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Global Inequalities in Colorectal Cancer Incidence, Mortality, and Mortality-to-Incidence Ratio in Relation to Human Development Index: An Analysis Based on the Global Burden of Disease Study, 1990–2023

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Abstract

Background: Over recent decades, colorectal cancer (CRC) burden measures have changed worldwide, showing variations associated with differences in the Human Development Index (HDI). The purpose of this study was to examine the relationship between HDI and CRC incidence, mortality, and the mortality-to-incidence ratio (MIR) from 1990 to 2023, and to explore HDI-related inequalities in these measures over time.

Methods: Age-standardized CRC incidence and mortality rates from the Global Burden of Disease study were analyzed alongside HDI data from the UN. This ecological study used countries as units of analysis. The association between HDI and CRC indicators from 1990 to 2023 was assessed using Generalized Estimating Equations (GEE). HDI-related inequality in CRC indicators for 1990 and 2023 was measured with the Concentration Index (CI), and the contribution of HDI to temporal inequalities was evaluated via Blinder-Oaxaca decomposition analysis.

Results: Global socioeconomic inequalities in CRC incidence ($CI_{1990}=0.28$ vs. $CI_{2023}=0.27$) and mortality (0.29 vs. 0.15) decreased significantly while inequality in MIR (-0.29 vs. -0.39) increased significantly from 1990 to 2023, with these trends varying according to HDI levels. Higher HDI was associated with increased CRC incidence and mortality across low to high HDI countries. However, in very high HDI countries (HDI > 0.80), incidence continued to rise while mortality showed a declining trend, resulting in a substantially lower MIR. Spline analysis confirmed significant non-linear relationships with a threshold at HDI 0.80 ($P<0.001$). The strength of the association between HDI and CRC incidence and mortality decreased over time, especially in higher HDI countries (HDI > 0.70). The distribution of HDI was associated with the reduction in MIR, especially among low (HDI < 0.55) and very high HDI countries (HDI > 0.80).

Conclusion: Our study found evidence of an association between HDI distribution and temporal variations in CRC burden measures from 1990 to 2023.

Keywords: Colorectal cancer, Human development index, Human development index inequality incidence, Mortality, Mortality-to-incidence ratio

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Introduction

Globally, colorectal cancer (CRC) ranks among the top three global cancers in both incidence and mortality rates. Epidemiological data from 2022 showed that approximately one in ten new cancer cases (9.6%) and a similar proportion of cancer deaths (9.3%) were attributed to CRC.[1] The trend of CRC incidence varied worldwide from 1990 to 2021, showing stabilization and a slight decline in high-income countries and a rise in low- and middle-income countries.[2] Projections for 2040 suggest a remarkable rise in CRC burden, reaching an estimated 3.2 million new cases and 1.6 million deaths.[3]

The human development index (HDI) is an important factor in the geographic and temporal variations of CRC incidence and mortality.[1] HDI is a composite measure of three human development dimensions including education, income, and life expectancy.[4,5] CRC ranks in the top five cancers for incidence and mortality across all HDI levels.[1] There is evidence indicating that accessibility and availability of screening programs, healthcare services and healthy living habits could be attributed to HDI levels, which affects CRC incidence and mortality.[6] The implementation of screening programs, early diagnosis, and effective treatment modalities can lead to lower mortality to incidence ratios (MIR),[7,8] although the effect of lead time bias from early diagnosis should be still

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considered.

The HDI components may influence CRC outcomes through distinct and different ways. Higher income levels are associated with greater investment in early detection and treatment, which may lead to reduced mortality and MIR.[9] However, economic development is also associated with adoption of Westernized dietary patterns, and sedentary lifestyles are more common in higher-income nations, which may increase CRC incidence.[10] Education is associated with health literacy and adherence to screening, potentially contributing to better prognosis.[11] Longer life expectancy increases the proportion of the population at older ages, where CRC risk is highest.[12] Moreover, life expectancy is associated with screening participation,[13] and clinical guidelines recommend continued screening for those with adequate life expectancy.[14] It is important to note that these components may exert opposing effects on CRC outcomes. For instance, while higher life expectancy increases the population at risk for CRC through aging, higher income and education may counteract this by enabling preventive behaviors and early detection. Therefore, the association between HDI and CRC outcomes represents the balance of these potentially divergent pathways.

The direction of relationship between the HDI and CRC burden measures has been reported in previous studies.[1,15,16] However, further clarification of the strength of this relationship between two factors is needed through the application of different analytical methodologies. One appropriate approach to better understand the entity relationship between two factors is to analyze repeated and correlated data,[17] where data on both HDI and CRC burden measures over a time period for each country are included in the analysis. Additionally, it can be important to determine how much of the difference in the CRC indicators between two different socioeconomic statuses or two time periods is due to differences in the HDI. Based on the type and scale of the data, there are several available techniques to analyze correlated data and decomposition of differences between two groups or two time periods.[18]

Although sufficient evidence exists regarding the temporal trend of CRC and related determinants based on Global Burden of Disease (GBD) data,[2,19,20] assessing the trend of CRC and the impact of the HDI through different statistical analyses can provide new insight into how HDI affects the changes in CRC burden measures over time. Therefore, the purpose of the present study was to assess global inequalities in CRC incidence, mortality, and MIR in relation to HDI from 1990 to 2023, using correlated data analysis and inequality decomposition methods.

Materials and Methods

Data Sources

The age-standardized incidence and mortality rates of CRC per 100,000 people for both genders in each country from 1990 to 2023 were obtained from the GBD study conducted by the Institute for Health Metrics and Evaluation (IHME).[15] Our primary analyses utilized point estimates of incidence and mortality without incorporating the associated uncertainty intervals. Subsequently, MIR was calculated by dividing the mortality rate by the incidence rate. This ratio is commonly used as a proxy for survival and healthcare disparities in ecological studies.[21,22]

HDI data for each country from 1990 to 2023 was obtained from the United Nations Human Development (UNDP) Report. Countries were classified based on their HDI levels as low (< 0.55), medium (0.55 to 0.70), high (0.70 to 0.80), and very high (> 0.80).[18] The final analytical sample included 191 countries with available data on HDI and CRC measures variables for the longitudinal analysis, and a subset of 140 countries with available data on CRC measures; HDI for both 1990 and 2023 was used for the inequality decomposition analysis.

Statistical Analysis

We employed the Generalized Estimating Equations (GEE) method with the exchangeable correlation structure to analyze the association between HDI and CRC incidence, mortality and MIR across different countries during the period 1990 to 2023. The GEE method can model longitudinal and panel data (e.g. CRC incidence rate) while accounting for the correlation within countries and across different time points. In the GEE analysis, HDI was treated in two ways: as a continuous variable to estimate the overall linear trend across development levels, and as a categorical variable to examine differences between specific HDI categories, with low HDI as the reference group. The GEE model with exchangeable correlation structure was specified as:

$$E(Yit) = \beta 0 + \beta 1 \mathrm{HDI}_{it} + \beta 2 \mathrm{Year}_{t}$$

where Y_{it} is the incidence rate for location i at year t.

To flexibly model potential non-linear relationships, we used restricted cubic splines with four knots placed at the 5th, 35th, 65th, and 95th percentiles of the HDI distribution. The spline terms were included in the GEE model to test for deviation from linearity. All models were adjusted for year to control for temporal trends.

The relative concentration index (CI) was applied to assess HDI-related inequality in CRC outcomes in 1990 and 2023. CI quantifies the extent to which CRC outcomes are concentrated among countries ranked by HDI, with values ranging from -1 to +1. A positive CI indicates that the outcome is more concentrated among countries with higher HDI (pro-rich inequality), while a negative CI indicates concentration among countries with lower HDI (pro-poor inequality). A zero value represents perfect equality. For the CI analysis, HDI was used as a continuous ranking variable. Given that all three outcomes are bounded variables (i.e. incidence and mortality rates have finite upper limits, and MIR is bounded between 0 and 1), we specified theoretical bounds for each outcome: limits 0–100 for incidence, 0–50 for mortality (per

100,000 population), and 0–1 for MIR. We employed the appropriate normalization methods recommended for bounded health variables.[23] CIs were calculated using the conindex command in Stata.[23] To ensure robustness and comparability of our findings, we computed both the Erreygers and Wagstaff normalized concentration indices.

The Oaxaca-Blinder (BO) decomposition analysis was applied to determine the contribution of HDI in explaining the temporal gaps i.e., the differences in CRC mortality-to-incidence ratio between high- and low-HDI countries over time. The BO decomposition quantifies how much of the observed difference in CRC outcomes between 1990 and 2023 is associated with changes in HDI levels (endowments) versus changes in the relationship between HDI and outcomes (coefficients).[24] For the BO decomposition analysis, we compared CRC outcomes between 1990 and 2023 by treating each year as an independent population, analogous to comparing two distinct groups. We chose 1990 as the comparison group and 2023 as the reference group. HDI was treated as a continuous variable.

Consider two groups defined by years, 2023 and 1990. The effect of HDI on the outcome (e.g. CRC incidence0 for these two years is as follows.

$$Y_{Incidence,\ Mortality,\ MIR2023} = \bar{X}_{HDI\ 2023}\beta_{2023} + c_{2023}$$

$$Y_{Incidence,\ Mortality,\ MIR1990} = \bar{X}_{HDI\ 1990\ \ 1990} + c_{1990}$$

$$\Delta = Y_{Incidence,\ Mortality,\ MIR2023} - Y_{Incidence,\ Mortality,\ MIR1990} = \left(\bar{X}_{HDI\ 2023} - \bar{X}_{HDI\ 1990}\right)\beta_{1990} + \bar{X}_{1990}\left(\beta_{2023} - \beta_{1990}\right) + \left(c_{2023} - c_{1990}\right) + \left(\bar{X}_{HDI\ 2023} - \bar{X}_{HDI\ 1990}\right) \times \left(\beta_{2023} - \beta_{1990}\right)$$

Where $\bar{X}$ is mean, β is the regression coefficient and C is the intercept.

The BO method can decompose the difference into three main components:

1. The Endowment Effect: The portion of the gap associated with differences in mean HDI levels between the two periods.
2. The Coefficient Effect: The portion attributable to differences in the strength of the association (the regression coefficients) between HDI and the outcome.
3. The Interaction Effect: The portion capturing the simultaneous interaction of differences in endowments and coefficients.

It should be noted that countries may have transitioned between HDI categories over the study period due to improvements in the HDI components; however, the decomposition method is designed to compare population-level distributions between two time points rather than to model within-country transitions. All statistical analyses were performed using Stata/SE, version 14.2.

Results

The results of HDI-related inequality in the CRC outcomes for 1990 and 2023 are shown in Table 1. Both Erreygers and Wagstaff normalized indices yielded consistent patterns. We report the Erreygers index here. In 1990, significant pro-rich inequality was observed for incidence (CI = 0.28 $P < 0.001$) and mortality (0.29, $P < 0.001$). Conversely, the MIR showed significant pro-poor inequality (-0.29, $P < 0.001$). By 2023, the relative CI of incidence (0.27, $P < 0.001$) and mortality (0.15, $P < 0.001$) in higher-HDI countries had diminished. In contrast, MIR inequality widened substantially (-0.39, $P < 0.001$), indicating worsening relative survival disparities.

For incidence, pro-rich inequality in low HDI countries (CI: 0.02, $P = 0.04$) dissipated by 2023 (-0.02, $P = 0.22$). Medium HDI countries showed a marked reduction from significant pro-rich inequality in 1990 (0.08, $P = < 0.001$) to near-zero in 2023 (0.01, $P = 0.731$). High HDI countries maintained non-significant CIs in both years. Notably, very high HDI countries developed significant pro-rich inequality by 2023 (0.12, $P < 0.001$), compared to non-significant in 1990. For mortality, low and high HDI countries showed non-significant CIs in both years. Medium HDI countries reversed from significant pro-rich inequality in 1990 (0.10, $P < 0.001$) to non-significant in 2023 (-0.01, $P = 0.76$). Very high HDI countries maintained non-significant negative CIs in both periods. For MIR, all HDI categories showed negative CIs in both years. This relative inequality intensified markedly in very high HDI countries, from -0.10 ($P = 0.020$) in 1990 to -0.21 ($P < 0.001$) in 2023. Low HDI countries showed diminishing inequality (from -0.08 to -0.02), while medium and high HDI countries maintained stable negative CIs.

The GEE analysis revealed significant associations between HDI and CRC outcomes across HDI categories (Table 2). Compared to low HDI countries, incidence rates were significantly higher in medium, high, and very high HDI countries. Within-category analysis showed a positive linear relationship between HDI and incidence across all development levels, though it was not statistically significant in low HDI countries ($P = 0.06$). A modest increasing temporal trend was observed ($\beta = 0.05$, $P = 0.02$). Mortality rates were significantly higher in medium, high, and very high HDI countries compared to the reference group. Within-category analysis revealed a positive association in low, medium, and high HDI countries, though not all reached statistical significance. Notably, in very high HDI countries, a non-significant negative association was observed ($\beta = -5.98$, $P = 0.42$). Mortality showed a significant decreasing trend over time ($\beta = -0.05$, $P = 0.001$). Higher HDI was associated with significantly lower MIR. This negative relationship was consistent across all HDI categories in within-category analysis, with the strongest effect in very high HDI countries ($\beta = -1.18$, $P < 0.001$). The temporal trend for MIR was significantly negative ($\beta = -0.004$, $P < 0.001$),

Table 1. Erreygers and Wagstaff Normalized Concentration Indices for Colorectal Cancer Outcomes by Human Development Index Level (1990 and 2023)

Year	HDI Category	N	Index	Incidence	*P*	Mortality	*P*	MIR	*P*
1990	Overall	140	Erreygers	0.28 (0.25, 0.31)	<0.001	0.29 (0.25, 0.32)	<0.001	-0.29 (-0.31, -0.26)	<0.001
			Wagstaff	0.47 (0.42, 0.52)	<0.001	0.38 (0.33, 0.43)	<0.001	-0.42 (-0.47, -0.38)	<0.001
	Low	45	Erreygers	0.02 (0.00, 0.04)	0.04	0.03 (-0.01, 0.06)	0.12	-0.08 (-0.11, -0.05)	<0.001
			Wagstaff	0.08 (0.01, 0.16)	0.04	0.06 (-0.01, 0.13)	0.12	-0.25 (-0.34, -0.17)	<0.001
	Medium	47	Erreygers	0.08 (0.05, 0.12)	<0.001	0.10 (0.05, 0.15)	<0.001	-0.10 (-0.14, -0.05)	<0.001
			Wagstaff	0.18 (0.10, 0.26)	<0.001	0.15 (0.07, 0.24)	<0.001	-0.16 (-0.24, -0.07)	<0.001
	High	31	Erreygers	0.07 (-0.00, 0.14)	0.07	0.01 (-0.08, 0.11)	0.82	-0.13 (-0.20, -0.06)	<0.01
			Wagstaff	0.08 (-0.00, 0.17)	0.07	0.01 (-0.09, 0.11)	0.82	-0.16 (-0.24, -0.07)	<0.01
	Very High	17	Erreygers	0.04 (-0.08, 0.16)	0.50	-0.05 (-0.15, 0.04)	0.29	-0.10 (-0.18, -0.03)	0.02
			Wagstaff	0.04 (-0.08, 0.17)	0.50	-0.05 (-0.15, 0.04)	0.29	-0.10 (-0.18, -0.03)	0.02
2023	Overall	140	Erreygers	0.27 (0.24, 0.30)	<0.001	0.15 (0.12, 0.18)	<0.001	-0.39 (-0.42, -0.36)	<0.001
			Wagstaff	0.38 (0.34, 0.42)	<0.001	0.20 (0.16, 0.24)	<0.001	-0.42 (-0.45, -0.38)	<0.001
	Low	16	Erreygers	-0.02 (-0.05, 0.01)	0.22	-0.04 (-0.09, 0.01)	0.17	-0.02 (-0.07, 0.02)	0.32
			Wagstaff	-0.07 (-0.16, 0.03)	0.22	-0.08 (-0.18, 0.03)	0.17	-0.06 (-0.17, 0.05)	0.32
	Medium	28	Erreygers	0.01 (-0.03, 0.04)	0.73	-0.01 (-0.06, 0.05)	0.76	-0.07 (-0.13, -0.01)	0.02
			Wagstaff	0.02 (-0.08, 0.12)	0.73	-0.02 (-0.11, 0.08)	0.76	-0.12 (-0.21, -0.02)	0.02
	High	36	Erreygers	0.04 (-0.01, 0.10)	0.15	0.01 (-0.04, 0.06)	0.79	-0.13 (-0.21, -0.06)	<0.01
			Wagstaff	0.07 (-0.02, 0.16)	0.15	0.01 (-0.06, 0.08)	0.79	-0.14 (-0.23, -0.06)	<0.01
	Very High	60	Erreygers	0.12 (0.06, 0.17)	<0.001	-0.03 (-0.08, 0.02)	0.19	-0.21 (-0.27, -0.16)	<0.001
			Wagstaff	0.13 (0.07, 0.19)	<0.001	-0.04 (-0.10, 0.02)	0.19	-0.21 (-0.27, -0.16)	<0.001

Table 2. Effect of Human Development Index on Incidence, Mortality and Mortality to Incidence Ratio from 1990 to 2023

			Human Development Index							
	β (95% CI)	*P*	Low		Medium		High		Very high	
			β (95% CI)	*P*	*β* (95% CI)	*P*	*β* (95% CI)	*P*	*β* (95% CI)	*P*
Incidence										
Low	Reference									
Medium	1.01 (0.23, 1.79)	0.01	6.79 (-0.28, 13.86)	0.06	25.92 (16.58, 32.25)	<0.001	27.64 (9.48, 45.81)	0.003	95.60 (47.88, 143.23)	<0.001
High	3.19 (1.82, 4.56)	<0.001								
Very high	6.39 (4.47, 8.31)	<0.001								
Year	0.05 (0.008, 0.09)	0.02	0.02 (-0.1, 0.06)	0.19	0.04 (-0.008, 0.09)	0.10	0.11 (0.03, 0.20)	0.01	-0.44 (-0.64, -0.24)	<0.001
Mortality										
Low	Reference									
Medium	1.91 (1.27, 2.54)	<0.001	5.39 (-0.87, 11.64)	0.09	12.65 (6.65, 18.65)	<0.001	7.02 (-3.80, 17.13)	0.17	-5.98 (-20.59, 8.62)	0.42
High	3.62 (2.48, 4.76)	<0.001								
Very high	3.80 (2.31, 5.30)	<0.001								
Year	-0.05 (-0.09, -0.02)	0.001	0.01 (-0.01, 0.05)	0.32	0.02 (-0.008, 0.05)	0.14	0.01 (-0.03, 0.06)	0.57	-0.24 (-0.30, -0.18)	<0.001
MIR										
Low	Reference									
Medium	0.01 (0.0003, 0.02)	0.04	-0.13 (-0.24, -0.02)	0.02	-0.42 (-0.64, -0.21)	<0.001	-0.52 (-0.65, -0.38)	<0.001	-1.18 (-1.50, -0.85)	<0.001
High	-0.01 (-0.03, 0.005)	0.18								
Very high	-0.05 (-0.07, -0.03)	<0.001								
Year	-0.004 (-0.004, -0.003)	<0.001	-0.0008 (-0.001, -0.0001)	0.02	-0.002 (-0.003, -0.0007)	0.001	-0.003 (-0.003, -0.002)	<0.001	-0.001 (-0.002, -0.0002)	0.01

MR, mortality to incidence ratio; Human development index as categorical (left, low HDI as reference) and HDI as continuous (right)

reflecting improving survival over time across all development levels.

The spline analysis revealed significant non-linear patterns for all three outcomes, confirming the threshold effect observed in the categorical analysis. For incidence, the spline terms were jointly significant ($P<0.001$),

showing a gradual increase at lower HDI levels, a steeper rise at moderate HDI, and a plateau at very high HDI (Figure 1A). After adjusting for the non-linear effect of HDI, the temporal trend was no longer significant ($P=0.962$). Mortality also demonstrated significant non-linearity ($P<0.001$), increasing with HDI up to 0.80, then plateauing and declining in very high HDI countries (Figure 1B). The year effect was not significant after spline adjustment ($P=0.264$). The MIR showed a consistently negative association with HDI, with the steepest decline at higher HDI levels (Figure 1C). Unlike incidence and mortality, the improving trend over time remained significant ($P<0.001$), indicating survival gains independent of development level.

We found 4.38, 0.45 and 0.15 units in mean difference of CRC incidence ($mean_{2023}=22.77$ vs. $mean_{1990}=18.39$) mortality (12.19 vs. 12.65) and MIR (0.63 vs. 0.78) (Table 3). If the distribution of HDI in 1990 had been similar to that in 2023, the mean incidence and mortality of CRC would have increased by 10.23 and 5.28 units, respectively, while the MIR would have decreased by 0.11 units. The Coefficients section indicates that the effect of HDI on CRC incidence ($\beta=-6.73$) and mortality ($\beta=-3.61$) has decreased significantly from 1990 to 2023, while the effect of HDI on MIR ($\beta=0.01$) showed no meaningful change between the two years. Moreover, the significant interaction effect between the Endowments and Coefficients sections for mortality and MIR reflects the significant combined effects of changes in the distribution of HDI and changes in its impact on these indicators over time (Table 2). By HDI levels, the impact of HDI on CRC incidence and mortality significantly decreased from 1990 to 20231 in countries within high and very high HDI levels. Moreover, if the HDI distribution in 1990 had been the same as in 2023, the mean MIR of CRC would have decreased by 0.04 and 0.13 units in countries within low and very high HDI levels, respectively (Table 2).

Discussion

The CRC incidence and mortality were more concentrated in countries with higher HDI, while MIR was higher in less developed countries in the two years. From 1990 to 2023, HDI inequality in incidence and mortality decreased, but inequality in MIR increased. The association between HDI and CRC outcomes is not uniform across development levels. While CRC incidence and mortality increased with HDI up to the 0.80 threshold, a divergent pattern emerged in very high HDI countries (HDI > 0.80), where incidence continued to rise but mortality declined. The MIR decreased consistently across all HDI levels, with the most pronounced reduction in very high HDI countries, indicating improved survival in the most developed settings. Non-linearity was confirmed by spline analysis, with a clear threshold at HDI 0.80. The association between HDI and CRC incidence and mortality has declined over time, particularly in countries with an HDI above 0.70. The distribution in HDI also contributes to decreased MIR, especially in countries with low HDI values below 0.55 and very high HDI values above 0.80.

From a methodological perspective, it is important to distinguish between relative and absolute inequality when interpreting changes in the CI. A declining CI reflects reduced relative inequality meaning that the share of the health outcome concentrated among higher-HDI countries has decreased, which can occur even if absolute differences persist or widen. Our findings showed that, from 1990 to 2023, global inequalities in CRC incidence and mortality diminished, in contrast to the rise in MIR inequality. Although the distribution of attributable risk factors for CRC currently varies across different regions,[25] part of this reduction in the inequality of incidence and mortality is likely related to changes in the risk factors

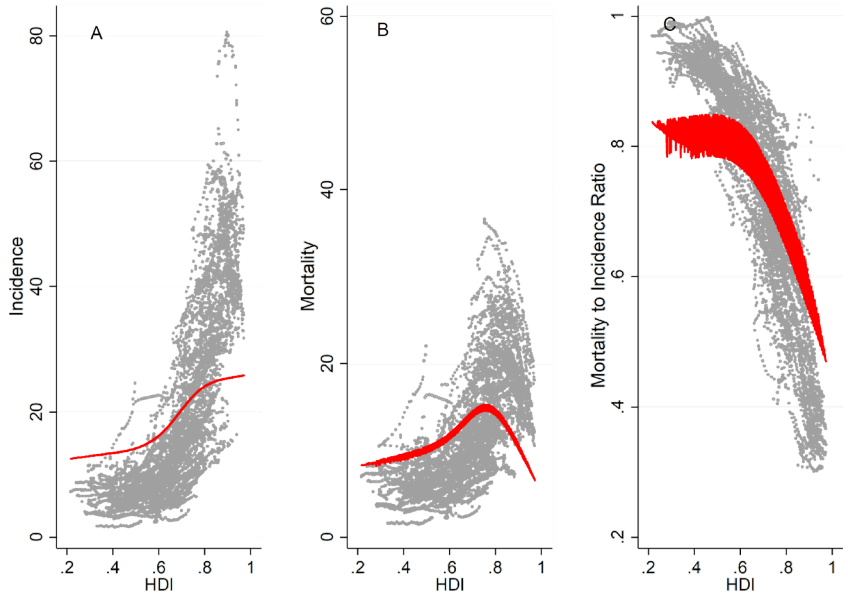

Figure 1. Non-linear relationship between human development index (HDI) and colorectal cancer outcomes using restricted cubic spline with 4 knots, Red lines show predicted values from spline model; gray circles show observed data

Table 3. Results of Blinder-Oaxaca Decomposition

	Incidence		Mortality		Mortality to incidence ratio	
Human development index	**β (95% CI)**	***P***	**β (95% CI)**	***P***	**β (95% CI)**	***P***
Global						
2023 (n=140)	22.77 (20.47, 25.07)	<0.001	12.19 (11.37, 13.02)	<0.001	0.63 (0.60, 0.66)	<0.001
1990 (n=140)	18.39 (15.98, 20.79)	<0.001	12.65 (11.37, 13.93)	<0.001	0.78 (0.76, 0.81)	<0.001
Difference	4.38 (1.06, 7.71)	0.01	-0.45 (-1.98, 1.07)	0.56	-0.15 (-0.19, -0.11)	<0.001
Endowments	10.23 (7.36, 13.10)	<0.001	5.28 (3.77, 6.79)	<0.001	-0.11 (-0.13, -0.08)	<0.001
Coefficients	-6.73 (-9.18, -4.27)	<0.001	-3.61 (-4.90, -2.32)	<0.001	0.01 (-0.01, 0.04)	0.32
Interaction	0.88 (-1.05, 2.81)	0.37	-2.12 (-3.24, -1.00)	<0.001	-0.06 (-0.08, -0.03)	<0.001
Low						
2023 (n=16)	7.27 (6.43, 9.02)	<0.001	6.86 (5.71, 8.00)	<0.001	0.89 (0.87, 0.91)	<0.001
1990 (n=45)	6.93 (6.03, 7.83)	<0.001	6.23 (5.53, 6.93)	<0.001	0.91 (0.89, 0.93)	<0.001
Difference	0.79 (-0.78, 2.37)	0.32	0.63 (-0.71, 1.96)	0.36	-0.02 (-0.04, 0.002)	0.08
Endowments	0.94 (-0.02, 1.91)	0.06	0.53 (-0.21, 1.27)	0.16	-0.04 (-0.05, -0.02)	<0.001
Coefficients	2.50 (-0.40, 5.41)	0.09	2.27 (-0.23, 4.78)	0.07	-0.006 (-0.05, 0.04)	0.78
Interaction	-2.65 (-5.39, 0.09)	0.06	-2.18 (-4.53, 0.16)	0.07	0.02 (-0.01, 0.06)	0.28
Medium						
2023 (n=28)	10.55 (8.95, 12.15)	<0.001	8.47 (7.27, 9.66)	<0.001	0.81 (0.78, 0.84)	<0.001
1990 (n=47)	12.67 (10.82, 14.52)	<0.001	9.96 (8.68, 11.24)	<0.001	0.81 (0.78, 0.83)	<0.001
Difference	-2.12 (-4.56, 0.32)	0.09	-1.49 (-3.24, 0.26)	0.09	0.003 (-0.03, 0.04)	0.87
Endowments	-0.87 (-2.79, 1.03)	0.37	-0.53 (-1.69, 0.63)	0.37	0.01 (-0.01, 0.03)	0.37
Coefficients	-2.04 (-4.46, 0.38)	0.10	-1.52 (-3.30, 0.26)	0.09	-0.004 (-0.04, 0.03)	0.81
Interaction	0.80 (-0.97, 2.57)	0.38	0.56 (-0.69, 1.81)	0.38	-0.003 (-0.01, 0.007)	0.52
High						
2023 (n=36)	18.51 (16.08, 20.93)	<0.001	11.24 (10.20, 12.29)	<0.001	0.64 (0.60, 0.67)	<0.001
1990 (n=31)	29.63 (26.40, 32.86)	<0.001	20.61 (18.55, 22.67)	<0.001	0.71 (0.67, 0.75)	<0.001
Difference	-11.11 (-15.16, -7.07)	<0.001	-9.36 (-11.67, -7.05)	<0.001	-0.07 (-0.12, -0.02)	0.006
Endowments	0.86 (-0.98, 2.71)	0.36	0.11 (-0.48, 0.70)	0.70	-0.01 (-0.04, 0.01)	0.33
Coefficients	-11.57 (-15.47, -7.67)	<0.001	-9.40 (-11.72, -7.08)	<0.001	-0.06 (-0.10, -0.01)	0.01
Interaction	-0.41 (-1.67, 0.84)	0.52	-0.07 (-0.68, 0.54)	0.81	0.0008 (-0.01, 0.01)	0.89
Very High						
2023 (n=60)	35.05 (32.33, 37.77)	<0.001	15.93 (14.86, 17.00)	<0.001	0.48 (0.45, 0.51)	<0.001
1990 (n=17)	44.03 (38.70, 49.37)	<0.001	22.59 (20.50, 24.69)	<0.001	0.52 (0.48, 0.56)	<0.001
Difference	-8.98 (-14.97, -3.00)	0.003	-6.66 (-9.02, -4.30)	<0.001	-0.04 (-0.09, 0.007)	0.10
Endowments	6.45 (-7.97, 20.88)	0.38	-3.13 (-8.75, 2.49)	0.27	-0.13 (-0.23, -0.04)	0.006
Coefficients	-14.48 (-20.80, -8.16)	<0.001	-5.89 (-8.49, -3.29)	<0.001	0.06 (0.009, 0.10)	0.02
Interaction	-0.96 (-15.51, 13.58)	0.90	2.36 (-3.35, 8.70)	0.42	0.03 (-0.06, 0.12)	0.46

among these regions. For example, certain factors, such as obesity, high blood glucose, and alcohol consumption, which were previously more common in high-income countries, are increasingly observed in low-income regions.[26] Expanding CRC screening in high-burden countries, even if not yet universal, could substantially reduce disparities.[27]

Consistent with the study by Sharma,[28] our longitudinal analysis in this study showed that HDI is related positively with CRC incidence and mortality and negatively with MIR. By HDI level, in regions with an HDI below 0.70, CRC incidence and mortality increased as the HDI level increase between 1990 and 2023. However, in regions with a very high HDI level, this relationship was reversed. According to Global Burden of Disease data, CRC trends diverged markedly by region between 1990 and 2021, with a decreasing trend across most world regions but increasing in several high-income Western nations.[19] Previous studies have demonstrated that the greatest increase in early-onset CRC incidence and mortality occurred in regions with a middle sociodemographic index (SDI) quintile from 1990 to 2019.[29] For example, on average, early-onset CRC incidence and mortality increased by 2.05% and 0.33% annually in the middle SDI region, while the corresponding figures in the high SDI region were 0.51% and -0.76%, respectively.[29] The

decomposition analysis results in the aforementioned study found that aging and population growth played a key role in the CRC burden from 1990 to 2019.[29]

Our analysis showed that in four HDI levels, MIR decreased as HDI increased, although this relationship was more pronounced in regions with a very high HDI. Ramadan *et al.*[30] demonstrated a global decrease in MIR, with the decline being more pronounced in high-income Asian and Middle Eastern countries compared to Western Europe and the United States. Regional differences in MIR come from gender disparities within each area. In the US and Western Europe, men have higher MIRs, while in some Middle Eastern countries, women have higher MIRs. These opposite pattern may be one reason for the observed difference between regions and over time.[30]

The positive association between HDI and CRC incidence up to the 0.80 threshold, which we found, may reflect lifestyle changes associated with economic development. However, the plateau in incidence and declining mortality in very high HDI countries (HDI > 0.80) likely reflects the counterbalancing effect of improved detection and treatment. This interpretation is supported by the substantially lower MIR observed in very high HDI countries, indicating better survival despite continued high incidence. These findings are consistent with previous global analyses that have identified similar patterns of CRC incidence and mortality across development levels.[31]

It has been previously reported that an increase in CRC incidence was observed in regions with a high SDI, but this increase was short-lived.[29,32] Since HDI and SDI are comparable indices reflecting development levels, this finding is consistent. The increased removal of precancerous polyps through effective screening and widespread colonoscopies,[29,32] along with greater adoption of healthy lifestyles,[33] both contribute to a real reduction in CRC incidence in these regions. Additionally, improved medical technology has reduced mortality.[31,34]

Inequality analysis in the current study revealed a declining global association between HDI and CRC incidence and mortality over time. This reduction in effect remained significant in region with high and very high HDI levels, which may indicate a generational shift in risk factors and the significance of early-life exposures in these high-income countries.[34,35] A study conducted on Latin American countries using GBD data indicated that although the HDI levels of the countries increased over time, the correlation coefficient between HDI and CRC mortality was similar in 1990 and 2019.[36] Moreover, the Endowment component in the BO analysis for the global MIR, as well as in regions with low and very high HDI levels, remained statistically significant. This observed significance can be explained by the impact of HDI on healthcare expenditures, which in turn influence the implementation of screening programs, early treatment utilization, and ultimately the MIR of CRC.[37,38]

This study has several limitations and methodological issues that should be considered. Our findings are subject to the ecological fallacy and should not be interpreted at the within-country level. The BO decomposition provides insight into potential contributors rather than definitive causal pathways. The BO decomposition assumes exchangeability between groups, which may not hold when comparing outcomes across time. The endowment and coefficient effects should be interpreted as statistical associations rather than causal counterfactuals. Since the analysis was univariate, the contribution of the HDI to inequality may be different in presence of other covariates in the model. The HDI data was available for only 140 countries in both 1990 and 2023, which may affect the generalizability of the inequality analysis. Moreover, the limited number of countries in each HDI level may lead to non-significant results in the stratified BO decomposition analysis, although the results were important from a public health perspective in certain regions or country settings. Regarding MIR, it should be interpreted with caution due to its dependence on the quality of cancer registration systems and potential lead-time bias from screening programs, which may influence cross-country comparisons. The extent to which screening expansion contributed to the observed trends in incidence and mortality could not be quantified in this ecological study, as data on screening coverage and duration were not available across countries and time periods. Our secondary analysis was performed using only point estimates without incorporating these uncertainty intervals. This approach may lead to overprecision, where the statistical precision of our findings appears greater than what the underlying data quality warrants. Furthermore, although we used age-standardized rates to control differences in population age structures across countries, population aging continues to be a major contributor to the absolute burden of CRC, particularly in high-HDI settings. The dynamic process of demographic transition was not modeled as a separate independent variable.

Conclusion

Between 1990 and 2023, the CRC incidence and mortality remained more concentrated in countries with higher HDI, although a reduction in HDI inequality was observed in these two measures. HDI inequality in MIR increased from 1990 to 2023, indicating greater challenges in diagnostic and treatment services in the less developed countries. Longitudinal analysis over 34 years showed that higher HDI was associated with increased CRC incidence and mortality but lower MIR. While the positive HDI-incidence association persisted across all levels, the HDI-mortality relationship was reversed in very high HDI countries (HDI > 0.80), where mortality declined, leading to the lowest MIR. Non-linearity was confirmed by spline analysis, with a clear threshold at HDI 0.80. Inequality analysis further demonstrated significant changes over time in the distribution of HDI and its effect on CRC indicators; in high and very high HDI levels,

the relationship between HDI and CRC incidence and mortality decreased, and if the HDI distribution in 1990 had mirrored that of 2023, reductions in the MIR would have occurred in both low and very high HDI regions.

Authors' Contribution

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Competing Interests

The authors declare no competing interests.

Data Availability Statement

The datasets analyzed during the current study are publicly available at https://hdr.undp.org/data-center/documentation-and-downloads and https://vizhub.healthdata.org/gbd-results/. Also the Stata commands and prepared datasets supporting the findings of this study are available from the corresponding author upon reasonable request.

Ethical Approval

The study was reviewed and approved by the ethics committee of Hamadan University of Medical Sciences, Hamadan, Iran (Ethical code: IR.UMSHA.REC.1404.542).

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