Review Article on Global GI Malignancies

Implications of the growing incidence of global colorectal cancer

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Contributions: (I) Conception and design: JF Gibbs, BW Vabi; (II) Administrative support: None; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Abstract: The expanding worldwide burden of colorectal cancer (CRC) is a significant public health issue. Understanding the shift in the geo-demographic, socioeconomic, environmental, and biogenetic distribution of CRC is paramount. The Human Development Index (HDI) measuring life expectancy, education, and gross national income is a composite index comparing health outcomes between countries. This has been shown to be a useful comparison tool in measuring the health dimension among high, middle, and low-income countries. CRC has a wide global distribution in incidence and mortality with majority of cases occurring in countries with a high or very high HDI. However, in developing countries and in those undergoing rapid socioeconomic growth, there has also been a marked rise in CRC rates as well. This pattern is noted globally and seems to correlate with increase in a country's specific HDI. Additionally, another unique pattern of CRC incidence has emerged with more cancers being diagnosed in adults younger than 50 years old. Further investigation is needed to determine CRC risks reduction and implementation of primary prevention and early detection strategies within different country specific healthcare systems. Globally, improvement in healthcare equality, access to medical care and screening for CRC particularly in resource-limited (low HDI) countries is essential.

Keywords: Colorectal cancer (CRC); global; Human Development Index (HDI)

Submitted Jan 29, 2020. Accepted for publication Jul 17, 2020.
doi: 10.21037/jgo-2019-gi-06
View this article at: http://dx.doi.org/10.21037/jgo-2019-gi-06

Introduction

According to the American Institute for Cancer Research, colorectal cancer (CRC) is the third most commonly diagnosed cancer in men and the second most CRC in women worldwide. In 2018 alone, approximately 1.8 million new cases of CRC were diagnosed with over 145,600 new cases occurring in the United States. Globally, the distribution of CRC burden varies widely (1). The Human Development Index (HDI) is a statistical tool to measure a country's overall achievement in its environmental and socioeconomic growth (2). It a snapshot of human development: a long and healthy life, being knowledgeable and having a decent standard of living. A long and healthy life expectancy is measured from birth (Life Expectancy Index). Knowledge is determined by the indicators of expected and mean years of schooling (Education Index). Finally, a decent standard of living is determined by the gross national index (GNI) per capital (3). The HDI is categorized as very high (mean 0.88; 0.80–0.95), high (mean 0.76; 0.71–0.78), medium (mean 0.61; 0.56–0.70), or low (mean 0.53; 0.38–0.55) (4). The United States (HDI 0.92) trends behind many other western countries with the 9th highest incidence of CRC at 38.6 per 100,000 populations with the highest incidence occurring in Hungary and South Korea (5) (*Table 1*). Strikingly, cancer-related death is expected to increase by 60% by 2030 (*Figure 1*). Understanding the paradigm shift in the geo-

demographic, socioeconomic, environmental, biogenetic distribution of CRC and the factors affecting early detection and management is paramount to identifying polices and interventions to eradicating it. The purpose of this expanded review is to address the trends and implications of CRC globally using their HDI. Ultimately, country specific resource allocation in formulating strategies in early CRC detection is fundamental in decreasing the global rise in incidence particularly among young adults.

Table 1 Global colorectal cancer rates: both sexes

Rank	Country	Age-standardized rate per 100,000
1	Hungary	51.2
2	South Korea	44.5
3	Slovakia	43.8
4	Norway	42.9
5	Slovenia	41.1
6	Denmark	41.0
7	Portugal	40.0
8	Barbados	38.9
8	Japan	38.9
9	U.S.A.	38.6
10	Netherlands	37.8

Produced with permission: Modified from (5).

Epidemiology and global distribution of CRC

CRC incidence and mortality rates vary widely across regions with the majority occurring in high-income (HDI) countries (6). The lowest rates are noted in Sub-Saharan Africa, except for South Africa, and Southern Asia (*Figures 2,3*). These global distribution and trends likely reflect changes in the prevalence of risk factors. Arnold *et al.* (3) noted the rise in incidence among most populations reflect lifestyle and behavioral factors including dietary patterns and obesity, whereas the mortality decline may be attributed to improvements in survival through the adoption of best practices in cancer diagnosis and treatments in developed countries.

Additionally, low and medium-income countries lack of CRC screening has significantly impacted the overall incidence and disease burden within these populations compared to high and upper-middle income countries where screening is robust. Although the risk of developing CRC increases with age, there is a unique near-global rise in incidence and mortality in early on-set CRC with a 50% increase in CRC incidence among populations younger than 50 years (*Figures 4,5*) (7). Epidemiologic trends predict an increase in overall crude incidence of 1% to 3% annually for adults younger than age 50 (8). This shift may represent

Incidence					
		2018	2040		
		Number	Number	Demographic change	Overall change
World	Male	575789	1014471	438682 (+76.2%)	438682 (+76.2%)
World	Female	520812	905063	384251 (+73.8%)	384251 (+73.8%)
World	Both sexes	1096601	1919534	822933 (+75.0%)	822933 (+75.0%)

Mortality					
		2018	2040		
		Number	Number	Demographic change	Overall change
World	Male	184097	327212	143115 (+77.7%)	143115 (+77.7%)
World	Female	126297	220353	94056 (+74.5%)	94056 (+74.5%)
World	Both sexes	310394	547565	237171 (+76.4%)	237171 (+76.4%)

Figure 1 Estimated number of incidence cases and deaths from CRC among both sexes and all ages; 2018–2040. Data source: Globocan 2018. Global cancer observatory. http://gco.larc.fr

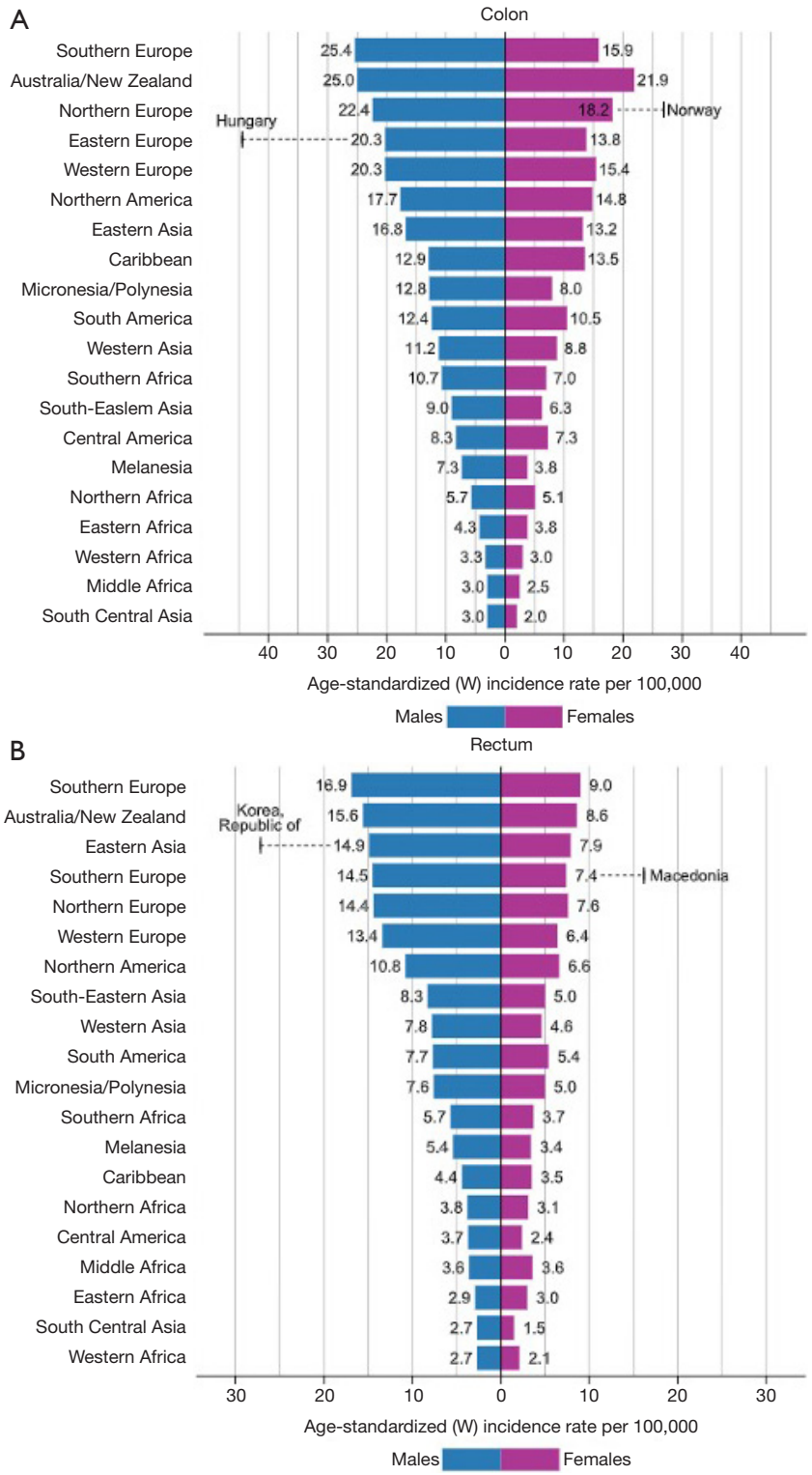
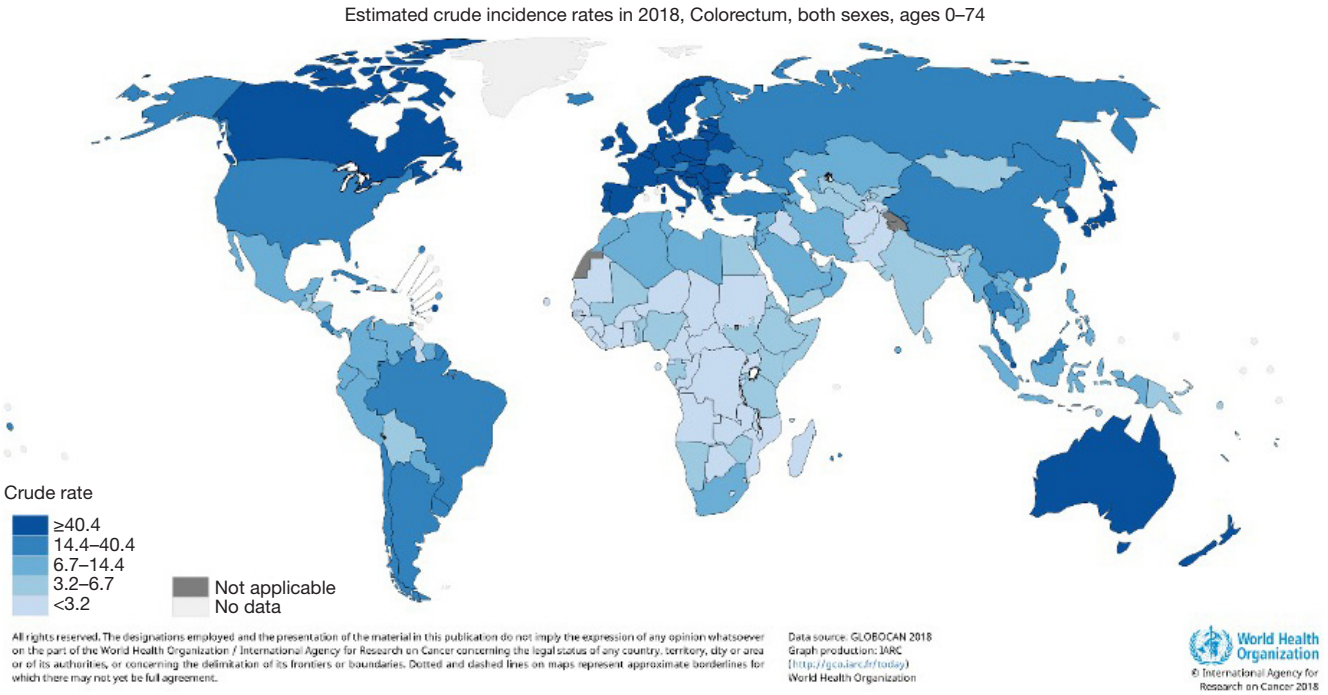


Figure 2 Worldwide age-standardized rates for CRC are in descending order world. Bar Chart of Region-Specific Incidence Age-Standardized Rates by Sex for Cancers of the (A) Colon and (B) Rectum in 2018. Rates for cancers of the colon and rectum are shown in descending order of the world (W) age-standardized rate among men, and the highest national rates among men and women are superimposed. Source: GLOBOCAN 2018.



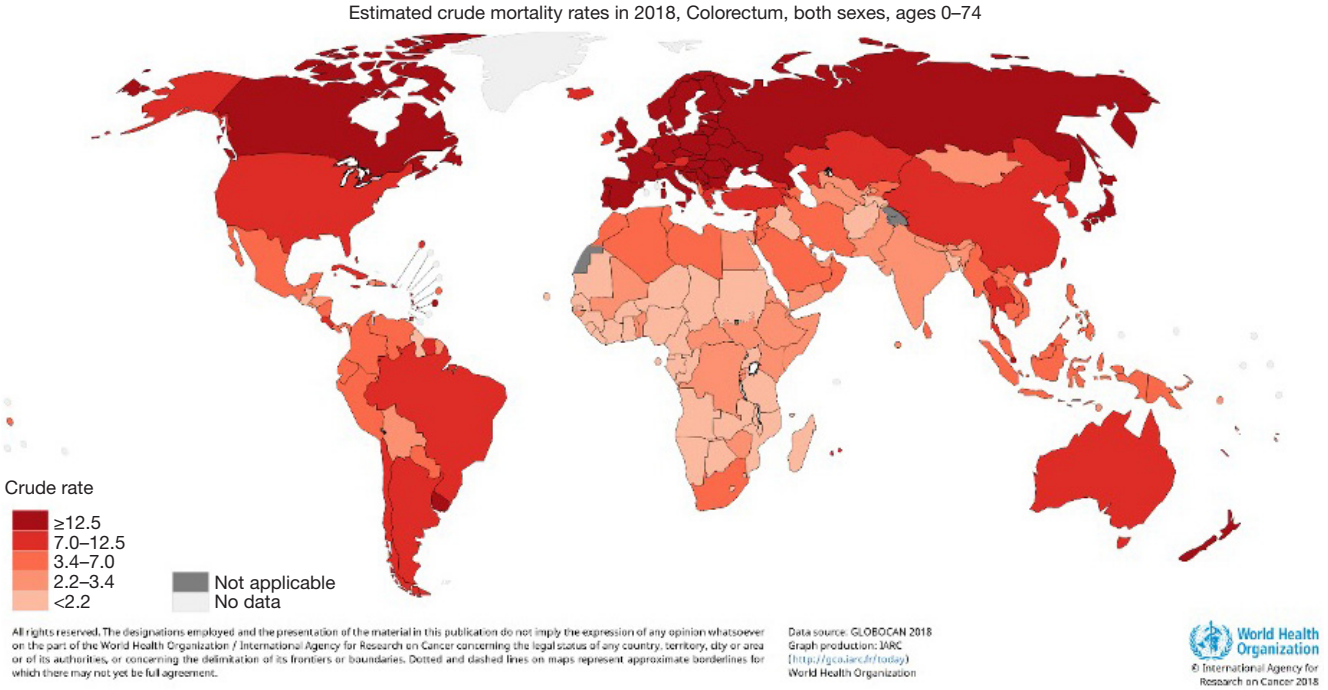


Figure 3 Worldwide estimated crude CRC incidence and mortality rates, both sexes in 2018. Source: Worldwide CRC incidence and mortality rates (age adjusted according to the world standard population, per 100 000) in both sexes in 2018 (GLOBOCAN 2018).

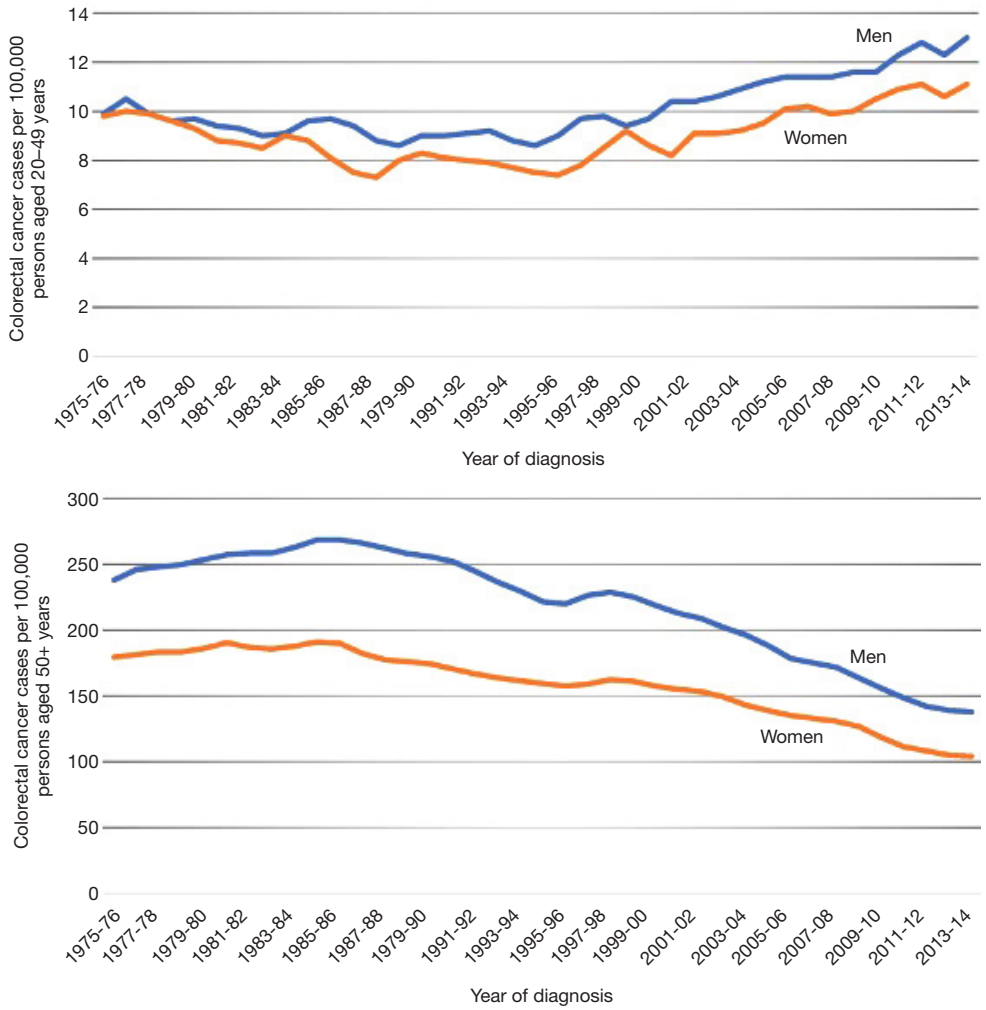


Figure 4 Trends in Colorectal Cancer Incidence (1975-2013) and Mortality (1970-2014) Rates by Age and Sex, Unite State. Data source: Surveillance, Epidemiology, and End Results program, National Cancer Institute, 2017. Rates are adjusted for delays in reporting and are plotted as a 2-year moving average.

a key to recent changes in risk factor exposures and disease pathogenesis and overall future cancer burden.

Environmental influence and socioeconomic impact on CRC risk acquisition

The gradual increase in the incidence of CRC in some low and medium HDI countries likely reflects the adoption of western lifestyles (*Figure 6*) (9). Among adults 50 years and older in these populations, there has been a rapid rise in the CRC incidence and mortality particularly in Eastern Europe, Asia, and South America. This is compared to very high HDI areas such as the USA, Australia, New Zealand and several Western European where the incidence and mortality have stabilized among same cohort (10) (*Figure 6*). Societal and socioeconomic factors appear to affect the development of CRC. In low and medium-to-high HDI countries, increased globalization and adoption of western lifestyle with its associated CRC risk factors such as obesity, lack of exercise, tobacco and alcohol use, dietary indiscretion and pollution may be the culprit. However, the stabilization and/or decline of rates in the highest indexed HDI countries, although multifactorial, may reflect early detection through screening, both invasive and non-invasive, and advanced techniques in the management of precancerous lesions as opposed to decreased in risk factors (11-13).

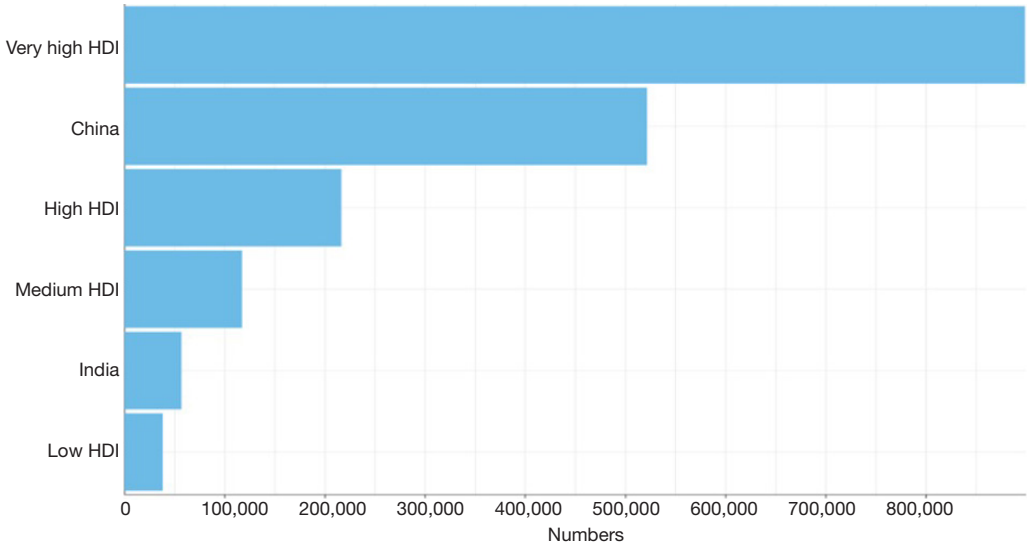


Figure 5 Estimated number of incident cases of CRC, both sexes, all ages according to country resource level. Data source: Globocan 2018. Global cancer observatory. http://gco.larc.fr

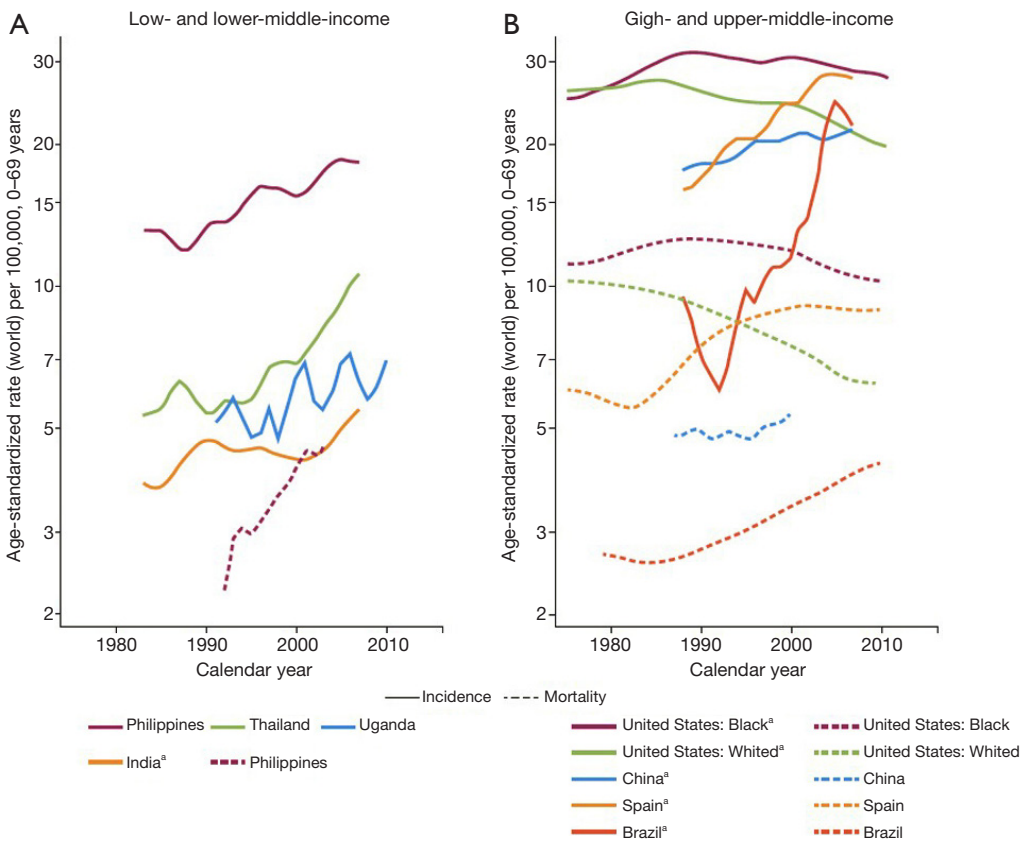


Figure 6 Trends in Age-Standardized Incidence and Mortality Rates of CRC in Men, Selected Countries by income level, 1980–2010. (Produced with permission: Bray F, Soerjomataram I. The Changing Global Burden of Cancer: Transitions in Human Development and Implications for Cancer Prevention and Control. doi: 10.1596/978-1-4648-0349-9_ch2)

Table 2 Relative risks for established colorectal cancer risk factors

Risk factors	Relative risk*
Factors associated with increased risk	
Hereditary and family history	
Family history	
• CRC	
1 or more first-degree relatives	2.2
1 or more first-degree relatives diagnoses before age 50	3.6
2 or more first-degree relatives	4
1 or more second-degree relatives	1.7
• Adenoma	
1 or more first-degree relatives	2
Inflammatory bowel disease	1.3
Type 2 diabetes	
Male	1.4
Female	1.2
Modifiable factors	
• Heavy alcohol (daily average >3 drinks)	1.3
• Obesity BMI ≥30 kg/m^2)	1.3
Colon, male	1.5
Colon, female	1.1
Rectum, male	1.3
Rectum, female	1.0^{L}
• Red meat (100 g/day)	1.1
• Processed meat (50 g/day)	1.2
Smoking (ever *vs.* never)	
Factors associated with decreased risk:	
Physical activity	0.7
Dairy (400 g/day)	0.9

*, relative risk compares the risk of disease among people with a particular "exposure" to the risk among people without that exposure. Relative risk for dietary factors compares the highest with the lowest consumption. If the relative risk is more than 1.0, then risk is higher among exposed than unexposed persons. Relative risks less than 1.0 indicate a protective effect; ^{L}, relative risk was not statistically significant. Produced with permission: Modified from (1). ©2020 American Cancer Society, Inc., Surveillance Research. CRC, colorectal cancer.

Pathogenetic changes and early-life exposures that influence colorectal carcinogenesis

There is mounting evidence to demonstrate the rising incidence and mortality of CRC in the previously perceived "lower risk" young adults. This effect has been demonstrated in both the US (14) and Canada (15) and now similar phenomenon across Europe and Asia (12). Modifiable known risk factors for CRC have been extensively investigated with previous epidemiological studies suggesting most predominantly alcohol consumption, diets high in red/processed meats, low fiber diet, obesity, smoking, and physical inactivity (*Table 2*). This certainly has been fueled by easy accessibility to readily available at-risk items particularly smoking and processed meats. Smoking alone in CRC will increase mortality by 23% and increase recurrence by 47%. Obesity certainly parallels the increase in CRC incidence in young adults and in countries with high HDI as excess diet intake may initiate a chronic low-grade inflammatory cellular response (*Figure 7*). According to WHO, obesity is defined by body mass index (BMI): obesity (BMI: 30.0–34.9 kg/m^2) and morbidly obese (BMI ≥40 kg/m^2) compared to normal weight (BMI: 18.5–24.9 kg/m^2).The clinical impact of obesity on CRC appears to be more pronounced in males compared to females. Compared to normal weight individuals, the incidence of CRC has been shown to be higher in both men and women with rates of over 35% and 15% respectively (16). Weight gain and obesity appears to have a greater influence on CRC risk when it occurs in early adulthood versus later in life (17-19). Central obesity in males has been cited one of the most significant predisposing factors for CRC and worse outcome (20,21).

CRC mortality is affected by obesity as high body weight measured prior to diagnosis reduces the likelihood of CRC survival. Other factors have been purported in attempt to explain the current trend. Vuik *et al.* proposed the low threshold for colonoscopy for diagnostic and screening purposes may have been responsible for a proportion of the detected CRCs in young adults (22). All these proposed factors remain speculative and further investigation is required to establish causation.

Factors affecting CRC screening and early detection

The CRC transition from adenoma-carcinoma is well-established (23). The detection and removal of premalignant

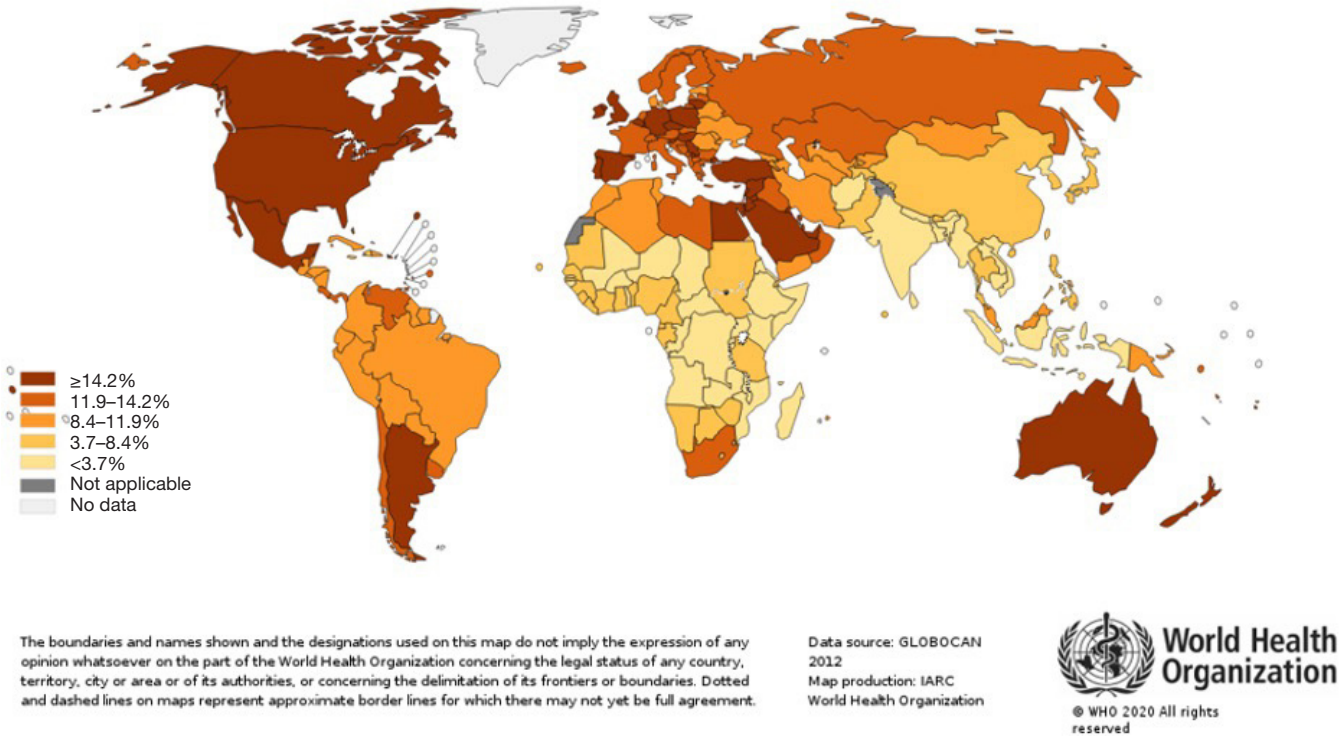


Figure 7 Fraction (%) of all CRC cases between both sexes (worldwide) in 2012 attributable to excess body mass index.

polyps is effective in preventing and treating cancer at an early stage both by decreasing the incidence and burden of CRC. Screening methods include stools-based testing, endoscopy, and radiographic modalities with varying degree of sensitivity and specificity. For average risk population, the United State Preventive Services Task Force (USPSTF) and the American Society for Gastrointestinal Endoscopy (ASGE), and previously American Cancer Society (ACS) recommend initial screening colonoscopy (24).

The optimal screening modality is a shared decision-making process, which incorporates individual patient preferences, values, and risk, as well as test effectiveness, resource availability, test safety, convenience, comfort, and cost. Most strategies are based either on an annual or biennial stool-based testing (FOBTs, Fecal DNA), CT colonography every five years, with optical colonoscopy reserved for positive finding requiring further investigation, or partial/complete colonic endoscopic procedures (25). Optical colonoscopy is the most preferred and accurate of all the screening methods for CRC screening. After a well-informed decision process, the best screening test is one that the patient is willing to complete according to the test instructions (26).

Studies evaluating the incidence of CRC following initial complete colonoscopy with polypectomy demonstrate significant reduction rates ranging from 76% to 90% (27,28). The National Polyp Study demonstrated a 53% reduction in CRC-related mortality after colonoscopic polypectomy (29). The screening uptake for CRC defines the cross-sectional assessment of compliance to the screening modality and according to the ACS of the average-risk population. In March 2014, the National Colorectal Cancer Roundtable (NCCRT) launched an ambitious initiative to reach an 80% CRC screening rate of eligible adults (30). If successful, an estimated 277,000 CRC cases and 203,000 CRC deaths will be prevented by 2030. In the US, the proportion of adults older than 50 years with a recent screening test ranged from 53% to 73% between 2011–2013 far below those of other recommended adult preventive services. Factors affecting CRC screening uptake include: sociodemographic factors, healthcare systems and provider factors, and psychosocial factors such as knowledge barriers, risk versus benefit perception concerns, and cultural biases (31). In a recent study from the ACS, Fedewa

Table 3 Predictors of CRC non-screening rates

System-based
Availability of health insurance
Out-of-pocket expense
Availability of screening options
Provider-based
Access to a personal doctor
Specialist availability
Patient-based
Income level
Educational status
Employment status
Obesity
Race

CRC, colorectal cancer.

and colleagues evaluated CRC screening beginning at age 45. Among people ages 45 to 49, past-year CRC screening rates rose from 4.8% in the first quarter of 2018 to 6.6% in the second quarter, 8.8% in the third quarter, and 11.7% in the fourth quarter. This was accompanied by a relatively stable rate among adults over the age of 50 (32). These factors affecting the CRC screening rate may become more relevant in the at-risk younger adult population as interventions are created to address the increasing incidence of CRC. *Table 3* shows the predictors of CRC non-screening rates with lack of health insurance often cited as a major predictor of non-screening. At a system-based level, implementing policies to decrease direct patient financial burden, increasing provider access, and standardizing screening modalities may improve on patient compliance and screening uptake. There has been tremendous progress in the field of medicine and despite the advancements in the world; there is still a lack of access to basic health needs and care. These are all issues that could be diminished by reducing the disparities that isolate these populations.

Some of these disparities are related to the geography and a shortage of physicians. In addition, income inequality with individuals and families simply unable to afford health care allows for the perpetuation of the process.

Global health professionals exploring opportunities to advocate for underrepresented communities in public health forums may solve these economic challenges. Encouraging physicians to practice in remote areas with incentives and introducing policies may reduce barriers and increase access to health care.

The USPSTF recommends the use of approved CRC screening methods in average-risk individuals. The ACS, based on its 2018 landmark population study, changed its CRC screening recommendation to 45 years of age. This recommendation has not been universally adopted particularly by the USPSTF. In the U.S., commercial health insurance and Medicare provide full coverage for the USPSTF approved screening modalities at the recommended age. However, there are some unique caveats that may affect screening colonoscopy coverage and subsequently influence out-of-pocket financial burden to the patient (33,34). There has been considerable effort aimed at raising CRC screening rates (35-37). Unfortunately, these initiatives and programs are only feasible in high, and some medium-HDI countries. In 2008, the International Colorectal Cancer Screening Network (ICRCSN) conducted a survey of pilot programs with organized CRC screening programs (38). In average risk individuals, stool-based test was the primary CRC screening modality, followed by FOBT and FIT tests. This was followed by colonoscopy if any of the initial screening modality was positive. This approach may help guide the development of public health policies for the early detection of CRC even in resource-limited populations. Rabeneck *et al.* proposed recommendations on implementing screening and diagnosis for CRC in four different resource environments (39,40) (*Table 4*). These recommendations, although remain to be validated, is very comprehensive and represent the basis for further research and broader implementation.

Conclusions

CRC remains one of the most preventable cancers worldwide with a clearly defined pathogenesis. However, it is a public health burden as it remains a commonly diagnosed cancer worldwide and one of the leading causes of cancer mortality. The incidence and mortality of CRC is decreasing in developed countries, while the incidence and mortality of this, based on trends, and has seen an increase in developing countries. Globally, there has been an exclusive increased in the incidence of CRC in young adults (<50) as opposed to stabilization or decreased among adults over the age of 50. The exact cause of these paradigm shifts is multifactorial. As has been noted, the higher incidence rates of CRC in countries with high HDI are associated

Table 4 Strategies for colorectal cancer screening and diagnosis, by country resource level

Level of resources	General principles	Diagnostic modality
Basic, low HDI	Capacity building: Establish at risk population, primary prevention strategies, create cancer registry	Barium enema if colonoscopy not available; in emergency situations, may be diagnosed at surgery
Limited, low-medium HDI	Establish capacity for colonoscopy (needed for diagnosis)	Opportunistic screening for those covered by health insurance
	Engage in partnership arrangements with cancer centers to build capacity	Diagnostic colonoscopy (or barium enema) for those with symptoms
	Establish national guidelines	
	Build quality assurance for lab testing	
Enhanced, medium-high HDI	Join international screening networks	Establish organized screening in high-incidence cities/regions starting at age 50 years in persons at average risk: use annual or biennial sensitive gFOBT or FIT; FS (see text for discussion of interval); or colonoscopy every 10 years
	Provide support to less-well-resourced countries in region	Considerable infrastructure is required to support organized screening, including invitations, recalls, reminders, tracking screening test results, ensuring follow-up of those with an abnormal screening test, etc.
Maximal, very high HDI		National (or jurisdiction-wide) organized screening: starting at age 50 years in persons at average risk: use annual or biennial sensitive gFOBT or FIT; or colonoscopy every 10 years; in those at increased risk because of family history, consider colonoscopy

HDI, Human Development Index. Adapted from Cancer: Disease Control Priorities, Third Edition (Volume 3). Washington (DC): The International Bank for Reconstruction and Development / The World Bank; 2015 Nov 1. Chapter 6. The recommendations are meant to be cumulative: any intervention that is feasible at a lower resource level is also an option at higher resource levels (Produced with permission).

with a sedentary lifestyle, obesity, diets high in red meat, and smoking. Low mortality rates in counties with low HDI may be due to low incidence of CRC or incorrect diagnosis. Identification of independent risks factors and implementation of interventions to mitigate risk factors and increase screening uptake are paramount in the prevention of CRC. The Global correlation with the incidence of CRC and the HDI is very strong. Further work needs to continue in low HDI countries for greater access to medical care and screening for CRC.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Journal of Gastrointestinal Oncology* for the series "Global GI Malignancies". The article has undergone external peer review.

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/jgo-2019-gi-06). The series "Global GI Malignancies" was commissioned by the editorial office without any funding or sponsorship. John F Gibbs served as the unpaid Guest Editor of the series and serves as an unpaid editorial board member of *Journal of Gastrointestinal Oncology* from Jan 2019 to Dec 2020. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Vabi BW, Gibbs JF, Parker GS. Implications of the growing incidence of global colorectal cancer. J Gastrointest Oncol 2021;12(Suppl 2):S387-S398. doi: 10.21037/jgo-2019-gi-06