcinoma cases. The distribution of the rest of the cases was as follows: 10 lymphomas, 2 carcinoid, 2 leiomyosarcomas and 11 metastatic tumors. Regarding the lymphoma cases, 6 were in female patients and 4 in males, with the age range being between 22 and 79 years. Both carcinoid cases were in females aged 34 and 70. One of the leiomyosarcomas was in a
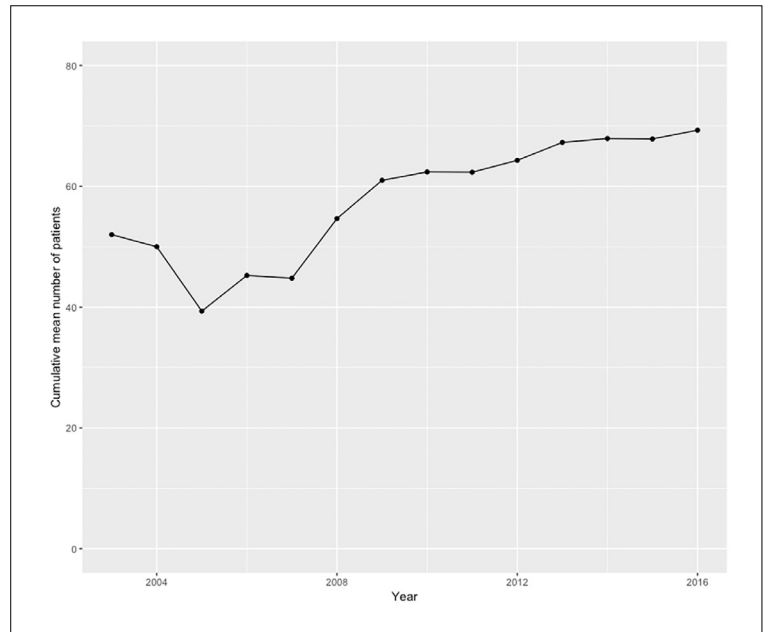

Figure 1. Cumulative mean number of cases by year (95% CI: 51.99-63.49) (n=970).
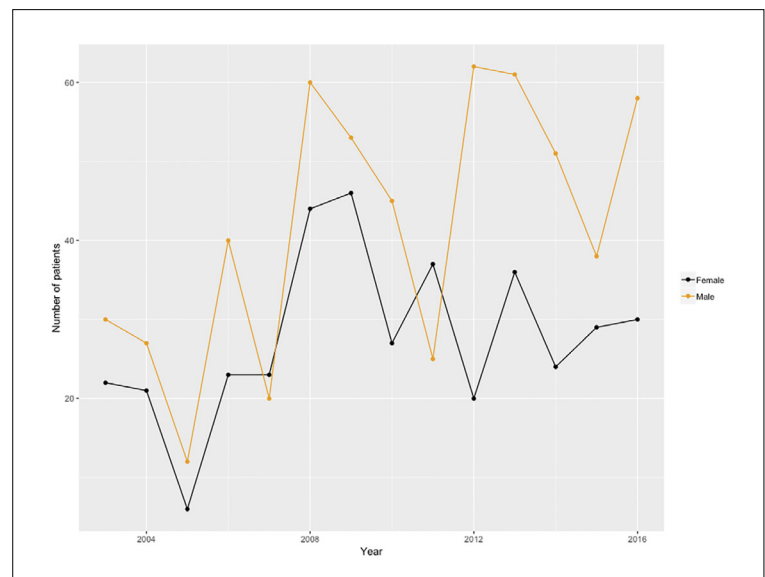

Figure 2. Mean number of cases by year by gender (n=970) (mean and standard deviation for number of cases: 41.6 [16.7] for males, 25.5 [10.5] for females).

66-year-old female, the other was in a 57-year-old male. Regarding the metastatic tumors, 10 were carcinomas and 1 was a malignant mixed Mullerian tumor.

Unfortunately, in a large number of cases, especially the small biopsy specimens, the tumor site was described only as colonic biopsy without further qualification. We could assess the exact site of the tumor

Table 1. Number of cases by age group and gender.

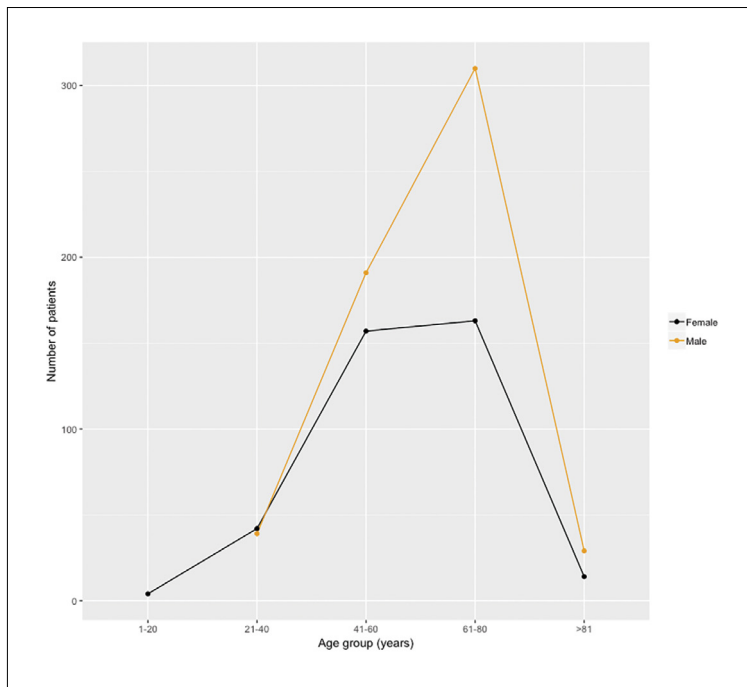| Gender	Age group (years)	Frequency	Percent
Female	1-20	4	1.0
	21-40	42	10.8
	41-60	156	40.2
	61-80	163	42.0
	81-100	15	3.9
	Total	380	97.9
	Missing	8	2.1
Male	21-40	39	6.7
	41-60	190	32.6
	61-80	311	53.4
	81-100	29	5.0
	Total	569	97.8
	Missing	13	2.2

Figure 3. Number of patients by age category and gender (n=949).

in 498 cases; of these the rectosigmoid was the most common site (241 cases accounting for 48.4%). In 68 cases (13.7%) the tumor was in the descending colon. As such, left-sided tumors (descending colon and rectosigmoid) accounted for 62.1% of our cases. The right colon was involved in 168 cases (33.7%); of these 58

cases were cecal tumors (34.5 % of the right colonic tumors were cecal). There was no correlation between tumor site and gender (P=.08) or tumor site and age group (P=.355). Regarding tumor stage, TNM classification was recorded in 505 cases; the majority of these (47.1%) were stage III tumors (296 cases). Forty-four cases (9.5%) were stage IV with metastatic spread at the initial diagnosis, 13 (29.6%) of which had metastasized to the liver.

Predicting future trends

To predict future trends in CRC, three mathematical models were used. **Table 2** demonstrates the accuracy of these forecasting models. All models had a MAPE between 0.20 and 0.50, indicating a reasonable forecasting potential. The accuracy of all was increased with Fourier modification. The least MAPE, hence the greatest accuracy, was obtained by using the optimized NGBM with Fourier residual modification, on the non-linear data. This model showed an expected increase in the number of CRC cases both for males and females as shown in **Figure 4**. The expected number of diagnosed cases in both genders is 95 in 2017, 97 in 2018, 140 in 2019 and 154 in 2020 according to this model.

DISCUSSION

This study describes the epidemiologic features of CRC among JUH patients over a 14-year period. It shows a rising number of diagnosed cases since 2008 and predicts a further increase in the near future. It also shows that CRC presents at an advanced stage in Jordan. The number of CRC cases among JUH patients has increased since 2008 with the mean number of cases diagnosed annually doubling from 45 between 2003-2007 to 83 between 2008 and 2016. This rise was also documented in the JCR as the mean number of CRC cases diagnosed between 2000 and 2007 was 194.5 rising to 273.8 between 2008 and 2012.[2] This rise was statistically significant, with a two-tailed P<.0001.

Similar trends are observed in the Arab and Middle Eastern countries. In Saudi Arabia the ASR doubled from 5.0/100 000 in 1994 to 9.6/100 000 in 2010.[8] In Kuwait CRC incidence increased from 6.2 per 100 000 between the years 1983-87 to 13.7 in 1998-2002.[9] The ASR of CRC in Algeria has increased from 10.6 per 100 000 in 1985 to 18 per 100 000 in 2008 for males and from 8.5 to 13.4 for females.[10] A study from Iran showed that the incidence of CRC increased in both genders between 2003 and 2008.[11] These rising trends in the Middle East are in contrast with trends in Western countries where CRC incidence has stabilized or is even decreasing. In the United Kingdom the incidence of CRC has stabilized

since 1990[12] whereas the incidence of these cancers has decreased by 2.6% annually over the last decade in the United States.[13]

The increased incidence of CRC in Jordan is probably related to changing dietary habits from the traditionally healthy Middle Eastern diet rich in fruit and vegetables to a Western type diet that is rich in fat and refined carbohydrates.[14,15] Decreased physical activity is also a risk factor for CRC and could be a contributing factor to the increased incidence.[16] A Jordanian study supports this as it shows that Jordanian patients diagnosed with CRC had a diet rich in red meat and saturated fat and the majority reported low physical activity.[17]

Screening for CRC is essential for decreasing the incidence and mortality. It is thought that up to 50 percent of the decrease in CRC incidence and mortality in the United States is related to CRC screening.[18] Screening for CRC is not well understood among Jordanians according to a survey of more than 3000 participants; only 13% believed in the importance of screening for CRC and only 9% of the participants had performed a screening test.[19]

The mean age for diagnosing CRC among our patients is 60.5 years, the median is 62 years and the peak is between 61-80 years of age. Approximately 9% of our patients are 40 or younger and 25% of our patients were 50 years or younger. Other studies from Jordan show a high percentage of cases among young individuals; a study from North Jordan revealed that 12.8 percent of the patients were younger than 40 years of age.[20] Another Jordanian study found that 37% of patients with colonic cancer were younger than 55 years of age.[21] Again this trend is reported from neighboring countries, In Saudi Arabia the median age for CRC was 60 years for men and 55 years for women.[8] Twenty-one percent of cases in Saudi Arabia, and 38% in Egypt were diagnosed in patients below 40 years old whereas in the United States and Europe only 2-8% of CRC are diagnosed in this age group.[22] However, the highest ASR of CRC among Jordanian patients is in the 80-84 age group.[2] The ASR for the 20-24 and 25-29 year-old groups are the same as those of the United States (0.6 and 1.2 respectively) whereas the ASRs for Jordan are slightly more than those of the United States for the 35-39 age group (6.7 compared to 4.9).[8] There was no statistical difference between the Jordan ASR and the United States ASR for the different age groups as compared by chi-square test (P=.333).

The large proportion of CRC occurring at a young age is most likely a reflection of the young population of Jordan as 77.4% of Jordanian population is younger than 40 years of age.[3]
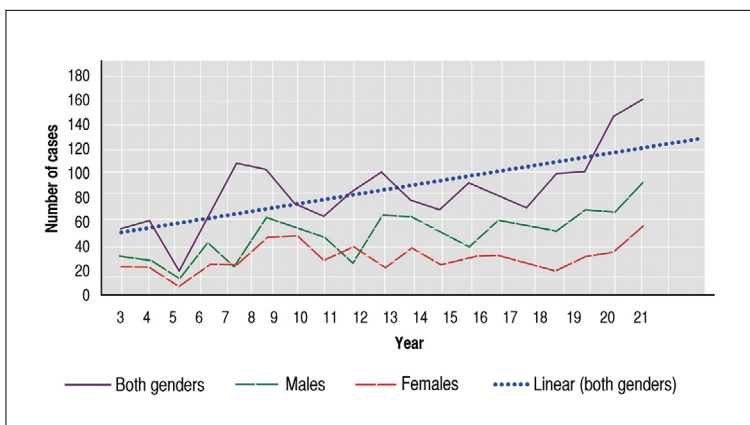

Figure 4. Grey prediction according to the optimized nonlinear Bernoulli grey model with Fourier modification.

Table 2. Comparison of accuracy of three mathematical forecasting models as judged by the mean absolute percentage error (MAPE).

Model	Group	Model accuracy (MAPE)	Model accuracy with Fourier modification
	Both genders		
GM		0.323477	0.289903
Verhm		0.254851	0.255277
ONGBM		0.27291	0.203195[a]
	Males		
GM		0.381432	0.308944
Verhm		0.299624	0.29857
ONGBM		0.307709	0.256616[a]
	Females		
GM		0.421249	0.356078
Verhm		0.333251	0.251514
ONGBM		0.337247	0.23963[a]

GM=traditional grey model, OMGBM=optimized nonlinear grey Bernoulli model {1,1} (first order difference equation with one independent variable). MAPE=mean absolute percentage error. [a]Least MAPE indicating the most reliable forecasting model.

As well as decreasing the incidence of cancer, screening helps in diagnosing CRC at an early stage where chances of survival are excellent.[23] According to UK statistics, the 5-year survival for stage I CRC is 95%, whereas it decreases to 7% for stage IV disease.[24] In our study, more than half of the cases were TNM stage III or IV indicating a delay in diagnosis. Other Jordanian studies reported a similar trend of late diagnosis. In one study about a quarter of the patients were diagnosed with stage IV disease.[20] The reasons for diagnostic delay were reportedly patient unawareness of CRC symptoms

and physician failure to fully investigate at first manifestation of symptoms.[20]

Although this study covers only one institution, it is the largest epidemiological study on CRC from Jordan. Some demographic data were missing, including the age of some patients as well as the exact site of the tumor. Other limitations are that the data are not detailed for 2013 and 2014, so we used the 2012 data, which was complete and detailed. Survival rates were not assessed

in this study and they are not documented in the JCR. This study demonstrated a rising number of CRC cases among JUH patients and predicts a further increase in the near future. It also shows that CRC presents at a late stage. These results demonstrate the importance of better health planning to prevent CRC through educating the public about the risk factors and the importance of screening. Better understanding of the symptoms can help to decrease the proportion of late diagnoses.

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