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

A study based on GLOBOCAN database

Chi-Chih Wang, MD, PhD\textsuperscript{a,b,c}, Wen-Wei Sung, MD, PhD\textsuperscript{b,c,d,e}, Pei-Yi Yan, MSS\textsuperscript{b}, Po-Yun Ko, MD\textsuperscript{b,e}, Ming-Chang Tsai, MD, PhD\textsuperscript{a,b,c}\textsuperscript{*}

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

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.\cite{1} 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.\cite{1,2} The factors contributing to the variation in incidence have been identified, including environment, lifestyle, and differences in dietary habits.\cite{3-5} 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.\cite{3,7}

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.\cite{6-9} 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.\cite{1} 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\cite{10} as a high incidence rate of CRC has been demonstrated to correlate with countries with a higher HDI.\cite{11} 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.\textsuperscript{11,12} 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.\textsuperscript{10} 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/).

The MIR was defined as the ratio of the CR of mortality to the CR of incidence as previously described.\textsuperscript{9,13-15} 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/GDP was lowest in Chad (0.32) and highest in Norway (0.953).

Table 1

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

| Region                        | New cases |          |          |          |                  |                  |                  |
|-------------------------------|-----------|----------|----------|----------|------------------|------------------|------------------|
|                               | Number    | CR       | ASR      | Number   | CR               | ASR               | MIR              |
| 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.
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 in 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 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 (p = -0.868, P < .001, Figure 2A; p = -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. 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 socioeconomic 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...
demonstrated to cause the variation in incidence between countries.\cite{16-19} One of the more important risk factors for cancer is aging.\cite{20} 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.\cite{21} Fecal occult blood test screening is a method used in many developed countries, like United Kingdom, Denmark, and America.\cite{21,22} 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.\cite{23-29}

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.
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.[9,14,30] 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.[31] 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.[32] 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.[32,33] Moreover, when the condition is detected early as a pre-cancerous 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.[34–37] 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.[39] 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
Conceptualization: Chi-Chih Wang, Wen-Wei Sung.
Data curation: Chi-Chih Wang, Wen-Wei Sung.
Formal analysis: Wen-Wei Sung.
Funding acquisition: Wen-Wei Sung.
Investigation: Chi-Chih Wang.
Methodology: Chi-Chih Wang.
Project administration: Chi-Chih Wang.
Software: Pei-Yi Yan.
Supervision: Ming-Chang Tsai.
Validation: Ming-Chang Tsai.
Writing – original draft: Pei-Yi Yan, Po-Yun Ko.
Writing – review & editing: Ming-Chang Tsai.

References
[1] Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality
worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68:394–424.

[2] Torre LA, Siegel RL, Ward EM, Jemal A. Global cancer incidence and mortality rates and trends—an update. Cancer Epidemiol Biomarkers Prev 2016;25:16–27.

[3] Huncharek M, Muscat J, Kupelnick B. Colorectal cancer risk and dietary intake of calcium, vitamin D, and dairy products: a meta-analysis of 26,335 cases from 60 observational studies. Nutr Cancer 2009;61:47–69.

[4] Park Y, Hunter DJ, Spiegelman D, et al. Dietary fiber intake and risk of colorectal cancer: a pooled analysis of prospective cohort studies. JAMA 2005;294:2849–57.

[5] Larson SC, Wolk A. Obesity and colon and rectal cancer risk: a meta-analysis of prospective studies. Am J Clin Nutr 2007;86:556–65.

[6] Sunkara V, Hebert JR. The application of the mortality-to-incidence ratio for the evaluation of cancer care disparities globally. Cancer 2016;122:487–8.

[7] Cordero-Morales A, Savitzky MJ, Stenning-Persivale K, Segura ER. Conceptual considerations and methodological recommendations for the use of the mortality-to-incidence ratio in time-lagged, ecological-level analysis for public health systems-oriented cancer research. Cancer 2016;122:486–7.

[8] Adams SA, Choi SK, Klang L, et al. Decreased cancer mortality-to-incidence ratios with increased accessibility of federally qualified health centers. J Community Health 2015;40:633–41.

[9] Chen SL, Wang SC, Hsieh TY, et al. Favorable mortality-to-incidence ratios are associated with cancer care disparities in 35 countries. Sci Rep 2017;7:40003.

[10] Fidler MM, Soerjomataram I, Bray F. A global view on cancer incidence and national levels of the human development index. Int J Cancer 2016;139:2436–46.

[11] Arnold M, Sierra MS, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global patterns and trends in colorectal cancer incidence and mortality. Gut 2017;66:683–91.

[12] Wild CP, Sylla BS. World Cancer Report 2012. Lyon: International Agency for Research on Cancer; 2014.

[13] Sunkara V, Hebert JR. The colorectal cancer mortality-to-incidence ratio as an indicator of global cancer screening and care. Cancer 2015;121:1563–9.

[14] Sung WW, Wang SC, Hsieh TY, et al. Favorable mortality-to-incidence ratios of kidney cancer are associated with advanced health care systems. BMC Cancer 2018;18:792.

[15] Wang SC, Sung WW, Kao YL, et al. The gender difference and mortality-to-incidence ratio relate to health care disparities in bladder cancer: national estimates from 35 countries. Sci Rep 2017;7:4360.

[16] Doubeni CA, Laiyemo AO, Major JM, et al. Socioeconomic status and the risk of colorectal cancer: an analysis of more than a half million adults in the National Institutes of Health-AARP Diet and Health Study. Cancer 2012;118:3636–44.

[17] Doubeni CA, Major JM, Laiyemo AO, et al. Contribution of behavioral risk factors and obesity to socioeconomic differences in colorectal cancer incidence. J Natl Cancer Inst 2012;104:1353–62.

[18] Klabunde CN, Cronin KA, Breen N, Waldron WR, Ambus AH, Nadel MR. Trends in colorectal cancer test use among vulnerable populations in the United States. Cancer Epidemiol Biomarkers Prev 2011;20:1611–21.

[19] Jochem C, Leitzmann M. Obesity and colorectal cancer. Recent Results Cancer Res 2016;208:17–41.

[20] Dugue PA, Bassett JK, Joo JE, et al. DNA methylation-based biological aging and cancer risk and survival: pooled analysis of seven prospective studies. Int J Cancer 2018;142:1611–9.

[21] Bond JH. Fecal occult blood testing for colorectal cancer. Gastrotest Endosc Clin N Am 2002;12:11–21.

[22] Medical Advisory S. Fecal occult blood test for colorectal cancer screening: an evidence-based analysis. Ont Health Technol Assess Ser 2009;9:1–40.

[23] Kiani B, Hashemi Amin F, Bagheri N, et al. Association between heavy metals and colon cancer: an ecological study based on geographical information systems in North-Eastern Iran. BMC Cancer 2021;21:414.

[24] Goshayeshi L, Pouramadid A, Ghayour-Mobarhan M, et al. Colorectal cancer risk factors in north-eastern Iran: a retrospective cross-sectional study based on geographical information systems, spatial autocorrelation and regression analysis. Geospat Health 2019;14.

[25] Mansori K, Mosavi-Jarrahia A, Ganbary Motlagh A, et al. Exploring spatial patterns of colorectal cancer in Tehran City, Iran. Asian Pac J Cancer Prev 2018;19:1099–104.

[26] Mansori K, Solaymani-Dodaran M, Mosavi-Jarrahia A, et al. Spatial inequalities in the incidence of colorectal cancer and associated factors in the neighborhoods of Tehran, Iran: Bayesian spatial models. J Prev Med Public Health 2018;51:33–40.

[27] Pakzad R, Moudi A, Pouramadid Z, et al. Spatial analysis of colorectal cancer in Iran. Asian Pac J Cancer Prev 2016;17:53:53–8.

[28] Pourhoseingholi MA, Najafzadeh H, Kavousi A, Pasharavesh L, Khanabadi B. The spatial distribution of colorectal cancer relative risk in Iran: a nationwide spatial study. Gastroenterol Hepatol Bed Bench 2020;13(Suppl 1):S40–6.

[29] Halmi L, Bagheri N, Hoseini B, Hashtr khani S, Goshayeshi L, Kiani B. Spatial analysis of colorectal cancer incidence in Hamadan Province, Iran: a retrospective cross-sectional study. Appl Spat Anal Policy 2020;13:293–303.

[30] Wang CC, Tsai MC, Peng CM, et al. Favorable liver cancer mortality-to-incidence ratios of countries with high health expenditure. Eur J Gastroenterol Hepatol 2017;29:1397–401.

[31] Schreuders EH, Ruco A, Rabeneck L, et al. Colorectal cancer screening: a global overview of existing programmes. Gut 2015;64:1637–49.

[32] Siegel RL, Miller KD, Fedewa SA, et al. Colorectal cancer statistics, 2017. CA Cancer J Clin 2017;67:177–93.

[33] Brenner H, Kloor M, Fox CP. Colorectal cancer. Lancet 2014;383:1490–502.

[34] Nishihara R, Wu K, Lochhead P, et al. Long-term colorectal-cancer incidence and mortality after lower endoscopy. N Engl J Med 2013;369:1095–105.

[35] Simon K. Colorectal cancer development and advances in screening. Clin Interv Aging 2016;11:967–76.

[36] Holme O, Loberg M, Kalager M, et al. Effect of flexible sigmoidoscopy screening on colorectal cancer incidence and mortality: a randomized clinical trial. JAMA 2014;312:606–15.

[37] Atkin W, Wooldrage K, Parkin DM, et al. Long term effects of once-only flexible sigmoidoscopy screening after 17 years of follow-up: the UK Flexible Sigmoidoscopy Screening randomised controlled trial. Lancet 2017;389:1299–311.