


# Favorable colorectal cancer mortality-to-incidence ratios in countries with high expenditures on health and development index

## A study based on GLOBOCAN database

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### Abstract

**Background:** Global variation in the incidence and outcomes of colorectal cancer (CRC) is associated with many factors, among which screening policies and early treatment play substantial roles. However, screening programs and intense treatment are expensive and require good health care systems. For CRC, no clear association has yet been established between clinical outcomes and health care disparities.

**Method:** We used the mortality-to-incidence ratio (MIR) of CRC as a measure of clinical outcomes for comparison with the Human Development Index (HDI), current health expenditure (CHE), and current health expenditure as a percentage of gross domestic product (CHE/GDP) using linear regression analyses. We included 171 countries based on data from the GLOBOCAN 2018 database.

**Results:** We found that the regions with the lowest MIRs for CRC are Oceania and North America. A significant correlation was observed between incidence, mortality and HDI, CHE, and CHE/GDP among the countries enrolled. Furthermore, lower MIRs of CRC significantly correlated with higher HDI, CHE, and CHE/GDP ( $P < 0.001$ ,  $P < 0.001$ , and  $P < 0.001$ , respectively).

**Conclusion:** CRC MIRs tend to be most favorable in countries with high health care expenditures and a high HDI.

**Abbreviations:** ASR = age-standardized rate, CHE = current health expenditure, CRC = colon rectal cancer, GDP = gross domestic product, HDI = Human Development Index, MIR = mortality-to-incidence ratio.

**Keywords:** colorectal cancer, expenditure, incidence, mortality, mortality-to-incidence ratio

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The datasets generated during and/or analyzed during the current study are publicly available.

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## 1. Introduction

Colorectal cancer (CRC) is currently the third most commonly diagnosed cancer in the world, affecting 1,800,977 individuals and accounting for 10% of all cancer diagnoses. It is also the second most deadly cancer globally, claiming 861,663 patients, which accounts for 9% of cancer-related death among all cancers.<sup>[1]</sup> The geographic distribution of CRC reveals a relatively high incidence rate mainly in Europe, Australia/New Zealand, and eastern Asia while countries in Africa have a lower incidence rate.<sup>[1,2]</sup> The factors contributing to the variation in incidence have been identified, including environment, lifestyle, and differences in dietary habits.<sup>[3–5]</sup> Among them, effective screening tools for the early diagnosis of CRC, such as the fecal immunochemical test, flexible sigmoidoscopy, and colonoscopy may have a substantial impact on the statistics of CRC, correlating with a lower rate of both incidence and mortality.<sup>[3,7]</sup>

The chief clinical outcome measures for cancer treatment are the 5-year survival rate and the mortality-to-incidence ratio (MIR), which may be used as an evaluation index for long-term success in cancer treatment.<sup>[6–9]</sup> For the past years, the number of newly-diagnosed CRCs has varied widely between countries, with eightfold and sixfold variations, respectively, in colon and rectal cancer.<sup>[1]</sup> The Human Development Index (HDI), known as a marker reflecting socioeconomic development, has been proposed to have a positive correlation with the incidence rate of CRC<sup>[10]</sup> as a high incidence rate of CRC has been demonstrated to correlate with countries with a higher HDI.<sup>[11]</sup> Furthermore,

most low-income countries in regions such as Eastern Europe, Latin America, and Asia have reported an increasing trend in both the incidence and mortality of CRC over a 10-year period while countries with a higher HDI, such as the United States, Australia, and New Zealand, are showing a stabilizing or decreasing trend in incidence as well as mortality.<sup>[11,12]</sup> These opposing trends suggest that countries with a higher HDI may have initiated more early pre-cancerous screenings and prompter therapy, thus reducing both the incidence and mortality rate of CRC despite having a greater absolute incidence rate than countries with a lower HDI.

Previous studies of CRC have focused mainly on the relationship between the incidence, mortality rate, and HDI.<sup>[10]</sup> The present study further employs the MIR as a clinical outcome and uses current health expenditure (CHE) and current health expenditure as a percentage of gross domestic product (CHE/GDP) as indicators of medical expenses, which may reflect the practices of screening programs and intensive treatment. Our primary goal was to discover the differences in CRC outcomes in 171 countries by analyzing the association between MIR and HDI, CHE, and CHE/GDP. The secondary goal was to identify the relationship between incidence, the mortality rate of CRC, and the aforementioned indexes. This study aims to provide an overview of the connection between MIRs and health care disparities among countries worldwide.

## 2. Materials and methods

CRC, ICD-10 C18-21, and epidemiological data for 2018 were obtained from GLOBOCAN (<https://gco.iarc.fr/today/>), a public access database that provides contemporary estimates of cancer epidemiology for 185 countries. The HDI was obtained from the United Nations Development Program, Human Development Report Office (<http://hdr.undp.org/en>). The data on health expenditures, including the per capita CHE and the CHE/GDP, were obtained from the World Health Statistics database ([https://www.who.int/gho/publications/world\\_health\\_statistics/en/](https://www.who.int/gho/publications/world_health_statistics/en/)).

The MIR was defined as the ratio of the CR of mortality to the CR of incidence as previously described.<sup>[9,13–15]</sup> The exclusion criteria for country selection comprised missing data in the WHO statistics (N=12) and missing data in the HDI (N=2). A total of 171 countries were included in the final analysis. We choose 26 countries whose incidence number of CRC was more than 9646 annually to demonstrate the conditions of HDI, the per capita CHE, the CHE/GDP, the crude and age-standardized rates (ASRs) of incidence and mortality of CRC and the MIRs (Table 2). The associations between the MIR and the other

factors in various countries were estimated using Spearman rank correlation coefficient and calculated using SPSS statistical software version 15.0 (SPSS Inc., Chicago, IL). Values of  $P < .05$  were considered statistically significant. Scatterplots were generated with Sigma Plot.

### 2.1. Ethics approval and consent to participate

Not applicable. The database is an open/public database which does not link to individual information. Therefore, ethical approval is not necessary.

## 3. Results

### 3.1. Epidemiology of CRC by region

The distributions of CRC by region were obtained from the GLOBOCAN 2018 database (Table 1). There were 1,679,784 newly diagnosed CRC cases and 743,687 deaths from CRC worldwide. Among regions, Asia had the highest numbers in both new cases and deaths (886,927 and 400,244, respectively) while the Oceania region had the fewest new cases and deaths (19,165 and 6171, respectively). However, Oceania had a higher ASR of new cases (30.8%) than other regions. In terms of death, despite being second to Asia in the number of deaths, Europe had the higher ASR (11.2%). By contrast, Africa had the fewest total deaths from CRC (38,049) and the lowest crude rate and ASR of death (3.0% and 5.0%, respectively). With respect to the MIR of CRC, Oceania had the lowest MIR (along with North America) despite having an ASR of death inferior only to the Europe region. By contrast, although it had the lowest ASR in both new cases and deaths, Africa had the highest MIR among all the regions.

### 3.2. Epidemiology and disparity of health expenditure and development by country

We intended to study the observed differences among 171 countries by including countries based on national data from WHO World Health Statistics. The HDI, CHE, CHE/GDP, crude rate of incidence and mortality, and ASR of incidence and mortality are listed in Table S1, Supplemental Digital Content, <http://links.lww.com/MD2/A560> while representative countries with an incidence number greater than the mean value worldwide are shown in Table 2. The highest HDI was found in Norway (0.953), followed by Switzerland (0.946) and Ireland (0.942), while the lowest HDI was seen in Niger (0.377), followed by Central African Republic (0.381) and Chad (0.401). The CHE/

**Table 1**

**Summary of the number, crude rate, age-standardized rate, and mortality-to-incidence ratio of colorectal cancer by region.**

Region	New cases			Deaths			MIR
	Number	CR	ASR	Number	CR	ASR	
Africa	59,914	4.7	7.8	38,049	3.0	5.0	0.64
Asia	886,927	19.6	16.6	400,244	8.9	7.3	0.45
Europe	439,130	60.5	28.4	192,573	26.5	11.2	0.44
Latin America and the Caribbean	116,209	18.0	15.8	55,401	8.6	7.3	0.48
North America	158,439	44.4	24.9	51,249	14.4	7.6	0.32
Oceania	19,165	47.2	30.8	6171	15.2	9.3	0.32

ASR = age-standardized rate, CR = crude rate, MIR = mortality-to-incidence ratio.

**Table 2**

**Summary of the Human Development Index, current health expenditure, cancer incidence, cancer mortality, and mortality-to-incidence ratio in colorectal cancer of selected countries with an incidence number of >9646, the mean of all countries (N=26).**

Country	HDI	Current health expenditure		Incidence			Mortality			Mortality-to-incidence ratio
		Per capita	% of GDP	Number	CR	ASR	Number	CR	ASR	
Argentina	0.830	998	6.8	14,029	31.8	23.9	7266	16.5	11.5	0.52
Australia	0.938	4934	9.4	15,180	62.6	34.6	4567	18.8	9.5	0.30
Brazil	0.761	780	8.9	47,617	22.8	18.5	21,359	10.2	8.1	0.45
Canada	0.922	4508	10.4	21,393	59.3	29.7	7085	19.6	8.7	0.33
China	0.758	426	5.3	490,273	34.7	22.3	216,374	15.3	9.5	0.44
France	0.891	4026	11.1	38,348	60.8	28.6	13,507	21.4	8.8	0.35
Germany	0.939	4592	11.2	49,240	61.6	24.5	20,677	25.9	8.7	0.42
Hungary	0.845	894	7.2	9910	104.3	49.1	4366	46.0	19.7	0.44
India	0.647	63	3.9	55,009	4.1	4.3	41,391	3.1	3.2	0.76
Indonesia	0.707	112	3.3	29,290	11.0	11.6	15,497	5.8	6.2	0.53
Italy	0.883	2700	9.0	41,644	72.9	28.3	15,267	26.7	8.8	0.37
Japan	0.915	3733	10.9	122,526	100.7	36.8	40,528	33.3	10.5	0.33
Mexico	0.767	535	5.9	13,794	10.6	10.7	6317	4.9	4.9	0.46
Netherlands	0.934	4746	10.7	13,262	79.4	35.8	5011	30.0	12.0	0.38
Philippines	0.712	127	4.4	15,002	14.1	17.6	8033	7.6	9.5	0.54
Poland	0.872	797	6.3	22,074	59.1	28.9	12,039	32.3	14.7	0.55
Romania	0.816	442	5.0	10,260	53.5	25.8	5525	28.8	12.7	0.54
Russian Federation	0.824	524	5.6	67,394	47.5	25.9	37,983	26.8	13.7	0.56
South Korea	0.906	2013	7.4	40,135	79.5	43.1	7824	15.5	7.3	0.19
Spain	0.893	2354	9.2	31,665	70.6	31.8	11,906	26.6	10.5	0.38
Thailand	0.765	217	3.8	16,314	23.8	14.8	8764	12.8	8.0	0.54
Turkey	0.807	455	4.1	18,869	23.2	20.0	9080	11.2	9.3	0.48
Ukraine	0.750	125	6.1	21,448	49.5	25.3	12,909	29.8	14.5	0.60
United Kingdom	0.920	4356	9.9	40,251	62.1	30.0	14,792	22.8	9.4	0.37
United States of America	0.920	9536	16.8	136,995	42.8	24.3	44,151	13.8	7.4	0.32
Vietnam	0.693	117	5.7	13,666	14.3	13.0	6907	7.2	6.5	0.50

ASR = age-standardized rate, CR = crude rate, GDP = gross domestic product, HDI = Human Development Index.

GDP ranged from 2.5% in South Sudan to 18.3% in Sierra Leone. In terms of the crude rate of the ASR of incidence and mortality in CRC, the Republic of the Gambia had the lowest rates and Hungary the highest. Of all the countries included, the highest MIR for CRC was found in Comoros Congo (1.00), followed by Central African Republic (0.93) and Vanuatu (0.89), while the lowest was observed in South Korea (0.14), followed by Belgium (0.29), Australia (0.3), and Denmark (0.3).

### 3.3. Significant correlation between HDI, CHE, and CHE/GDP and the crude rate of incidence and crude rate of mortality of CRC

We analyzed the association between HDI, CHE, and CHE/GDP and the crude rates of incidence and mortality of CRC of various countries (Fig. 1). We found that HDI, CHE, and CHE/GDP have a significant correlation with the crude rates of incidence/mortality as shown in Figures 1A to F. Countries with a higher value of the above indexes are significantly correlated with higher crude incidence rates and crude mortality rates of CRC.

### 3.4. Significant correlation between MIRs and HDI, CHE per capita, and CHE/GDP in CRC

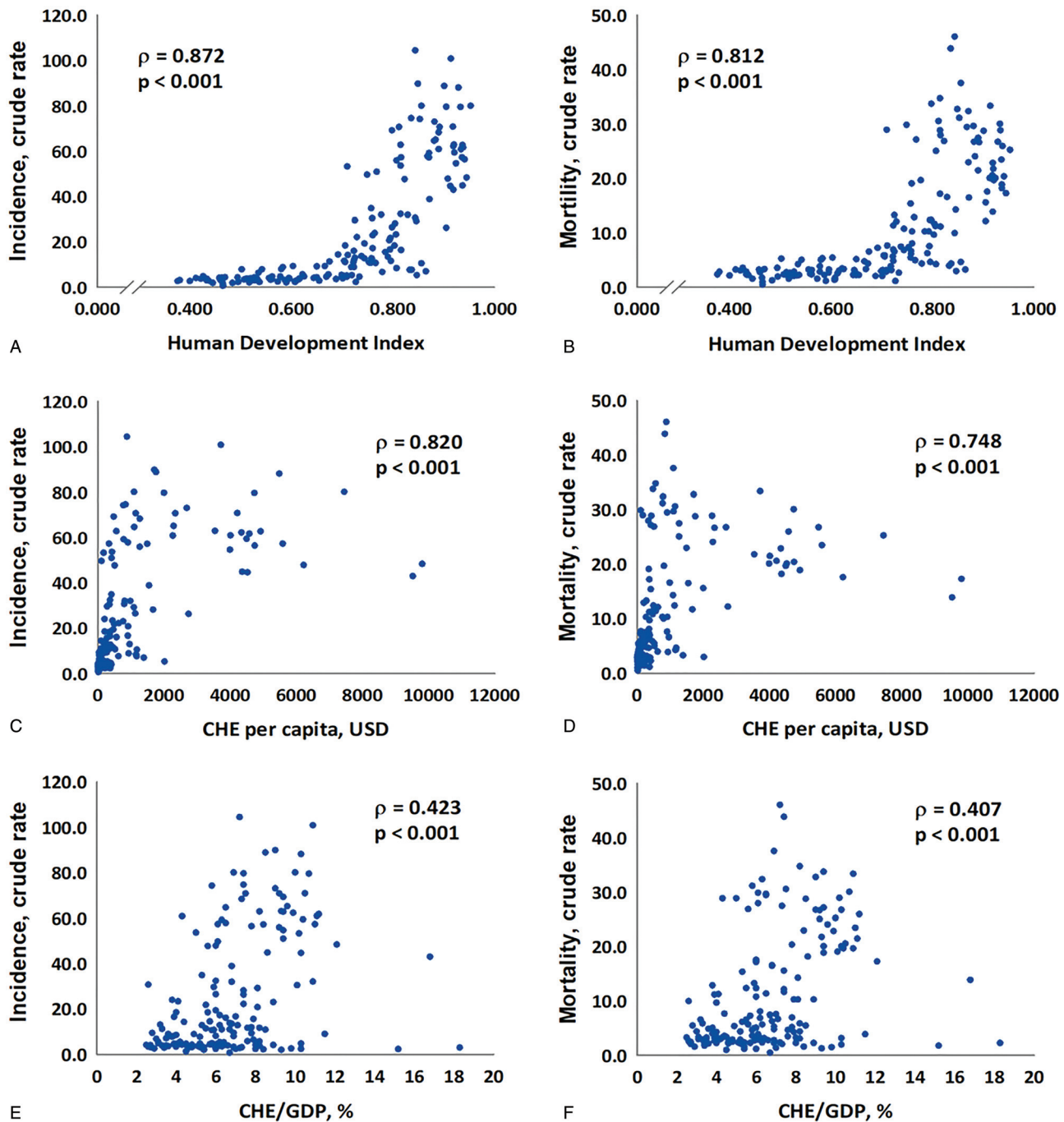
We then investigated the correlation between HDI, CHE, and CHE/GDP and MIRs in CRC. All the above indexes showed significant correlations with the MIRs of CRC. Countries with a higher value of the above indexes are significantly correlated with lower MIRs as shown in Figure 2A to C ( $\beta = -0.867$ ,  $P < .001$ ,

Figure 2A;  $\beta = -0.868$ ,  $P < .001$ , Figure 2B;  $\beta = -0.383$ ,  $P < .001$ , Figure 2C).

## 4. Discussion

In this study, we employed data from the GLOBCAN database and WHO World Health Statistics. Our primary goal was to evaluate treatment quality by using the MIR as an indicator of clinical outcome, which is also considered to be a promising parameter for comparing health care systems in different countries.<sup>[13]</sup> As the first to determine the association between MIRs and the novel markers of HDI, CHE, and CHE/GDP in CRC, our study provides information on the relationship between clinical outcomes and economic status and medical expenses in 171 countries. The results show that HDI, CHE, and CHE/GDP are significantly correlated with both the incidence and mortality rate of CRC. Furthermore, the MIR for CRC, as we expected, is significantly inversely correlated with HDI, CHE, and CHE/GDP in 171 countries. In general, the countries with higher HDIs, CHEs, and CHE/GDPs present lower MIRs. The results reflect that the countries with a higher HDI ranking and greater medical expenditures may have better public health care policies, such as screening programs, and a better quality of treatment for CRC.

The statistics and trends in both the incidence rate and mortality rate of CRC are quite complicated to interpret due to various factors that contribute to the incidence, such as differences in environmental exposures and behaviors related to socioeconomic status, including physical inactivity, smoking, an unhealthy diet, and obesity. The above conditions have been

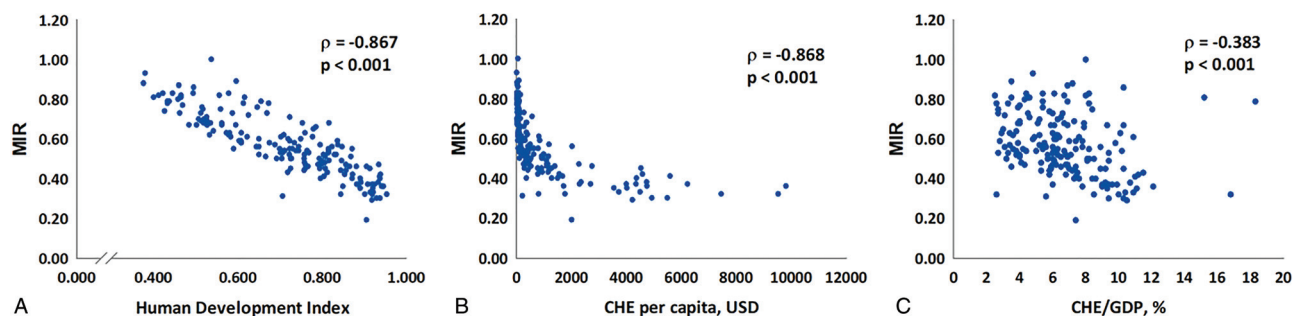


**Figure 1.** The association between the Human Development Index, current health expenditure, and the crude rates of (A, C, and E) incidence and (B, D, and F) mortality in colorectal cancer.

demonstrated to cause the variation in incidence between countries.<sup>[16–19]</sup> One of the more important risk factors for cancer is aging.<sup>[20]</sup> The people living in high HDI, CHE, and CHE/GDP countries have a higher average life expectancy, and their higher probability of having CRC can be explained by this phenomenon.

Furthermore, screening policies that achieve early detection and the practice of early treatment may profoundly reduce the rates of both incidence and mortality.<sup>[21]</sup> Fecal occult blood test screening is a method used in many developed countries, like

United Kingdom, Denmark, and America.<sup>[21,22]</sup> The highest MIR of CRC happened in India, where the incidence of CRC is lowest implies that the increase of medical expenses in CRC screening should be helpful. In countries with high ASR incidence, mortality and median MIR of CRC, like Hungary, diet habit and hereditary factors should be taken into considerations. Environmental factors can affect the incidence of CRC and then affect the MIRs of CRC among countries. There are evidences between heavy metals pollution in environments and CRC in Iran as a good example.<sup>[23–29]</sup>



**Figure 2.** The (A) Human Development Index, (B) current health expenditure per capita, and (C) current health expenditure as a percentage of gross domestic product are significantly associated with the mortality-to-incidence ratio in lung cancer.

To sum up, the mere observation of incidence and mortality rate are not sufficient to adequately assess the treatment quality of CRC globally due to multifactorial effects on both incidence and mortality. At the same time, the use of MIRs as an indicator of clinical outcome as well as the positive impact of health care expenditure on favorable MIRs has been proven in several types of cancer.<sup>[9,14,30]</sup> Patients in countries with greater health care expenditures may have easier access to advanced screening programs as well as to prompt, effective treatment and thus experience better clinical outcomes.

A previous study provided a map of the widely varied popularity of early screening programs worldwide.<sup>[31]</sup> Several countries with population-based screening programs, such as Finland, France, Slovenia, the UK, Japan, and Canada had completed the launch of their organized programs. By contrast, Romania and Hungary lacked screening programs.<sup>[31]</sup> We found a strong correlation between the implementation of screening programs and the MIRs of CRC in the data from GLOBOCAN. Countries reported to have completed the launch of organized screening programs show a tendency to have lower MIRs; conversely, the lack of a screening policy was associated with higher MIRs. The correlation, again, strongly supports the vital role of screening in improving the clinical outcome of CRC.

Though malicious and not curable at an advanced stage, CRC can be treated with excellent clinical outcomes at the early stage. Among the prognostic factors of CRC, the diagnosis stage is the most important. The 5-year survival rate of patients with CRC is nearly 90% in the early stages (stages I and II) but only 11% and 12% in patients with metastatic or stage IV CRC, respectively.<sup>[32,33]</sup> Moreover, when the condition is detected early as a precancerous polyp through screening modalities such as colonoscopy, computed tomography colonography, and fecal occult blood test, the polyp can be resected before it progresses to malignancy.<sup>[34–37]</sup> These characteristics of CRC highlight the crucial role of screening programs in reducing both the incidence rate and mortality caused by CRC. Countries with higher CHEs and CHE/GDPs probably make greater expenditures on screening programs and achieve both less incidence and less mortality.

This study has a few limitations. First, we examined cross-sectional data for only 1 year, creating the possibility of overlooking the dynamic change of the disease over the past few years. Second, because countries with low or unknown data quality were excluded to prevent concerns about misleading effects, this study may not be sufficiently comprehensive to provide an adequate overall view of global trends. Moreover, several factors contributing to the disparity in the prognosis of

CRC were not documented, such as age and stage at diagnosis, the results of screening examinations, and different screening program policies. These conditions may play a role in explaining some of the variation in incidence and mortality rates among the countries enrolled. Furthermore, using HDI, CHE, and CHE/GDP to represent the health care disparities between countries might not be sufficiently comprehensive. Other medical factors, such as national health care systems, insurance coverage, and disparities in access to cancer care, could be considered in a more comprehensive review.<sup>[9]</sup> Also, the data from GLOBOCAN were limited to the year of 2012 and 2018 which might not fully represent real-world data. Although the above indexes may not be sufficiently representative to reflect medical settings worldwide, the consistent correlation between them and MIR speaks to its credibility in serving as a valid indicator for clinical outcome.

The association demonstrated in the present study between the MIRs of CRC and health care disparities indicates that medical expenditures play an important role in the improvement of CRC outcomes. Future investigations using more details might help to provide a reasonable explanation for our finding.

## 5. Conclusion

The countries with higher HDIs, CHEs, and CHE/GDPs present lower MIRs in our analysis. The MIRs of CRC are significantly inversely correlated with health care expenditures and is useful as an index for health care disparities.

## Author contributions

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**Methodology:** Chi-Chih Wang.

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**Supervision:** Ming-Chang Tsai.

**Validation:** Ming-Chang Tsai.

**Writing – original draft:** Pei-Yi Yan, Po-Yun Ko.

**Writing – review & editing:** Ming-Chang Tsai.

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