International Socioeconomic Predictors of Colon and Rectal Cancer Mortality: Is Colorectal Cancer a First World Problem?

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PURPOSE Colorectal cancer (CRC) is a leading cause of international morbidity and is the second highest cause of cancer-related mortality in the world. The purpose of this study was to investigate the relationship between international health care spending on CRC mortality over time.

METHODS This is a retrospective study using a publicly available data from the WHO Global Health Observatory database. General estimating equations were used to analyze the relationship between total health care expenditure per capita (THEpc) and CRC mortality at the country level. The primary predictors of interest were quartiles of THEpc. Other exposure variables included gross domestic product per capita (GDPpc), smoking (% of adult population smoking), physician density (per 10,000), and time.

RESULTS Mortality decreased significantly from 2000 to 2016 (coefficient [95% CI], −2.2 [−3.3 to −1.1]; $P <$ .001). THEpc, GDPpc, time, and percentage of adult population smoking were significant predictors of CRC mortality. Patients in the top two quartiles of THEpc had 3% higher rates of CRC mortality compared with countries in Q1 THEpc (Q3: 3.4 [1.9-4.8], $P <$ .001; Q4: 3.2 [1.4-5.0], $P =$ .001). Similar trends were seen in GDPpc (Q4: 3.2 [1.4-5.0], $P =$ .001; Q3: 3.4 [1.9-4.8], $P <$ .001; Q2: 1.7 [0.7-2.6], $P <$ .001; Q1: reference).

CONCLUSION Overall, mortality decreased significantly over the study period. Countries with higher health expenditures and higher gross domestic products experienced higher rates of CRC mortality. Further research will be necessary to determine the cause for this, but we postulate that it may be a result of more robust diagnostic and follow-up methods in countries with more resources.

INTRODUCTION

Colorectal cancer (CRC) is a leading cause of international morbidity and mortality and is the second highest cause of cancer-related mortality in the world.[1] In 2017, 1.8 million cases were documented with 896,000 deaths. The incidence of CRC has increased about 10% in the past 2 decades and is projected to continue to increase, particularly among developed countries and among populations younger than 50 years.[2] Although overall 5-year survival has improved to at least 60% in many countries,[3] one of three countries continues to experience increases in CRC-attributed mortality,[2] suggesting that CRC will continue to incur a high international burden of disease.

The role of preventable lifestyle factors in the development of CRC has been increasingly studied. Factors linked to Western lifestyles, including smoking, alcohol, and elevated body mass index, are associated with increased risk for CRC.[4,5] Globalization has popularized this lifestyle.[6] Dietary choices and exercise patterns are influenced by social determinants of health, including income and food availability. Therefore, understanding the socioeconomic trends driving these changes may help to facilitate the creation of effective interventions that target these preventable risk factors.

Although preventable risk factors associated with Western lifestyles undoubtedly contribute to CRC mortality, diagnostic and treatment capabilities may also heavily influence country-level CRC mortality.[7,8] As such, national health systems seeking to decrease burden from CRC often focus on screening, surgical, and chemotherapy/radiation capabilities.[9] Indeed, ASCO has recognized that resource availability influences best practices and has set forth guidelines suggesting that patients with operable metastatic liver disease should only be effectively treated in maximal-level resource settings.[10] Treatment according to these standards requires high-income regions with access to multidisciplinary treatment; only one third of countries can meet this standard.[11] In fact, many countries that

CONTEXT

Key Objective

Does international health care spending affect colorectal cancer (CRC) mortality over time?

Knowledge Generated

CRC mortality decreased over time, but only among the countries with the highest total health care expenditure. Developing countries with lower health expenditures did not experience any improvement in CRC mortality during this 16-year span.

Relevance

Efforts should be focused on expanding and developing best practices for CRC in under-resourced areas throughout the world.

would most benefit from increased screening and treatment capacity, including rapidly expanding countries, do not meet these criteria.[11,12] Clearly, differences in screening and treatment capabilities contribute to the widening divide in CRC mortality among developed and developing countries,[13] and improvements in CRC detection and treatment may parallel improvements in a region's economic status.[14]

In the context of everexpanding costs of health care and limited resource environments, we speculated as to whether health care expenditure was directly related to CRC mortality.

Few studies have explored this correlation; therefore, here, we aimed to investigate the effects of health care spending and equity on international trends in CRC mortality over time.

METHODS

This study used publicly available epidemiologic data between 2000 and 2016 from the WHO Global Health Observatory database, which includes health-related statistics for 194 member states.[15] Data collected and presented are determined by the WHO Reference Group on Global Health Statistics, last convened in March 2017.[16] The specific data set used falls under the noncommunicable diseases and mental health sustainable development goal.[17] These data were derived from various surveillance and household surveys administered every 3-5 years by the WHO. After incorporating available covariates, data sets were merged by date and country of origin. A total of 183 countries had complete data for this study.

CRC was defined per the *International Classification of Diseases*. No specification was made between types of CRC. Total health care expenditure per capita (THEpc) is the total value of government and private expenditures in the health sector per person. Gross domestic product per capita (GDPpc) is the total value of all goods and services produced in a country divided by its population. All expenditures were converted to US dollars and inflation adjusted to the year 2020. Smoking was measured as percentage of adult population who smokes, with time-varying measures of smoking rates per country. Time was

treated as a factor with observations collected at four time points: 2000, 2010, 2015, and 2016. Since this analysis used publicly available, aggregate data, no Institutional Review Board approval was needed.

General estimating equations (GEEs) were used to analyze the relationship between THEpc and GDPpc with CRC mortality. GEE modeling was chosen because this method is a robust and efficient alternative to the maximum likelihood estimation and is best suited for data with few time points (four time points: 2000, 2010, 2015, and 2016) and many cases (N = 183 countries). Additionally, GEE produces robust results in the presence of missing data.

The primary predictor of interest was THEpc. Other exposure variables included were GDPpc, smoking rates, physician density (per 10,000 midyear population), and time. THEpc and GDPpc were grouped into quartiles, as per the World Bank standards, and treated as ordinal variables. The outcome variable was age-standardized CRC mortality rate (per 100,000 people); the WHO database provided age-standardized mortality rates using the world standard population.

We calculated means and standard deviation (SD) for THEpc and GDPpc among all 183 evaluable member nations. Our primary analysis sought to evaluate the association between changes in CRC mortality rates and changes in THEpc and GDPpc among UN member nations over time. We used clinical relevance to select our model covariates. Our final model included the following predictors: THEpc quartiles, GDPpc quartiles, time, smoking, and physician density. Exchangeable correlation matrix structure was selected on the basis of the lowest Quasi-likelihood under independence model criterion information criteria. We tested all possible two-way interactions, but none were significant; therefore, they were not included in our final model.

We did two follow-up analyses using the same modeling methods as described above. First, we evaluated changes in CRC mortality rates with changes in THEpc and GDPpc among UN member nations separately within each THEpc quartile. For these analyses, the selected covariates were THEpc, GDPpc, smoking, physician density, and time. For

these analyses, we analyzed THEpc and GDPpc as continuous variables as we had already restricted the groups to the THEpc quartiles.

Second, we evaluated changes in sex-specific CRC mortality rates. For this analysis, our outcome variables were age-standardized CRC mortality rates in men and women. Our covariates were THEpc, GDPpc, smoking, time, and physician density. THEpc and GDPpc were treated as categorical variables using quartiles while smoking and physician density were continuous. All analyses were completed using SPSS statistical software version 26.0 (SPSS Inc, Chicago, IL). P values $< .05$ were considered statistically significant.

RESULTS

Descriptive Statistics

Our analysis included data from 183 UN member countries. Table 1 lists the mean GDPpc (Table 1A) and THEpc (Table 1B) for each of their respective quartiles for the 4 years of the analysis. The mean (SD) percentage of adult population smoking is 23.4 (10.8) for all 183 countries. The mean (SD) country-level annual colorectal mortality rate for all ages and sexes is 13.7 (13.5) per 100,000 people.

CRC Mortality Results

We analyzed the relationship between CRC mortality over time compared independently with GDPpc (Fig 1A) and THEpc (Fig 1B). Countries with higher GDPpc or THEpc had substantially elevated rates of CRC mortality compared with countries with lower GDPpc or THEpc. Despite the difference in baseline rates, the rates of CRC mortality appear to decrease over the study period for all GPDpc quartiles and THEpc quartiles.

Table 2 demonstrates the results of the full GEE multivariable model with the outcome of CRC mortality and predictors of both GDPpc and THEpc, as well as year, smoking rate, and physician density. Similar to the

unadjusted analysis in Figures 1A and 1B, this full model demonstrates that the rates of CRC mortality have decreased across the study period, with lower rates in 2010, 2015, and 2016 compared with the reference year of 2000. Compared with the lowest quartile of GDPpc, the highest GDPpc quartile had an increased rate of CRC mortality of 3.2 ([95% CI, 1.4 to 5.0], $P = .001$) per 100,000. Compared with the lowest quartile of THEpc, the highest THEpc quartile had an increased CRC mortality rate of 1.9 ([95% CI, 0.3 to 3.4], $P = .02$) per 100,000. Smoking was also significantly associated with increased CRC mortality rates; for every percentage point increase in percentage of adult population who smokes, the colorectal mortality rate increased by 0.092 ([95% CI, 0.005 to 0.18], $P = .039$) per 100,000. Of note, the impact of physician density on CRC mortality rates did not reach statistical significance ($P = .079$), although there was a trend toward higher rates of CRC mortality with increased physician density.

Subgroup Analysis: THEpc Quartiles

The results of analyses for the association between CRC mortality and THEpc and GDPpc for countries within the different THEpc quartiles are listed in Table 3. For the lowest THEpc quartile, smoking and physician density were significant predictors of CRC mortality, whereas THEpc and GDPpc were not. Within countries in the lowest quartile of THEpc, for a one percentage point increase in percentage of adult population who smokes, the CRC mortality rate increases by 0.11 ([95% CI, 0.001 to 0.22], $P = .047$). For a one person increase in physician density (per 10,000), the CRC mortality rate increased by 0.15 ([95% CI, 0.002 to 0.30], $P = .047$).

For the second lowest THEpc quartile, none of the predictors were significant. For the second highest THEpc quartile, smoking was a significant predictor, whereas THEpc, GDPpc, and physician density were not. For a one percentage point increase in percentage of adult population who smoked in the second lowest THEpc quartile, the CRC

TABLE 1. Demographics
A: Mean GDPpc in USD for Each GDP Quartile

Year	First Quartile	Second Quartile	Third Quartile	Fourth Quartile
2000	535.5 (300.9)	2,262.4 (802.1)	7,079.2 (2,806.1)	26,423.8 (8,351.2)
2010	710.8 (265.1)	2,351.1 (841.4)	7,120.4 (2,474.3)	38,005.9 (19,678.0)
2015	764.4 (290.4)	2,558.7 (870.2)	6,808.0 (2,169.6)	34,733.8 (19,923.1)
2016	706.6 (275.6)	2,524.2 (873.4)	6,868.3 (2,310.4)	35,292.1 (19,877.3)

B: Mean THEpc in USD for Each THE Quartile

Year	First Quartile	Second Quartile	Third Quartile	Fourth Quartile
2000	25.6 (15.8)	129.0 (52.9)	438.6 (181.0)	2,061.0 (894.5)
2010	35.7 (13.4)	121.8 (48.5)	435.7 (161.7)	2,970.7 (2,152.4)
2015	38.1 (12.9)	124.5 (48.0)	447.5 (154.7)	2,904.4 (2,195.4)
2016	37.8 (13.1)	121.9 (48.8)	411.5 (146.1)	2,883.1 (2,237.0)

Abbreviations: GDP, gross domestic product; GDPpc, gross domestic product per capita; THE, total health care expenditure; THEpc, total health care expenditure per capita; USD, US dollars.
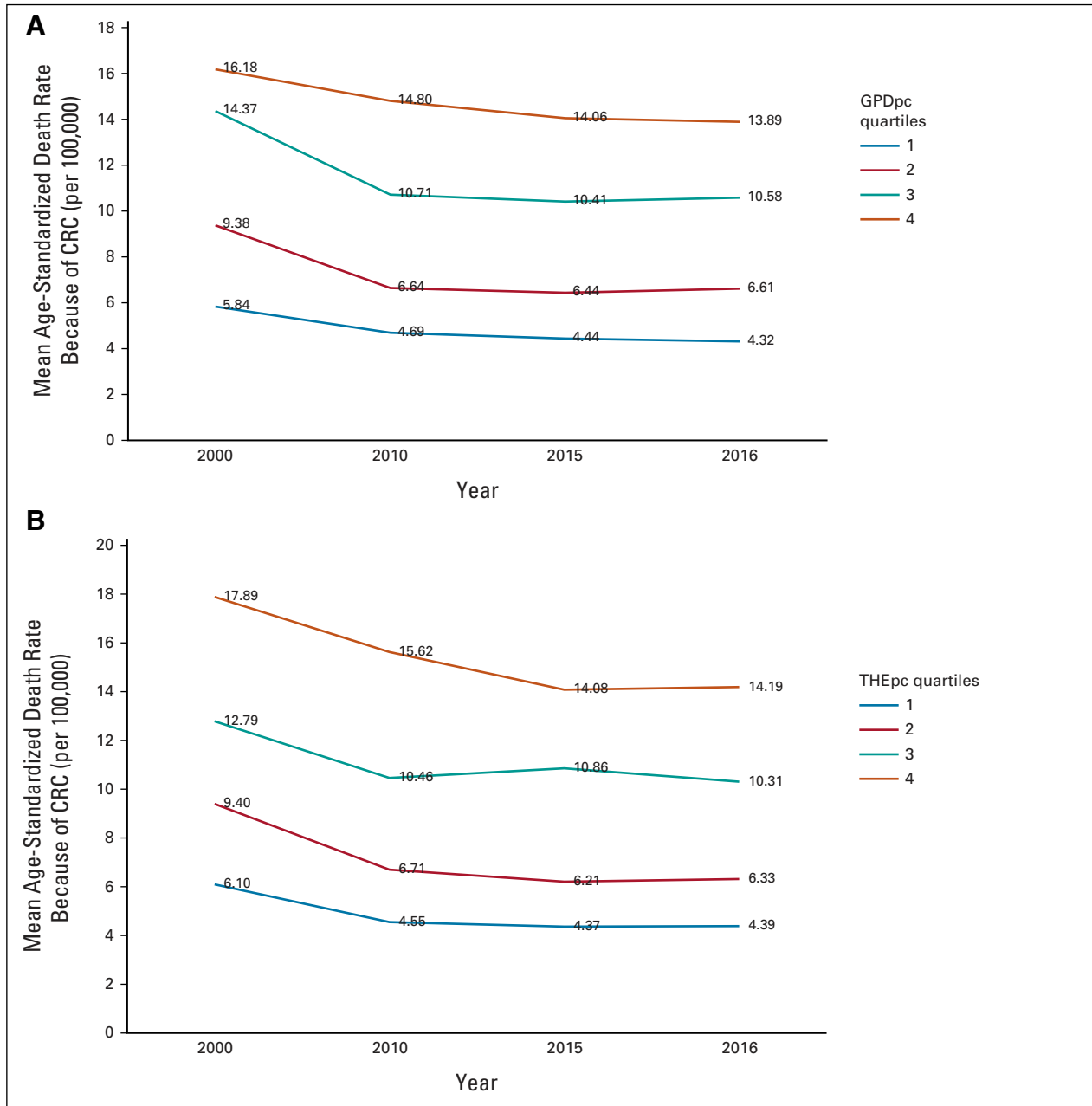
FIG 1. Mean CRC mortality rate (per 100,000) over time grouped by (A) GPDpc quartiles and (B) THEpc quartiles. CRC, colorectal cancer; GDPpc, gross domestic product per capita; THEpc, total health care expenditures per capita.

mortality rate increased by 0.22 ([95% CI, 0.12 to 0.33], $P <$ .001).

For the highest THEpc quartile, time was the only significant predictor. From 2000 to 2016, the CRC mortality rate decreased significantly by an estimated factor of 3.2 ([95% CI, −5.3 to −1.2], P = .002).

Subgroup Analysis: Colorectal Mortality, Men

We analyzed the relationship between THEpc and GDPpc and CRC mortality in men. In our model, GDPpc was the only significant predictor. Neither THEpc, smoking, and

physician density nor time was significant. Compared with this reference category (lowest GDPpc quartile), the annual CRC mortality rate for men in countries in the highest quartile of GDPpc was significantly higher by 3.9 ([95% CI, 0.83 to 7.03], P = .013) per 100,000 (Table 4).

Subgroup Analysis: Colorectal Mortality, Women

Here, we analyzed the relationship between THEpc and GDPpc and CRC mortality in women. In our model, THEpc, GDPpc, time, density of physicians, and percentage of adult population smoking were all significant predictors of CRC mortality.

TABLE 2. Parameter Estimates for Adjusted Relationship Between THEpc, GDPpc, and Colorectal Cancer Mortality

Variable	Coefficient (95% CI)	P
Year		.001
2000	Reference	—
2010	**−1.593 (−2.450 to −0.737)**	**< .001**
2015	**−2.158 (−3.235 to −1.081)**	**< .001**
2016	**−2.179 (−3.305 to −1.052)**	**< .001**
Smoking (% of adult population)	**0.092 (0.005 to 0.180)**	**.039**
Physician density (per 10,000)	0.039 (−0.004 to 0.082)	.079
GDPpc		**< .001**
Quartile 1	Reference	—
Quartile 2	**1.714 (0.783 to 2.644)**	**< .001**
Quartile 3	**3.394 (1.942 to 4.846)**	**< .001**
Quartile 4	**3.204 (1.389 to 5.019)**	**.001**
THEpc		**.032**
Quartile 1	Reference	—
Quartile 2	0.257 (−0.892 to 1.407)	.662
Quartile 3	1.314 (−0.104 to 2.732)	.069
Quartile 4	**1.855 (0.300 to 3.411)**	**.019**

NOTE. Significant values are in bold.

Abbreviations: GDPpc, gross domestic product per capita; THEpc, total health care expenditure per capita.

In general, CRC mortality in women decreased over time. Compared with the lowest GDPpc quartile, the annual CRC mortality rate for countries in the highest quartile of GDPpc was significantly higher by 2.6 ([95% CI, 1.3 to 4.0], P < .001) per 100,000. Compared with the countries in the lowest THEpc quartile, the annual CRC mortality rate for countries in the highest quartile of THEpc was significantly higher by 1.7 ([95% CI, 0.5 to 3.0], P = .007) per 100,000.

For every one unit increase in number of physicians per 10,000, the colorectal mortality rate increased by 0.064 ([95% CI, 0.019 to 0.1], P = .001). In summary, CRC mortality rates in women decreased between 2000 and 2016, but at all time points, countries with higher THEpc and GDPpc had higher CRC mortality rates in women compared with countries with lower THEpc and GDPpc (Table 4).

DISCUSSION

In this study analyzing CRC mortality in 183 countries over 16 years, we found that CRC mortality decreased significantly over the 16-year course of the study. Additionally, GDPpc, THEpc, and smoking were each significantly associated with CRC mortality. Our analyses revealed that countries with highest GDPpc and THEpc experienced higher rates of CRC mortality. Gross domestic product (GDP) is known to correlate with the incidence and mortality of CRC. Global Cancer Incidence, Mortality and Prevalence reports that 60% of CRC mortality occurs in countries with high development index.[18] Similarly, a recent study demonstrated a strong correlation between CRC mortality and economic growth, suggesting that CRC burden may function as an index of economic development.[19] Exposure to behavioral risk factors, such as diet and sedentary lifestyle, is thought to explain these findings as countries in the highest GDPs are likely to have increased exposure to lifestyle risk factors for CRC.[9] Unfortunately, we were unable to control for risk factor exposure within this study because of data constraints. Still, it will be important to further examine contributions to mortality associated with lifestyle risk factors in comparison with other factors such as screening and other preventative measures. Notably, our study agrees with modeling studies suggesting that, although developed countries are responsible for the majority of global cancer death, these rates are declining.[8]

TABLE 3. Parameter Estimates for Colorectal Cancer Mortality, Stratified by THEpc Quartile

Variable	THEpc Quartile 1		THEpc Quartile 2		THEpc Quartile 3		THEpc Quartile 4	
	Coefficient (95% CI)	P	Coefficient (95% CI)	P	Coefficient (95% CI)	P	Coefficient (95% CI)	P
Year		.83		.41		.59		.004
2000	Reference	—	Reference	—	Reference	—	Reference	—
2010	−0.49 (−2.29 to 1.30)	.59	−4.14 (−9.89 to 1.60)	.16	−1.48 (−3.71 to 0.75)	.19	**−2.20 (−3.88 to −0.51)**	**.01**
2015	−0.47 (−2.53 to 1.59)	.65	−7.27 (−16.42 to 1.87)	.12	−1.40 (−3.74 to 0.95)	.24	**−3.29 (−5.32 to −1.26)**	**.002**
2016	−0.30 (−2.35 to 1.76)	.78	−6.54 (−14.93 to 1.85)	.13	−1.47 (−3.83 to 0.88)	.22	**−3.23 (−5.30 to −1.15)**	**.002**
Smoking (% of adult population)	**0.11 (0.001 to 0.22)**	**.047**	0.65 (−0.36 to 1.66)	.20	**0.22 (0.12 to 0.33)**	**< .001**	0.062 (−0.06 to 0.18)	.31
Physician density (per 10,000)	**0.15 (0.002 to 0.30)**	**.046**	−0.25 (−0.78 to 0.27)	.35	0.07 (−0.04 to 0.17)	.21	0.06 (−0.03 to 0.15)	.17
GDPpc (per $1,000)	−0.081 (−1.76 to 1.60)	.93	2.82 (−1.85 to 7.50)	.24	−0.02 (−0.43 to 0.39)	.94	−0.03 (−0.09 to 0.03)	.35
THEpc (per $1,000)	47.27 (−30.46 to 125)	.23	28.92 (−28.16 to 85.99)	.32	4.30 (−3.39 to 11.99)	.27	0.13 (−0.41 to 0.66)	.65

NOTE. Significant values are in bold.

Abbreviations: GDPpc, gross domestic product per capita; THEpc, total health care expenditure per capita.

TABLE 4. Parameter Estimates for Male and Female Colorectal Cancer Mortality

Variable	Male			Female		
	Parameter Estimates	**95% CI**	***P***	**Parameter Estimates**	**95% CI**	***P***
Year			.13			**< .001**
2000	Reference			Reference		
2010	**−1.61**	**−3.1 to −0.10**	**.036**	**−1.82**	**−2.37 to −1.27**	**< .001**
2015	**−2.05**	**−3.93 to −0.17**	**.033**	**−2.56**	**−3.28 to −1.86**	**< .001**
2016	**−2.23**	**−4.18 to −0.29**	**.024**	**−2.47**	**−3.21 to −1.72**	**< .001**
GDPpc			**< .001**			**< .001**
Quartile 1	Reference			Reference		
Quartile 2	**1.92**	**0.89 to 2.96**	**< .001**	**1.41**	**0.52 to 2.31**	**.002**
Quartile 3	**4.24**	**2.07 to 6.41**	**< .001**	**2.64**	**1.55 to 3.72**	**< .001**
Quartile 4	**3.93**	**0.83 to 7.04**	**.013**	**2.63**	**1.29 to 3.97**	**< .001**
THEpc			.23			**.007**
Quartile 1	Reference			Reference		
Quartile 2	0.09	−1.25 to 1.43	.90	0.46	−0.62 to 1.54	.41
Quartile 3	1.48	−0.49 to 3.45	.14	**1.35**	**0.14 to 2.55**	**.03**
Quartile 4	**2.16**	**−0.27 to 4.60**	**.08**	**1.75**	**0.47 to 3.03**	**.007**
Smoking	0.05	−0.13 to 0.22	.62	**0.07**	**0.02 to 0.12**	**.006**
Physician density	−0.06	−0.14 to 0.02	.16	**0.06**	**0.03 to 0.10**	**.001**

NOTE. Significant values are in bold.

Abbreviations: GDPpc, gross domestic product per capita; THEPc, total health care expenditure per capita.

Although GDP has clearly been shown to correlate with CRC mortality, the role of health care expenditure is less clear. A study in 2006 concluded that increasing health care expenditures in developed nations show a marginal benefit with diminishing returns, further asserting that health care expenditures in developing nations are expected to be more impactful.[20] Although this inference is very rational, our results suggest a different state of affairs.

This discrepancy may be partially attributed to inherent differences between cancer-based registry studies that use mortality to incidence ratio[21] versus population-based studies that focus on disease-specific mortality. We used CRC mortality, a population-based statistic, to correlate with our population-based data source, but this may introduce some differences. Our use of THEpc as a single economic predictor may also contribute to this discrepancy. We focused on THEpc because our primary interest was economic expenditures, but other social determinants of health may play important roles. For example, increasing THEpc among low-resource countries may diminish funding for measures that may have greater impact on overall health but could not be represented by a potentially oversimplified variable such as THEpc. Other studies have found that a composite health care ranking, including measures of overall health, health care financing, health inequality, health care responsiveness, and distribution, may be a better predictor for CRC outcomes than THEpc.[22] Thus, although economic measures may be appropriate for

countries with average health care expenditures, more complex sociologic measures may be necessary for countries that fall well below the mean.

Furthermore, the impact of underdeveloped infrastructure in countries with few resources may also contribute to our results. For example, countries that spend the least on health care may not see patients diagnosed or dying from cancer because patients have lower age expectancy because of death from infectious diseases and nutritional deficiencies, etc.[23] Additionally, when patients develop cancers, low-resource countries may not have the capacity to diagnose and track CRC diagnoses and mortality,[24] reflected by the positive association in this analysis. Indeed, a recent study indicated that globally, over 50% of all childhood cancers go undiagnosed.[25] Furthermore, it is conceivable that spending above a certain point does not improve outcomes. Therefore, countries spending excessively on health care may not see proportionate improvement in health outcomes. This would seem to hold true in the United States, where rates of avoidable mortality are higher than other countries of comparable wealth, despite higher per capita health spending.[26]

Our results also agree with existing studies on the role of smoking in CRC mortality. Smoking is a well-studied carcinogen for several cancers, including CRC. In a meta-analysis of over 100 international studies, 6.0 deaths per 100,000 person-years (95% CI, 4.2 to 7.6) could be attributed to smoking.[27] Our analysis found that every one

percent increase in smoking in the adult population was associated with a 0.09 percent increase in the CRC mortality rate. Although direct comparisons cannot be made between changes in mortality rate and person-years, both results suggest that addressing smoking should decrease CRC incidence and mortality.

We also demonstrated a positive association between physician density and CRC mortality among the lowest THEpc quartile and women. This may again relate to health care infrastructure diagnosis and tracking capabilities. Previous studies on provider densities have noted decreased incidence[28] and improved screening[29] with increased physicians. However, most of these studies were conducted in the United States, which has one of the highest THEpc in the world. Countries with low THEpc but greater proportion of physicians may have the human resources to diagnose patients but may not have the infrastructure to effectively treat patients. This marker of physician density also does not differentiate between physician specialties. Further studies with more granular data are required to identify resource availability at each step of the treatment pathway.

In our model, women also experienced increases in mortality with increases in physician density. It is unlikely that these findings are solely explained by sex-based differences in pathophysiology, although studies have suggested that women have longer transverse colons,[30] are more likely to develop right-sided lesions,[31] and have decreased sensitivity for fecal occult blood test.[32] An economic explanation is more likely, given that women showed increased mortality with increased THEpc and GDPpc. Globally, women also experience increased CRC mortality when compared with men.[33] Countries with greater physician density likely have improved documentation to capture this mortality.

We also show that mortality associated with CRC has improved over the course of our study. This is both promising and in agreement with existing literature.[34] However, this is only true among countries in the highest THEpc. Developing countries with decreased health expenditures did not experience any improvement in CRC mortality during this 16-year span. In fact, many of the countries with lower health expenditures saw increasing incidence of CRC, indicating that further efforts should be made to expand and develop best practices for under-resourced areas.

Some limitations to this study include those typical for population-based studies: incomplete data entry and sampling biases within each country, among others. However, the WHO Global Health Observatory database is used regularly in international WHO reports and multiple publications and is, therefore, regarded as a reliable source of data. There are also limited data on other covariates, including availability of specialists, screening rates, and imaging capabilities, among others. These data would better elucidate underlying mechanisms for associations uncovered in this study. Data on screening rates and imaging capabilities would also elucidate the potential for misclassification error as countries with fewer resources may misdiagnose CRC as other pathology. These data also span a 16-year period at irregular intervals. Although GEEs can account for differences in follow-up, data collected at regular intervals would provide greater specificity.

Overall, we found that CRC mortality decreased over time and that smoking significantly contributed to CRC mortality. Although countries with highest health expenditures and highest GDPpcs experienced higher rates of CRC mortality, the mortality rates in these countries decreased significantly over the course of the study, whereas this difference was less apparent in lower GDPpc/THEpc groups.

The findings we present indicate a complex interplay of factors contributing to CRC mortality. The differences we noted between developed and developing nations call attention to the need for more granular country-based data, as well as thoughtful, contextual research and planning to better address cancer care in regions throughout the world.

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EQUAL CONTRIBUTION

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Final approval of manuscript: All authors

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