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Original Article

Trends of Colorectal Cancer Incidence, Prevalence and Mortality in Worldwide From 1990 to 2017

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Abstract

Background: Colorectal cancer is a major health problem both in developing and developed countries. This cancer is among the top three commonly diagnosed cancers in males and females. In this context, assessing the Incidence, Prevalence and Mortality Rate trend of this cancer is of great importance.

Methods: We used the data from the GBD 2017 study to assess the global trend of 3 important indicators of colorectal cancer burden and to examine the relationship between trends of these indicators with Human Development Index (HDI). We used the multivariate mixed effects modeling framework with time and HDI as the covariates.

Results: Trend analysis of colorectal cancer burden indicators showed a rather steady trend for mortality rate, while it revealed increasing slopes for both the incidence and prevalence rates. In addition, our findings showed a direct relationship between prevalence and incidence rates of this cancer and HDI level and indirect association between mortality rate and level of HDI.

Conclusion: There were significant changes in indicators of colorectal cancer during the study period. The inverse relationship between mortality due to this cancer and socio-economic status of the countries indicated an urgent need for screening the patients and promoting the level of care in countries with lower levels of HDI.

Keywords: Multivariate mixed effects model; Colon and rectum; Colorectal; Incidence; Prevalence; Mortality rate

Introduction

Colorectal cancer (CRC) starts in the colon or rectum and depending on the place it can be named colon cancer or rectal cancer. These two cancers are often categorized together as they have many features in common. Colorectal cancers almost start in the inner lining of the colon or rectum as a growth called *polyp* (1,2). The polyp can change into cancer during a long period of time depending on the type of polyp. Adenomatous polyps (adenomas) and Hyperplastic polyps and inflammatory polyps are three main types of polyps. The extent of spread of a colorectal cancer called stage depends on the depth of growth into the wall of the colon or rectum and its spread outside the colon or rectum. The followings are different types of colon and rectum cancers: Adenocarcinomas (start in the mucus-making glands lining the colon and rectum), Carcinoid tumors (start in hormone-producing intestinal cells), Gastrointestinal stromal tumors (GISTs) (start in hormone-producing intestinal cells), Lymphomas (immune system cancers that form in the colon or rectum), and Sarcomas (start in blood vessels, occasionally form in colorectal walls). About 96% of colorectal cancers is Adenocarcinomas, other types are much less common (1-3).

Colorectal cancer is known as one of the important public health problems around the world(4-6). Over 9% of all cancer incidences are due to this type of cancer (5,7). Every year nearly one million new cases of colorectal cancer are diagnosed and half a million deaths are registered throughout the world (4). This type of cancer is an important leading cause of morbidity and mortality world-wide. Colorectal cancer is the third most common cancer in the whole world and the fourth most common cause of death (5-7). Most of colorectal cancers happen in elderly people (4). Burden of colorectal cancer diseases is growing worldwide and it is expected to be increased due to aging of the population (5). Thus, very important priorities are screening research, treatment strategies, recommendations and implementation for this subgroup of the population (4).

Different related factors can increase the chance of developing colorectal cancer for an individual. These are in two types: Colorectal cancer risk factors that can be changed and those that cannot be changed (1,4). Factors such as being overweight or obese, physical inactivity, diets, smoking, and heavy alcohol use are related to an individual's lifestyle that can be changed (categories 1). Being older, personal or family history of colorectal cancer or adenomatous, personal history of inflammatory bowel disease (IBD), having an inherited syndrome, Lynch syndrome, Familial adenomatous polyposis (FAP), rare inherited syndromes linked to colorectal cancer, racial and ethnic background, and having type 2 diabetes are those risk factors that cannot be changed and controlled (categories 2) (1,4,7).

Many published studies have pointed to the important role of gender in colorectal cancer development. Death due to this type of cancer strongly influenced by sex. Colorectal cancer mortality rate in males is significantly higher than females (8,9). In addition, there are relationship between socioeconomic status and colorectal cancer indicators. There is disparity for colorectal cancer indicators according to development indexes like Human Development Index (HDI) might be expected. The numerical value of HDI is between zero and one and consists of three components: longevity (life expectancy at birth), knowledge (adult literacy rate and average years of schooling) and income (the internal impure income capitation in purchasing power- in dollars)(10-12).

The incidence, prevalence, and mortality rates of colorectal cancer are varying at different times in different countries and geographical regions. Thus, assessing the trend and its related factors are necessary. In order to evaluate the trend of change in these 3 indicators, the data should be longitudinally (repeatedly measured in different time points).

There were many different papers about colorectal cancer incidence, prevalence, and mortality rate in different parts of the world, little knowledge is available about the trend of different colorectal indicators in the last three decades.

Therefore, we designed the present study to evaluate the trend of important indicators of colorectal cancer burden around the world using the data from the global burden of diseases (GBD) database. Moreover, we aimed to assess the effect of HDI on the trend of colorectal indicators.

Methods

GBD Data Set

We utilized a multivariate longitudinal random intercept and slope model to determine the trend of these indicators simultaneously. To analyze the trend more efficiently, a Multivariate Linear Mixed Effects Model (MLMM) was applied because of its flexibility in accounting different levels within country variability and considering multiple response variables(13,14).

The indicators of colorectal cancer burden (mortality, incidence, and prevalence rate) were obtained from the online available database of GBD based on the Institute for Health Metrics and Evaluation (IHME) reports. The GBD uses available data to estimate key indices for all diseases, both sexes, different age groups, and world countries. These countries are classified into regions and super regions based on the IHME classification. These indicators are estimated using various sources including vital registration systems, sample registration systems, household surveys, and censuses. Spatiotemporal Gaussian process regression model (ST-GPR) is used in order to estimate the sex-specific indicators. Different data sources can be merged together using mixed effects in order to get unified estimates of levels and trends using information of sex, age, time, and locations (15-17). We used the GBD data for colorectal cancer age standardized rates in 195 world countries from 1990 to 2017(16).

HDI Data Set

One of the important indicators of social and economic progress level in a given country is HDI. HDI is a summary measure of human development, which is a compound index of three basic dimensions of human development including education as mean years of schooling, health as life expectancy at birth, and living standards as gross national income per capita. Countries can be ranked by their HDI level. The amount of HDI is between 0 and 1. There are four levels for HDI: Low (HDI of less than 0.550), Medium (HDI of 0.550–0.699), High (HDI of 0.700–0.799) and Very high (HDI of greater than 0.800). The HDI data is available in the United Nations Development Program (UNDP) website. In this study, we used the HDI data of 188 world countries from 1990 to 2017(18).

Statistical Analysis

For descriptive purposes, we summarized the age specific rate (ASR) data by mean and standard deviation (SD) and represented the mean trend of rates using the line plots. For analytic purposes, since repeated measures (longitudinal) ASR observations for each country are available from 1990 to 2017, the multivariate linear mixed effects model was applied. The multivariate Linear Mixed Effects Models (MLMMs) are extensions of simple linear models which include both random and fixed effects. Fixed effect term signifies population characteristics assumed to be shared by all individuals. Subject-specific effects which are unique to a particular individual are called random effects. Inclusion of these two distinct parts in the model provides the chance for analysts to consider both between-subject and within-subject sources of variation in the longitudinal responses. To analyze non-independent longitudinal or correlated data, the linear mixed effects models (LMMs) are the one of the most appropriate choices (14,19,20).

Suppose Y_{ijk} is the response for the i^{th} sampling unit in j^{th} response at k^{th} occasion, β is a $(p\times1)$ vector of fixed effects, b_i is a $(q\times1)$ vector of random effects, X_i is a $(n_i\times p)$ matrix of covariates, Z_i is a $(n_i\times q)$ matrix of covariates, with $q\leq p$ (the columns of Z_i are subsets of the columns of X_i) and e_i is $(n_i\times1)$ is vector of error term (14,19). The general form of LMMs can be written as follows:

$Y_{ijk} = X_{ij}\beta + Z_{ij}b_i + e_{ijk}$ (1)

The random effects, b_i, is assumed to have multivariate normal distribution with mean zero and covariance matrix G ($b_i \sim MVN(0,G)$). The error term, e_{ijk}, is assumed to have normal distribution with mean zero and variance R_i ($e_{ijk}\sim N(0,R_i)$)(19). Measuring a set of several responses at each occasion for subjects is a common procedure which results in multivariate longitudinal data. The correlation between the outcome variables is crucial. Advanced methods of statistical analysis should be used to properly account for intra-subject correlation and cross-correlation between outcomes; otherwise it will result in invalid inferences. Repeated measures of multivariate continuous responses could be best modeled through multivariate linear mixed effects models (20).

Here, we apply two different statistical models in multivariate linear mixed effects model framework to achieve our goals. First, to assess the trend of three indicators of colorectal cancer burden, we fitted the following multivariate linear mixed effects model, separately for male and female:

$Y_{ijk} = \beta_0 + \beta_1 \text{ time}_{ij} + b_{0i} + b_{1i} \text{ time}_{ij} + e_{ijk}$ (2)

where Y_{ijk} represents the k^{th} outcome (k=1, 2 and 3 for prevalence, incidence and mortality rate) for i^{th} country (i=1, … , 195) at j^{th} year under the study (j= 1990, 1991, … , 2017). The time covariate denotes the study time point (time=0,1, … , 27 as a proxy for year= 1990, 1991, … , 2017).

Second, to examine the effect of HDI on these indicators for total world countries in the period of 1990-2017, the following model was applied:

$Y_{ijk} = \beta_0 + \beta_1 \text{ HDI}_{ij} + \beta_2 \text{ time}_{ij} + b_{0i} + b_{1i} \text{ time}_{ij} + e_{ijk}$ (3)

Where HDI_{ij} shows the HDI value of i^{th} country at j^{th} time of years measurement.

To fit the models (2) and (3), the R software version 3.3.2 was utilized.

Results

The colorectal cancer burden and HDI data from 195 world countries during years 1990 to 2017 was analysed. In the first step of data analysis, the colorectal cancer burden indicators were described, separately for different IHME super regions in years 1990 and 2017(starting and ending points of the study). The high income and South Asia super regions had, respectively, the highest and lowest rates of Incidence and prevalence rate in year 1990. In this year, the highest and lowest mortality rates of colorectal cancer were related to high income and south Asia super regions, respectively. The High income and South Asia super regions had, respectively, the highest and lowest rates of Incidence and prevalence rate in year 2017 just similar to year 1990. In this year, the highest and lowest mortality rates of colorectal cancer were related to the mentioned super regions (Table 1).

In the next step, we focused on the global trend of these indicators. Fig. 1 displays the trend of colorectal cancer burden indicators, separately for males, females, and total world population. One can observed that both the prevalence and incidence rates of colorectal cancer had an upward trend, but the mortality rate of this cancer shows a rather steady trend during these years. All the three CRC indicators was higher for men than women during the study period, and male seems to be at greater risk for this kind of cancer.

Now to illustrate the observed trends in Fig. 1 in a statistical manner, we fitted the model 2 (described in the methods section) to the data. Table 2 shows the obtained estimates. For the total population data, although the estimated positive slopes in prevalence and incidence rates imply an upward trend for these indicators, the non-significant and nearly zero estimate for slope of mortality rate tells us that the trend of this important indicator of CRC burden was rather fixed in this time period.

In the final step, we applied the model 3, (described in the methods section), to assess the relationship between CRC burden indicators and HDI for all world countries during years 1990 to 2017. Table 3 represents the obtained results from fitting this model. The estimated parameter for the HDI variable is -20.87, 18.97 and 30.30, respectively for mortality, incidence, and prevalence rates of colorectal cancer.

Table 1: Descriptive statistics for CRC Indicators in different IHME super regions in year 1990 and 2017

Indicator of Burden	*Super Region*	*Gender*	*1990*		*2017*	
			Mean	SD	Mean	SD
Mortality Rate	Central Europe, Eastern Europe, and Central Asia	Male	18.40	9.70	20.29	8.80
		Female	12.73	5.48	11.81	4.16
		Both	14.89	7.07	15.17	5.96
	High-income	Male	21.92	6.50	18.42	4.21
		Female	15.88	5.63	12.12	3.58
		Both	18.37	5.76	14.92	3.69
	Latin America and Caribbean	Male	10.18	4.77	11.99	3.86
		Female	9.44	3.22	10.22	2.65
		Both	9.76	3.85	11.05	3.03
	North Africa and Middle East	Male	8.78	3.17	9.73	3.12
		Female	8.54	3.54	7.71	2.99
		Both	8.58	3.01	8.81	2.74
	South Asia	Male	7.00	2.46	7.34	0.68
		Female	6.51	0.64	7.07	1.68
		Both	6.61	0.85	7.22	0.74
	Sub-Saharan Africa	Male	10.67	3.85	12.76	4.75
		Female	9.26	2.61	9.74	2.97
		Both	9.87	2.97	11.08	3.68
	Southeast Asia, East Asia, and Oceania	Male	9.96	3.13	11.30	3.38
		Female	8.16	2.14	8.14	1.66
		Both	9.00	2.45	9.56	2.21
Incidence Rate	Central Europe, Eastern Europe, and Central Asia	Male	25.68	14.94	34.46	18.17
		Female	17.97	8.50	20.04	8.98
		Both	20.98	10.96	25.92	12.64
	High-income	Male	38.34	13.47	44.09	10.47
		Female	28.33	10.32	29.38	7.53
		Both	32.54	11.37	36.07	8.46
	Latin America and Caribbean	Male	12.86	5.42	19.16	8.54
		Female	12.65	5.06	17.63	6.13
		Both	12.68	5.30	18.36	6.97
	North Africa and Middle East	Male	10.25	3.86	14.75	6.08
		Female	10.31	4.91	12.20	5.57
		Both	10.15	3.79	13.44	5.41
	South Asia	Male	6.94	2.62	7.96	1.83
		Female	6.71	0.91	8.16	0.86
		Both	6.84	1.68	8.26	1.01
	Sub-Saharan Africa	Male	12.52	5.10	19.09	11.13
		Female	11.00	3.24	14.56	7.20
		Both	11.39	3.93	16.62	9.02
	Southeast Asia, East Asia, and Oceania	Male	10.06	3.06	12.04	3.60
		Female	8.26	2.11	8.54	1.72
		Both	9.09	2.39	10.13	2.33
Prevalence Rate	Central Europe, Eastern Europe, and Central Asia	Male	94.81	58.44	151.91	91.34
		Female	73.33	38.32	96.42	50.86
		Both	82.00	46.09	120.06	67.27
	High-income	Male	172.37	72.31	240.46	68.81
		Female	135.87	56.32	166.38	47.40
		Both	151.82	62.48	200.90	55.51
	Latin America and Caribbean	Male	43.13	26.62	80.18	45.13
		Female	45.15	23.03	79.21	36.03
		Both	44.04	24.14	79.19	39.93
	North Africa and Middle East	Male	33.58	12.81	61.49	31.82
		Female	35.77	18.07	54.18	30.96
		Both	34.08	13.28	57.61	29.91

South Asia	Male	21.14	8.19	26.30	4.33
	Female	20.49	3.02	25.66	5.33
	Both	20.85	5.33	25.97	2.99
Sub-Saharan Africa	Male	42.94	21.80	78.82	64.34
	Female	38.83	14.80	62.28	44.14
	Both	40.74	17.80	70.19	53.73
Southeast Asia, East Asia, and Oceania	Male	28.96	8.19	35.93	10.49
	Female	24.31	6.03	26.25	5.38
	Both	26.52	6.57	30.71	7.03

The interpretation of these estimates is rather straight forward. Setting other variable at a fixed level, every 0.1 unit increase in the HDI value of a country was related to about 2 per 100000 decrease in mortality rate, 1.4 per 100000 increase in incidence rate, and about 30 per 100000 increase in prevalence rate of colorectal cancer, in the period of 1990-2017.

Table 2: Modelling the trend of CRC burden indicators in the period of 1990-2017

Gender	*Indicator*	*Parameter*	*Estimate*	*Standard Error*	*P-value*
Male	Mortality Rate	Intercept	13.78	2.65	<0.001
		Year	0.07	0.29	0.810
	Incidence Rate	Intercept	19.08	2.65	<0.001
		Year	0.61	0.29	0.040
	Prevalence Rate	Intercept	72.64	2.65	<0.001
		Year	4.31	0.29	<0.001
Female	Mortality Rate	Intercept	10.91	1.86	<0.001
		Year	-0.09	0.20	0.650
	Incidence Rate	Intercept	15.17	1.86	<0.001
		Year	0.23	0.20	0.250
	Prevalence Rate	Intercept	60.97	1.86	<0.001
		Year	2.29	0.20	<0.001
Total	Mortality Rate	Intercept	12.09	2.18	<0.001
		Year	-0.01	0.24	0.950
	Incidence Rate	Intercept	16.79	2.18	<0.001
		Year	0.41	0.24	0.080
	Prevalence Rate	Intercept	65.90	2.18	<0.001
		Year	3.25	0.24	<0.001

Table 3: Estimated from the multivariate mixed effects model to assess the relationship between CRC burden indicators and HDI

Indicator	*Independent Variable*	*Estimate*	*Standard Error*	*P-value*
Mortality Rate	Intercept	23.34	5.04	<0.001
	Year	0.36	0.22	0.280
	HDI	-20.87	8.16	<0.001
Incidence Rate	Intercept	5.29	5.04	<0.001
	Year	0.12	0.22	0.100
	HDI	18.97	8.16	0.580
Prevalence Rate	Intercept	-108.17	5.04	<0.001
	Year	18.97	0.22	0.010
	HDI	30.30	8.16	0.020

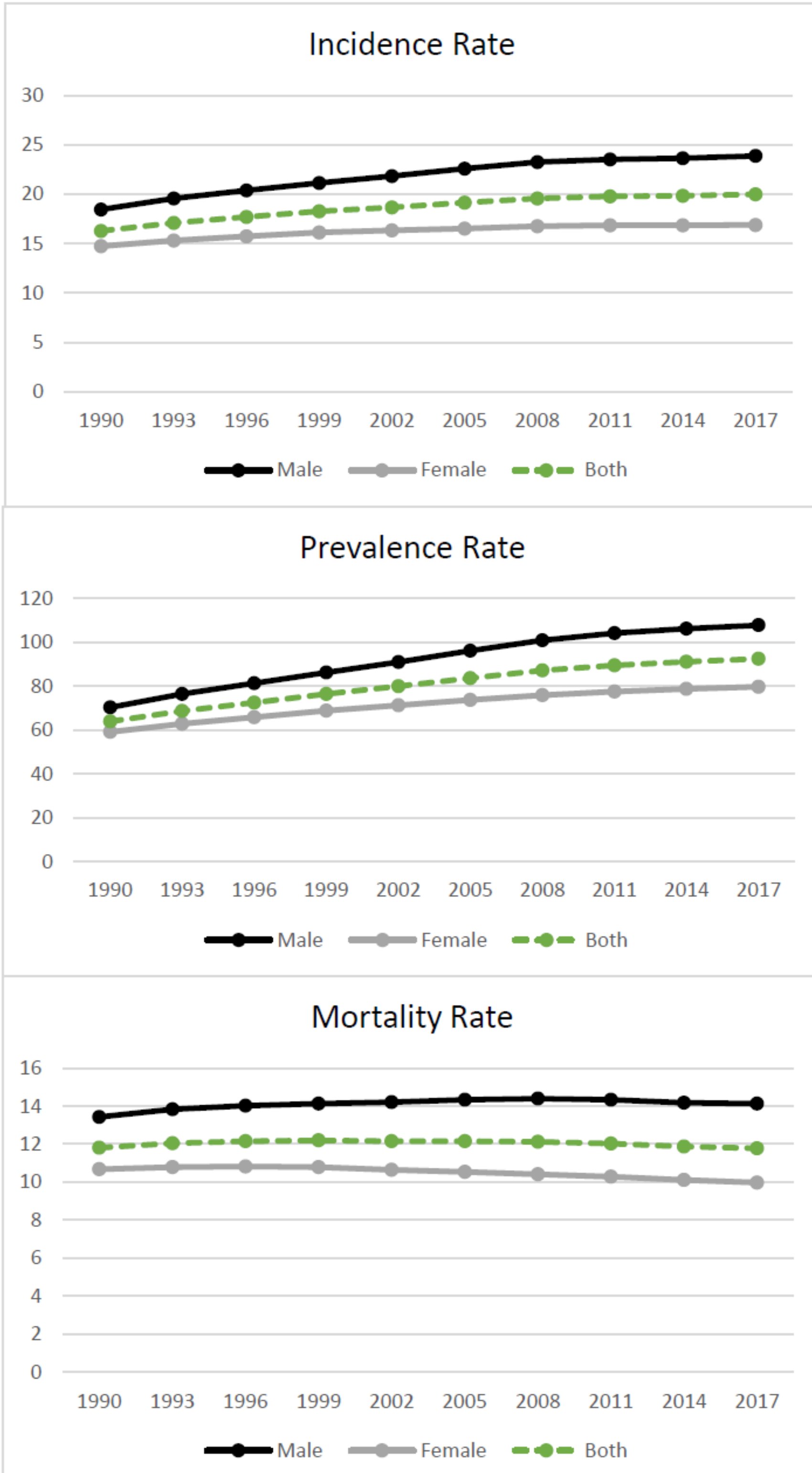

Fig. 1: Trend of Colorectal Cancer Indicators by Gender (1990-2017)

Discussion

The present study tried to determine the trend of colorectal cancer indicators (mortality, incidence, and prevalence rate) between the years 1990-2017. We, simultaneously, fitted the multivariate mixed effects model to the CRC indicators for countries worldwide. Evaluating the trend of response variables mean using multivariate analysis illustrated an approximately fixed and steady trend (The very slow downtrend) for mortality rate level and increasing trends for incidence and prevalence rate level for male, female, and both genders. The negative sign of year estimate indicated a colorectal cancer mortality rate reduction and the positive sign indicated a colorectal cancer incidence and prevalence rate increase over the study period. Our results showed changes in the colorectal cancer indicators during these years.

Almost all researches reported an increasing trend for incidence and decreasing trend for mortality rate. For example, incidence data and mortality data were used from 50 countries selected in 2016. The two rates were age-standardized. There was substantial variation in colorectal cancer incidence trends throughout the world but incidence rates were increasing in the most countries. Despite rising incidence in almost all countries, colorectal cancer mortality rates were decreasing in many countries (21).

The incidence and mortality rate estimates of colorectal malignant neoplasms for 184 countries in 2012 with 15 consecutive years were analyzed using Global Cancer Observatory database (GLOBOCAN). The related trends were evaluated according to the annual percentage change using joint point regression; these were analyzed and explained in relation to human development levels. Three patterns of colorectal cancer incidence and mortality trends were clarified as the following: first, increases in both incidence and mortality in the most recent decade, second, increases in incidence with concomitant decreases in mortality, third, decreases in both incidence and mortality (22,23).

A retrospective cohort study was conducted on patients aged 20 yr and older diagnosed with invasive colorectal cancer between years 1974-2013 in the USA. The trends of incidence were evaluated considering five-year age groups by joint point. After showing a decrease in the previous decade, colorectal cancer incidence rates increased annually(24).

In Korea, cancer incidence used data of the years 1999-2013 and 1999-2015; the data were collected from Korea National Cancer Incidence Database. Mortality data were obtained from Statistics Korea. The prevalence was determined as the number of cancer patients alive (among all cancer patients diagnosed since 1999) in 2014 and 2016 for first and second studies, respectively. They also calculated crude and age-standardized rates (ASRs) for incidence, mortality, prevalence and 5-year relative survivals using joint point regression. The ASR for colorectal cancer incidence increased annually. However age specific rate for colorectal cancer mortality decreased (25,26).

In the Europe a study was done on Colorectal cancer incidence and mortality between years 1990-2016 were obtained from national and regional cancer registries in 2019. Trends were analyzed using joint point regression and clarified as annual percent change. On average, the incidence increased per year. Most European countries showed increase in incidence; some heterogeneity was also found between countries. Mortality rate did not show a significant change among the youngest adults, but decreased per year between 1990 and 2016 (27). The trend of colorectal incidence rate is increasing while mortality rate is decreasing.

This study tried to determine the effect of HDI on these three CRC indicators for total world countries in this period (1990-2017). We fitted the multivariate mixed effects model to the CRC indicators for countries worldwide to examine the HDI effect. The negative sign of HDI estimate indicated a colorectal cancer mortality rate reduction and the positive sign indicated a colorectal cancer incidence and prevalence rate increase over the study period. Our results showed HDI effect in the changes of colorectal cancer indicators during these years.

Various studies have been done to investigate the relationship between the cancer indicators and HDI in these years. These researches demonstrated relationship between the incidence and mortality for all types of cancers, especially colorectal with HDI. These studies used regression, bivariate correlation, and descriptive statistics to investigate HDI effects(10-12). HDI can be important in reducing the colorectal cancer mortality rate and increasing the colorectal cancer incidence and prevalence rate that is similar to our result in this study.

This study is the first to give an overview of CRC incidence, prevalence and mortality rates simultaneously in worldwide in the last three decades and to examine the effect of gender and HDI. A major strength is the use of data from both type of developing and developed countries. Still, several limitations need to be addressed. First, the information was available until year 2017 and was not available newer information. Second, the quality of data differed between countries. Third, individual data were not accessible and just aggregated data were accessible. Fourth, only the variables of year, gender and HDI were examined, while the effect of other important influential variables also needs to be examined.

Conclusion

Although the incidence and prevalence rates of colorectal cancer had an upward trend during the previous decades, the global mortality rate of this cancer had a rather fixed trend in this period of time. On the other hand, the negative relationship between socio-economic status of the world countries and deaths from this cancer is worrisome. The wealthier countries experienced lower mortality rate due to this cancer in recent years while countries with lower levels of HDI experienced an increasing trend of mortality rate during this period of time. The health policy makers should put more efforts on screening and diagnosing the patients in the early stages and promoting the level care, especially in countries with lower levels of HDI.

Journalism Ethics considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

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Conflict of interest

The authors declare that there is no conflict of interests.

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