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Global trends in colorectal cancer mortality: projections to the year 2035

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Novelty & Impact: This is a first effort to predict the future burden of colorectal cancer mortality globally. Colon and rectal cancer mortality rates are projected to decrease in most countries apart from some Latin American and Caribbean countries, but increases are predicted for several countries from Europe, North America and Oceania. Despite this heterogeneity, the number of deaths from colorectal cancer is expected to rise in all countries due to population growth and ageing.

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Author Contributions: Marzieh Araghi designed the study, acquired and analysed the data, interpreted the findings and wrote the manuscript. Melina Arnold helped with supervision, edited manuscript and provided important intellectual content. All the other authors critically reviewed the manuscript and gave final approval.

Abbreviation used: colorectal cancer (CRC), World Health Organization (WHO), age-period-cohort (APC), International Classification Diseases (ICD), age-standardized rates (ASR), United Nation (UN), body mass index (BMI), incidence rate ratio (IRR), confidence interval (CI), Australia (AUS), Austria (AUT), Belgium (BEL), Brazil (BRA), Bulgaria (BGR), Canada (CAN), Chile (CHL), China, Hong Kong (HGK), Colombia (COL), Costa Rica (CRI), Croatia (HRV), Cuba (CUB), Czech Republic (CZE), Denmark (DNK), Estonia (EST), Finland (FIN), France (FRA), Germany (DEU), Hungary (HUN), Ireland (IRL), Israel (ISR), Italy (ITA), Japan (JPN), Kyrgyzstan (KGZ), Latvia (LVA), Lithuania (LTU), Mexico (MEX), Moldova (MDA), New Zealand (NZL), Norway (NOR), Republic of Korea (KOR), Romania (ROU), Slovakia (SVK), Slovenia (SVN), Spain (ESP), Sweden (SWE), Switzerland (CHE), The Netherlands (NLD), United Kingdom (GBR), United States (USA), Uruguay (URY), Venezuela (VEN)

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Abstract

Colorectal cancer (CRC) is the third most common cancer worldwide and the fourth most common cause of cancer death. Predictions of the future burden of the disease inform health planners and raise awareness of the need for cancer control action. Data from the World Health Organization (WHO) mortality database for 1989-2016 were used to project colon and rectal cancer mortality rates and number of deaths in 42 countries up to the year 2035, using age-period-cohort (APC) modelling. Mortality rates for colon cancer are predicted to continue decreasing in the majority of included countries from Asia, Europe, North America and Oceania, except Latin America and Caribbean countries. Mortality rates from rectal cancer in general followed those of colon cancer, however rates are predicted to increase substantially in Costa Rica (+73.6%), Australia (+59.2%), United States (+27.8%), Ireland (+24.2%), and Canada (+24.1%). Despite heterogeneous trends in rates, the number of deaths is expected to rise in all countries for both colon and rectal cancer by 60.0% and 71.5% until 2035, respectively, due to population growth and ageing. Reductions in colon and rectal cancer mortality rates are probably due to better accessibility to early detection services and improved specialized care. The expected increase in rectal cancer mortality rates in some countries is worrisome and warrants further investigations.

Keywords: Colorectal cancer, Mortality, Projections, Worldwide

Introduction

Colorectal cancer (CRC) is the third most common malignant neoplasm and the fourth main cause of cancer death in the world, with nearly 1.8 million new cases and 881,000 deaths in 2018.[1] Several studies have shown that CRC mortality rates have been steadily decreasing for at least two decades in many high-income countries in Northern America, Oceania and Northern and Western Europe.[2, 3] On the other hand, significant increases are seen in CRC mortality rates in less developed countries in Asia, Africa, and Latin America, where rates have been historically low.[4-6]

Early detection through screening through the removal of adenomatous polyps and identification of early stage disease,[7, 8] as well as advances in CRC treatment and an increase in colorectal cancer survival,[9-12] may partly explain decreasing mortality trends in high-income countries.[13] In contrast, the majority of transitioning countries suffer major challenges in realising such trends given limited resources, health infrastructure and a consequent lack of effective screening,[14, 15] alongside issues of access to cancer services and appropriate care.[14]

Predicting future mortality trends is an important aspect of cancer surveillance, as it often points to the need for specific interventions and aids the prioritization of resources and future research.[16] In this study, we predicted the future burden from colon and rectal cancer mortality separately in 42 countries in eight world regions up to the year 2035.

Materials and Methods

Deaths from malignant neoplasms of the colon (International Classification Diseases (ICD)-10 C18) and rectum (C19-C21) were obtained from the latest update of the World Health Organization (WHO) mortality database; countries were included if they could contribute at least 25 years of data and more than 50 deaths from either colon or rectal cancer in the most recent year available to allow for robust projections. A detailed assessment of data completeness and quality has been conducted previously.[17] In brief, completeness of death registration data was assessed against estimated total deaths for the

population. Moreover, the proportion of deaths with underlying cause coded to a short list of so-called "garbage codes" (ill-defined cancers: C67, C80, and C97) were estimated. A summary usability score was calculated as follows: "(Percent Usable) = Completeness (%) * (1-Proportion Garbage)" All countries with a mean percent of usable below 65% were excluded for the remaining countries and three broad categories were defined as follows: a) High-quality data: There is >90% completeness and ill-defined codes appear on <10% of registrations, b) Medium-quality data: There is 70-90% completeness and ill-defined codes appear on 10-20% of registrations, c) Low-quality data: There is <70% completeness and ill-defined codes appear on >20% of registrations.[17] We only included only countries with at least medium data quality, applying to 42 countries from eight world regions. Since there are reported differences in the epidemiology and clinical characteristics of colon and rectal cancer, we examined these separately. Moreover, as overall mortality trends are similar in males and females, we present the final results for both sexes combined and by sex in the supplementary material (**Supplementary Tables 1-4**).

To predict the number of deaths and mortality rates of colon and rectal cancer up to 2035 by country, gender, and age, we fitted a log-linear age–period–cohort model that levels-off exponential growth and limits linear trend projection to recent trends (1989-2013). The NORDPRED software package, developed and implemented in **R**, has been shown to perform well empirically in projecting trends into the future.[18] The three or four most recent 5-year observed periods (depending on data availability) were extrapolated using a power function to level off the growth, with a projection of the linear trend for the last ten years that was attenuated by 25%, and 50% in the second and third prediction period, respectively, and 75% for both the fourth and fifth prediction period. Projections were carried out in 5-year periods.

The numbers of deaths were predicted up to the year 2035 by taking a weighted average of the projected mortality rates in the last two future prediction periods, centering on 2035, and then applying the United Nation (UN) national population forecasts available for each country for that year. This is based on the assumption that trends observed in the recent past will continue into the future. Population predictions (based on the UN medium-fertility variant) were obtained from the UN World Population Prospects 2017

Revision, by country, year, sex, and age.[19] We calculated and present age-standardized mortality rates (ASR) per 100,000 person-years using the world standard population.[20] To graphically summarize the direction of the trends, locally weighted regression (lowess) curves were fitted to provide smoothed lines through scatterplots observed of ASRs by year. Stata 13 and R 2.15 were used for analysis, including the functions available in Epi package version 1.1.36, R Studio and the NORDPRED package.[21]

Results

Predicted changes in mortality rates 2013-2035

The observed and predicted trends in colon and rectal cancer mortality rates are presented in **Figures 1 & 2**. **Tables 1 & 2** show the observed number of deaths and mortality rates in the latest year available for colon and rectal cancer, respectively, alongside the respective predicted values for 2035 and the percentage changes over the predicted period.

Decreases in colon cancer mortality rates are predicted in 32 of the 42 countries (mainly in Northern and Western Europe but also Oceania and North America), with the largest mortality projected declines seen in Australia (-50.0%), Ireland (-49.2%), Czech Republic (-37.8%), Austria (-32.7%), and Germany (-25.8%). In contrast, colon cancer mortality rates are predicted to increase in the remaining 11 countries (mainly located in Latin America and Caribbean), with the most substantial increases in Chile (+16.9%), Brazil (+14.3%), Uruguay (+13.0%), Romania (+10.3%), and Finland (+8.0%) (**Table 1**).

Rectal cancer mortality trends are predicted to follow only slightly different patterns from those of colon cancer. While decreases in rectal mortality rates are predicted in 25 out of 42 countries (no changes were detected for France), increases are predicted for some countries in the Latin America and Caribbean region as well as countries from Europe, Oceania, and North America, with the most substantial increases in Costa Rica (+73.6%), Australia (+59.2), United States (+27.8%), Ireland (+24.2%), and Canada (+24.1%) (**Table 2**).

On average, colon and rectal cancer mortality rates are predicted to drop only slightly by 8.4% and 5.1%, from 2013 to 2035 respectively, from 7.1 in 2013 to 6.5 per 100,000 in 2035 for colon cancer, and from 3.9 to 3.7 per 100,000 for rectal cancer (**Figure 3**). In supplementary analyses, countries were combined into two groups: 1) countries predicted to have decreasing mortality rates, 2) countries with increasing mortality rates predicted, for colon and rectal cancer separately. Countries with 0% change in mortality rates were excluded (France for rectal cancer). In countries with decreasing mortality trends, colon cancer mortality rate is predicted to drop by 13.0% and in countries with increasing trends, it is expected to increase by 8.0% (**Supplementary Figure 1**). Rectal cancer mortality in countries with decreasing trends is projected to fall by 16.2% and in countries with increasing trends, it is projected to rise by 18.1% (**Supplementary Figure 2**).

Predicted changes in the number of deaths 2013-2035

Deaths from colon and rectal cancer are predicted to increase substantially up to 2035 in almost all 42 countries, as a result of both changes in risk factors as well as population growth and ageing. In Latin American and Caribbean countries, the number of deaths is projected to double by 2035, for both colon and rectal cancer. In only two countries, in which a declining number of deaths is predicted by 2035, (colon cancer in Australia, and rectal cancer in Bulgaria and Czech Republic), this is paralleled by declining mortality rates over the next decades (**Tables 1 & 2**).

Overall, the total number of deaths from colon and rectal cancer across all included countries is predicted to increase by 60.0 and 71.5%, respectively, when comparing between 2013 and the projection for 2035 (colon cancer: 158,816 vs. 254,165 cases; rectal cancer: 72,649 vs. 124,614 cases) (**Figure 3**). The increase in number of deaths was most pronounced in countries where mortality rates are predicted to increase, while the increase in number of deaths was more modest in countries where colon and rectal cancer mortality rates are set to decrease (48.2 and 32.8%, respectively). (**Supplementary Figures 1 & 2)**.

Discussion

This study is the first, to our knowledge, to predict the future burden of colon and rectal cancer mortality in a global context. For colon cancer, other than in certain Latin American and Caribbean countries, most studied countries are expected to see ongoing declines in rates up to 2035. Rectal cancer followed the same trends as colon cancer, but with increases predicted for several countries in Europe, North America and Oceania. For the most part, this assessment of future mortality trends mirrors considerable advances in colon and rectal cancer control. Although mortality rates are set out to decrease in most parts of the world, the absolute number of deaths from colon and rectal cancer can be expected to continue growing in most countries due to population growth and ageing. A recent study with the focus on European countries, predicted continuing falls in CRC mortality rates in both sexes up to 2018.[22]

Previous studies[2, 3] demonstrated that CRC incidence and mortality rates have been decreasing in most European countries (mainly located in Northern and Western Europe), North America, Oceania and in some countries from Asia such as Japan. This study showed that this decrease is set to continue. Early detection and screening have been suggested to play a major role in this development. The implementation of screening has been shown to lead to short-term increases in CRC incidence as a result of increased detection of prevalent cases,[23] typically followed by a long-term reduction in incidence and mortality from CRC due to the removal of precancerous polyps.[24] This may for example explain the decrease in observed CRC mortality rates in Israel and Japan, countries with longstanding CRC screening programs in place since the early-1990s.[25]

The global variation observed in CRC mortality rates across countries may also be explained by risk factors impacting on incidence, including the underlying prevalence of obesity,[26, 27] physical inactivity,[28, 29] smoking,[30, 31] alcohol consumption,[32, 33] and a diet rich in red and processed meat, artificially sweetened foods, and salt, with minimal intake of fruits and vegetables.[34, 35] Other established risk factors for CRC such as a family history of CRC[36] and inflammatory bowel disease[37] are unlikely to explain such disparities between countries as only less than 1% of the CRC cases maybe attributable to these factors in

the general population. Driven by societal and economic gains, many countries have undergone a significant nutritional transition[38] and the overweight and obesity rates have increased dramatically,[39, 40] possibly due to increased consumption of energy-dense foods and decreasing physical activity. The results of a recent study indicate that overweight and obesity (body mass index (BMI) ≥25 versus <25 kg/m^2) are responsible for 12% of all colon and 6% of all rectal cancer cases that occurred in Latin American (including Caribbean) in 2012.[27]

Considering that more than half of Latin America's population is predicted to be overweight or obese by 2030,[41] this could thus be one of the key drivers of increasing rates in the region. Marked rises in CRC incidence in Uruguay and Brazil have led to rates similar to those in the U.S. and Canada.[42] Increases in mortality may thus be a result of equivalent increases in incidence. Irrespectively, the number of deaths from both colon and rectal cancer are set to double by 2035 for most countries in this region, suggesting an alarming increase in the future burden of CRC and the need for stronger prevention programmes intended to promote healthier lifestyles.

This study also highlights that rectal cancer mortality rates have been projected to rise in several high-income countries including Australia, Canada and the U.S. The underlying reasons have yet to be fully understood, but in recent years, increases in incidence of colon and rectal cancer have been observed in younger age groups (e.g. 55 years and younger), a development that was more pronounced for rectal cancer.[43] A study from the U.S.[43] showed that the risk of colon and rectal cancer was two- (incidence rate ratio (IRR) = 2.40, 95% confidence interval (CI) 1.11 to 5.19) and four times higher (IRR = 4.32, 95% CI 2.19 to 8.51), respectively for those born circa 1990, compared with adults born circa 1950. Similarly, in Western Australia, between 1982 and 2007, a 3.0% annual increase in CRC incidence was observed among adolescents and young adults (15–39 years).[44] As screening is usually recommended for adults aged 50 to 75, changes in incidence in this group is most likely not impacted by screening. Possible explanations are changes in the prevalence of risk factors such as increasing body weight and lower physical activity.[43, 44]

Advances in treatment options and regimens differ extensively among countries, which may also explain lower CRC mortality rates in some countries. Adjuvant chemotherapy is recommended for patients with more advanced stages of colon cancer, and is associated with an approximate reduction of 30% in the risk of disease recurrence, and a 22-32% reduction in mortality.[45] For limited metastatic disease, advances in surgical techniques can result in clinical cure, while significant progress in chemotherapy treatment during recent years in advanced metastatic colon cancer - which has been associated with 5-year survival in the range of 5-8% - may have resulted in improvements of short-term survival.[46] For rectal cancer, the major treatment advances are a result of improved surgical techniques often combined with preoperative chemo-radiation therapy or radiation alone.[47, 48] In many less developed countries, the lack of access to adjuvant therapy has been previously reported.[49] Moreover, lack of awareness, higher diagnostic costs, and delays in treatment may explain part of the higher mortality that was observed and projected in the Latin America and Caribbean region.[42]

Although these future predictions are based on long-term recorded mortality data from the WHO mortality database and extrapolation of rates using empirically evaluated APC models, a number of limitations should be noted. Trend-based predictions should be interpreted with caution since they are by definition based on the assumption that trends observed in the past will continue into the future. The predicted numbers of deaths are also reliant on population projections which are themselves future estimates based on assumptions on birth and death rates, immigration and emigration. In countries, where screening programmes have been launched only in recent years, effects would only be reflected in mortality rates with some delay. It should also be noted that ideally reliable data on incidence, risk factors, screening implementation, treatment and survival is needed to robustly predict the future burden of CRC – such information is however not available for all countries. Furthermore, the reliability of death certification may vary between countries, which in turn might have affected the accuracy of the mortality rates utilised, therefore our results should be interpreted with caution.[50] Lastly, data on rectal cancer mortality also included data on anal cancer as their codes are inseparable in the WHO mortality database,

yet we believe that it would not affect our analysis, as anal cancer is fairly rare and much less common than colon or rectal cancer.

In conclusion, we observe declining rates of colon and rectal cancer mortality in most countries, with the exception of Latin American and Caribbean countries where increases are projected to continue throughout 2035. The reductions seen in Europe, Oceania, and North America may reflect a combined influence of an increasing implementation of, and greater participation in screening, greater public awareness of the disease, and improved therapeutic procedures and patient management protocols. In contrast, the increase in cancer mortality predicted in certain countries may possibly be explained by underlying increases in incidence rates, late diagnosis and limited access to treatment. Increases in rectal cancer mortality in some high-income countries such as Australia, Canada, and the United States are worrisome and the underlying mechanisms warrant further research. In any case, ongoing demographic changes will lead to a rise in the number of deaths from colon and rectal cancer per year in the vast majority of countries, with a doubling of the number of predicted deaths by 2035 in some.

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