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Research Article

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Global Increasing Incidence of Young-Onset Colorectal Cancer Across 5 Continents: A Joinpoint Regression Analysis of 1,922,167 Cases

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Abstract

Background: Colorectal cancer incidence among young adults in the United States is on the rise, but whether this phenomenon is present in other parts of the world is not well documented. This study aims to explore the temporal change of incidence rates for colorectal cancer in various countries across the globe.

Methods: We extracted colorectal cancer incidence and population data from 1988 to 2007 based on data from the International Agency for Research on Cancer and compared incidence between age groups. Twelve representative jurisdictions from five continents were selected. Young-onset colorectal cancer cases were defined as those ages <50 years. Joinpoint regression was used to measure the trends of colorectal cancer incidence and to estimate the annual percent change (APC).

Results: The APC for those ages <50 years was noted to be increasing at a faster rate as compared with those ages ≥50 years in many regions, including Australia (+1.10% vs. −0.35%), Brazil (+9.20% vs. +5.72%), Canada (+2.60% vs. −0.91%), China–Hong Kong (+1.82% vs. −0.10%), China–Shanghai (+1.13% vs. −2.68%), Japan (+2.63% vs. +0.90%), the United Kingdom (+3.33% vs. +0.77%), and the United States (+1.98% vs. −2.88%). These trends were largely driven by rectal cancer, except in Brazil and the United Kingdom.

Conclusions: Increasing incidence of young-onset colorectal cancer was noted in many regions across the globe.

Impact: Further studies focusing on young-onset colorectal cancer, particularly with regard to risk factors and establishing the optimal age of screening, are warranted.

Introduction

Colorectal cancer is the third most common cancer worldwide with an estimated 1.8 million new cases and accounting for more than 800,000 deaths in 2018 (1). There are wide differences in the implementation of colorectal cancer screening strategies across the globe. Most countries adopt the age cut-off of 50 years with some variations in the screening interval as well (2). Screening modalities adopted in general are moving away from guaiac-based fecal occult blood test toward the more sensitive fecal immunochemical test, with flexible sigmoidoscopy or colonoscopy being increasingly used as a first-line option. Screening programs, either organized (majority of European nations) or opportunistic (e.g., most of the United States), are also highly heterogeneous and subject to differences in national healthcare policies (3). Despite this, recent studies have noted a decline in colorectal cancer incidence in many developed countries such as the United States (4). This may, in part, be due to improved uptake of screening among populations falling into screening range in countries where such programs have been promulgated.

In recent years, evidence suggests that there is a rising trend of colorectal cancer among younger adults in the United States (5), as well as in other Western countries such as Australia (6) and Canada (7). Although some of the cases may have a hereditary component, the majority appear to arise sporadically (8). Identifying these patients poses a difficult challenge to healthcare systems (9). Some small case series have suggested that young-onset colorectal cancer are more likely distributed distally in the colon and rectum, have a higher proportion of patients developing synchronous and metachronous tumors (10), present with a more advanced tumor stage, exhibiting a mucinous and signet ring histologic subtype, and be poorly differentiated (8). The reasons for this have yet to be fully elucidated, but a low awareness of colorectal cancer for both patients and physicians, with an underestimation of symptoms, leading to delays in diagnosis and management (11) is a possible contributing factor. Although, still uncommon in terms of the absolute number of cases, the societal impact of young-onset colorectal cancer cannot be understated. Whether this is an emerging global problem is not well established and will likely have significant ramifications on healthcare policy. We set out to analyze global colorectal cancer trends in

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different age groups and genders based on data extracted from the International Agency for Research on Cancer (IARC).

Materials and Methods

Study design

Cancer incidence and population data were extracted from the IARC, the specialized cancer agency of the World Health Organization. The CI5plus database (cancer incidence in five continents) was used, which contains updated annual incidence rates for 118 selected populations from 102 cancer registries up to the year 2007 (12).

We followed the colorectal cancer incidence of selected jurisdictions for roughly 20 years from 1988 through 2007. We selected representative jurisdictions based on the following criteria: (i) industrialized city/prefecture/province/state/country and (ii) having data with high completeness and validity from the CI5plus database, that is, data sets spanning the entirety from 1988 to 2007. The inclusion of datasets that are of higher quality and more complete minimizes the need for missing data imputations, which in turn would lead to less bias. Countries/jurisdictions included in this study are Australia, Brazil, Canada, China (Hong Kong and Shanghai), Germany, Italy, Japan, the Netherlands, Sweden, the United Kingdom, and the United States. As the economic development of Shanghai and Hong Kong had different trajectories in the past decades, they were analyzed separately in our study.

Younger adults in this study were defined as those ages under 50 years of age because most colorectal cancer screening programs around the world use this age cut-off for the initiation of screening for the average risk individual.

Statistical analysis

Joinpoint regression, which uses permutation analysis to fit a series of joined straight lines on a logarithmic scale, was used to measure the trends of colorectal cancer incidence. Log-linear model and the Grid Search Method were used. The dependent variable was the logarithm of incidence rate, whereas the independent variable was year. When log-linear model is chosen, APC (annual percent change) can be computed from the slope of the model (13). The Grid Search Method creates a "grid" of all possible locations for joinpoints specified by the settings, and calculates the sum of squared errors at each one to find the best possible fit (14). Outputs including joinpoints, APC, and fitted values from the program are used to conduct further testing and plotting. The latest period is the period starting from the location of the rightmost joinpoint to the end of the whole period (2007), with results reported in the tables. A maximum of three joinpoints were allowed.

APC was used to estimate the percentage changes in incidence for those below or above the age of 50 years. Subgroup analysis according to anatomic distribution (colonic vs. rectal cancers) and sex category were performed. All tests of statistical significance were two-sided, and a P value of less than 0.05 was considered statistically significant.

Results

A total of 1,922,167 colorectal cancer cases were included in this study, with the breakdown of cases by jurisdiction tabulated in Table 1. Comparison of APC trends by age group for colorectal, colon, and rectal cancer are listed in Table 2. For colorectal cancer, the APC for those ages <50 years was noted to be increasing at a faster rate as compared with those ages ≥50 in many regions including: Australia (+1.10% vs. −0.35%), Brazil (+9.20% vs. +5.72%), Canada (+2.60% vs. −0.91%), China–Hong Kong (+1.82% vs. −0.10%), China–Shanghai (+1.13% vs. −2.68%), Japan (+2.63% vs. +0.90%), the United Kingdom (+3.33% vs. +0.77%), and the United States (+1.98% vs. −2.88%), with these differences being statistically significant.

Table 1. Number of cancer cases by countries/regions

	Number of cases		
Country/region	Colon cancer	Rectal cancer	Colorectal cancer
Australia	145,227	80,209	225,436
Brazil	1,697	1,157	2,854
Canada	25,594	12,987	38,581
China (Hong Kong)	36,572	21,539	58,111
China (Shanghai)	29,337	19,514	48,851
Germany	11,416	7,021	18,437
Italy	61,423	28,180	89,603
Japan	97,776	53,744	151,520
Sweden	63,890	37,909	101,799
The Netherlands	112,035	62,118	174,153
United Kingdom	252,463	150,690	403,153
United States	425,906	183,763	609,669

If analyzed separately, the APC for individuals <50 years in rectal cancer was also shown to be increasing at a faster rate as compared with those ages ≥50 years in Germany (+2.71% vs. −4.90%), Sweden (+1.17% vs. +0.64%), and the Netherlands (+2.12% vs. +0.88%). However, this was not found to be the case in colon cancer, where the APC of individuals <50 years is increasing at a slower rate as compared with those ages ≥50 years in Germany (+0.18% vs. +0.94%), Italy (+0.29% vs. +2.33%), Sweden (+0.81% vs. +1.48%), and the Netherlands (+0.03% vs. +2.79%).

Subgroup analysis by anatomic distribution (Table 1) also showed a more prominent rise in the APC for rectal as compared with colon cancer for those ages <50 years in Australia (+2.27% vs. +0.26%), Canada (+4.72% vs. +1.19%), China–Hong Kong (+3.13% vs. +0.95%), Germany (+2.71% vs. +0.18%), Sweden (+1.17% vs. +0.81%), the Netherlands (+2.12% vs. +0.03%), and the United States (+2.64% vs. +1.94%).

Subgroup analysis by sex category (Tables 3 and 4) showed largely similar trends for both males and females for the majority of jurisdictions. Colorectal cancer trends for those ages <50 years seem to be driven by increases seen in males for Brazil (+12.55% vs. +6.98%), China–Shanghai (+1.50% vs. +0.77%), Germany (+2.30% vs. +0.38%), Italy (+0.51% vs. +0.16%), and the Netherlands (+1.90% vs. +0.72%). This is also probably the case for China–Hong Kong (+18.93% vs. +1.77%) as well, but the calculated APC range is very broad and crosses 0 from −7.23% to +52.48%. Conversely, colorectal cancer trends for those ages <50 years seem to be mainly driven by increases seen in females for Australia (+1.41% vs. +0.81%), Japan (+4.63% vs. +1.00%), and the United Kingdom (+5.61% vs. +3.05%).

The time trends for the incidence of colon cancer, rectal cancer, and colorectal cancer from 1988 to 2007 in the 12 studied regions are depicted in Fig. 1A–C, respectively. During this period, most American and European countries show either a plateau or decline in incidence of colon and rectal cancers among those above 50 years of age (Fig. 1A and B). Incidence rates for colorectal cancer in those ages ≥50 years were on the decline in Australia

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Table 2. Colorectal cancer trends comparing those below 50 years with those at or above 50 years across 12 countries/regions

		Age < 50 years		Age ≥ 50 years	
Country/region	**Cancer**	**Latest period**	**APC (95% CI)[a]**	**Latest period**	**APC (95% CI)[a]**
Australia	Colon cancer	1988–2007	0.26 (−0.19–0.72)	1994–2007	−0.32 (−0.65–0.02)
	Rectal cancer	1988–2007	**2.27 (1.87–2.67)**	1994–2007	**−0.41 (−0.67 to −0.14)**
	Colorectal cancer	1988–2007	**1.10 (0.88–1.33)**	1994–2007	**−0.35 (−0.64 to −0.06)**
Brazil	Colon cancer	1991–2007	**11.05 (8.06–14.12)**	1988–2007	**5.05 (3.11–7.02)**
	Rectal cancer	1988–2007	**6.59 (3.69–9.58)**	1988–2007	**6.92 (4.83–9.06)**
	Colorectal cancer	1991–2007	**9.20 (6.85–11.59)**	1988–2007	**5.72 (3.96–7.52)**
Canada	Colon cancer	1988–2007	**1.19 (0.18–2.21)**	1988–2007	0.01 (−0.28–0.30)
	Rectal cancer	1988–2007	**4.72 (3.58–5.87)**	1988–2007	**0.83 (0.39–1.26)**
	Colorectal cancer	1988–2007	**2.60 (1.87–3.34)**	2000–2007	−0.91 (−2.06–0.26)
China (Hong Kong)	Colon cancer	1988–2007	**0.95 (0.08–1.82)**	1998–2007	**−1.59 (−2.68 to −0.49)**
	Rectal cancer	1988–2007	**3.13 (2.11–4.17)**	1988–2007	**1.94 (1.26–2.62)**
	Colorectal cancer	1988–2007	**1.82 (1.18–2.47)**	1995–2007	−0.10 (−0.59–0.38)
China (Shanghai)	Colon cancer	1988–2007	**0.99 (0.17–1.82)**	2001–2007	−1.42 (−3.71–0.93)
	Rectal cancer	1988–2007	**1.28 (0.57–2.01)**	2002–2007	**−2.99 (−5.84 to −0.05)**
	Colorectal cancer	1988–2007	**1.13 (0.55–1.70)**	2002–2007	**−2.68 (−4.98 to −0.33)**
Germany	Colon cancer	1988–2007	0.18 (−1.52–1.90)	1988–2007	**0.94 (0.49–1.38)**
	Rectal cancer	1988–2007	**2.71 (0.21–5.27)**	2004–2007	−4.90 (−12.44–3.29)
	Colorectal cancer	1988–2007	1.30 (−0.27–2.89)	2002–2007	−1.56 (−3.98–0.92)
Italy	Colon cancer	1988–2007	0.29 (−0.06–0.64)	1988–2007	**2.33 (2.05–2.62)**
	Rectal cancer	1988–2007	0.38 (−0.29–1.06)	1988–2007	**0.59 (0.33–0.85)**
	Colorectal cancer	1988–2007	**0.32 (0.01–0.64)**	1988–2007	**1.78 (1.61–1.95)**
Japan	Colon cancer	2002–2007	2.48 (−0.74–5.80)	1994–2007	**1.01 (0.56–1.45)**
	Rectal cancer	2002–2007	2.83 (−2.24–8.17)	1994–2007	**0.69 (0.16–1.24)**
	Colorectal cancer	2002–2007	**2.63 (0.43–4.87)**	1994–2007	**0.90 (0.46–1.34)**
Sweden	Colon cancer	1988–2007	**0.81 (0.22–1.40)**	2001–2007	**1.48 (0.26–2.71)**
	Rectal cancer	1988–2007	**1.17 (0.37–1.97)**	1997–2007	**0.64 (0.14–1.14)**
	Colorectal cancer	1988–2007	**0.96 (0.50–1.42)**	1998–2007	**0.94 (0.50–1.38)**
The Netherlands	Colon cancer	1989–2007	0.03 (−0.34–0.40)	2002–2007	**2.79 (2.12–3.47)**
	Rectal cancer	1989–2007	**2.12 (1.70–2.54)**	1989–2007	**0.88 (0.64–1.13)**
	Colorectal cancer	1989–2007	**0.87 (0.60–1.14)**	2001–2007	**2.23 (1.80–2.67)**
United Kingdom	Colon cancer	2002–2007	**4.29 (0.41–8.33)**	2002–2007	0.69 (−0.36–1.75)
	Rectal cancer	1988–2007	**2.09 (1.63–2.55)**	1988–2007	0.14 (−0.06–0.34)
	Colorectal cancer	2001–2007	**3.33 (1.30–5.40)**	2002–2007	0.77 (−0.27–1.83)
United States	Colon cancer	1988–2007	**1.94 (1.54–2.33)**	1998–2007	**−2.94 (−3.26 to −2.61)**
	Rectal cancer	1997–2007	**2.64 (1.52–3.79)**	1998–2007	**−2.68 (−3.20 to −2.16)**
	Colorectal cancer	1998–2007	**1.98 (1.36–2.60)**	1998–2007	**−2.88 (−3.11 to −2.64)**

NOTE: Values in bold represent statistical significance ($P < 0.05$).
Abbreviation: CI, confidence interval.
[a]APC refers to the latest period before 2007.

(−0.35%), China (Shanghai; −2.68%), and the United States (−2.88%) with these figures being statistically significant. China and Brazil show the most substantial rise in colorectal cancers in this period among the older age group (Fig. 1C). In the younger populations below age of 50 years, there is a gradual incline in incidence of colorectal cancer in most countries, among which Brazil shows the most dramatic increase (Fig. 1C). Japan, after an initial increase until the mid-1990's shows a decline in increase in the past decade. The increasing trend among the young population is more consistently seen in the rectal cancer (Fig. 1B) than colon cancer (Fig. 1A). Of note, Italy is the only region that consistently showed an increase in colon, rectal, or colorectal cancer in those ages ≥50 years (the absolute incidence rates of the 12 studied regions depicted in Fig. 1 can be found in the Supplementary Tables S1–S12). This includes the age brackets from 0 to 19 years, with the absolute number of cases being minimal when compared with the age brackets 20–49 years and beyond.

Discussion

This study shows an increase in incidence of young-onset colorectal cancer for developed regions on a global scale. This increase for younger populations is in contrast to the general population trends of stabilization or decrease in incidence rates for colorectal cancer in developed countries, which was reported elsewhere using GLOBOCAN data (4) and also from our study. These findings are important to raise awareness of this emerging global problem. Although the absolute number of patients with young-onset colorectal cancer is still relatively low compared with those in older age groups, the trends demonstrated in our study suggest that the disease burden may shift in the near future.

We have noted a prominent rise in rectal cancer among younger populations when compared with colon cancer in Australia, Canada, China–Hong Kong, Germany, Sweden, the Netherlands, and the United States. This finding is compatible with several small series on young-onset colorectal cancer that were discussed previously (8, 10, 15). An emphasis on education, identifying (and avoid ignoring) alarming symptoms, and seeking early medical attention may be reasonable for both patients and physicians to avoid delaying the diagnosis and treatment for this subset of colorectal cancer, but further research is needed on the effectiveness of such an approach.

Regional differences were noted in our study. Brazil is notable for a rapid rise in both rectal and colon cancer, affecting both younger and older age groups. When evaluating the cancer trends between 1988 and 2007 (Fig. 1) for Japan, the trajectory shows

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Table 3. Cancer trends of males across 12 countries/regions

		Age < 50 years		Age ≥ 50 years	
Country/region	**Cancer**	**Latest period**	**APC (95% CI)[a]**	**Latest period**	**APC (95% CI)[a]**
Australia	Colon cancer	1988–2007	−0.07 (−0.63–0.50)	1995–2007	−0.38 (−0.83–0.08)
	Rectal cancer	1988–2007	**1.89 (1.26–2.53)**	1995–2007	**−0.46 (−0.82 to −0.10)**
	Colorectal cancer	1988–2007	**0.81 (0.44–1.19)**	1995–2007	**−0.41 (−0.80 to −0.01)**
Brazil	Colon cancer	1991–2007	**12.55 (7.58–17.75)**	1988–2007	**7.21 (4.50–10.00)**
	Rectal cancer	1988–2007	**6.30 (1.27–11.59)**	1988–2007	**7.53 (4.63–10.50)**
	Colorectal cancer	1993–2007	**12.55 (8.38–16.88)**	1988–2007	**7.20 (5.01–9.44)**
Canada	Colon cancer	1988–2007	**1.13 (0.01–2.26)**	1988–2007	0.08 (−0.30–0.46)
	Rectal cancer	1988–2007	**4.15 (2.69–5.62)**	1988–2007	**1.12 (0.65–1.58)**
	Colorectal cancer	1988–2007	**2.37 (1.54–3.21)**	1988–2007	**0.46 (0.11–0.82)**
China (Hong Kong)	Colon cancer	2005–2007	21.58 (−12.37–68.68)	1996–2007	−0.38 (−1.13–0.37)
	Rectal cancer	1988–2007	**3.69 (2.55–4.84)**	1988–2007	**2.75 (1.97–3.52)**
	Colorectal cancer	2005–2007	18.93 (−7.23–52.48)	1996–2007	0.47 (−0.24–1.18)
China (Shanghai)	Colon cancer	1988–2007	**1.13 (0.11–2.15)**	2002–2007	−2.23 (−5.52–1.17)
	Rectal cancer	1988–2007	**1.87 (0.85–2.91)**	2002–2007	−3.27 (−7.21–0.85)
	Colorectal cancer	1988–2007	**1.50 (0.72–2.27)**	2002–2007	−2.66 (−5.61–0.38)
Germany	Colon cancer	1988–2007	1.27 (−0.87–3.47)	1988–2007	**1.78 (1.20–2.37)**
	Rectal cancer	1988–2007	**3.65 (0.14–7.30)**	1988–2007	**2.06 (1.39–2.75)**
	Colorectal cancer	1988–2007	**2.30 (0.65–3.98)**	1988–2007	**1.90 (1.43–2.37)**
Italy	Colon cancer	1988–2007	**0.71 (0.14–1.28)**	1988–2007	**2.97 (2.59–3.34)**
	Rectal cancer	1988–2007	0.17 (−0.76–1.12)	1988–2007	**0.89 (0.62–1.15)**
	Colorectal cancer	1988–2007	**0.51 (0.11–0.91)**	1988–2007	**2.26 (2.04–2.49)**
Japan	Colon cancer	2003–2007	4.20 (−3.64–12.66)	1994–2007	0.52 (−0.02–1.07)
	Rectal cancer	1988–2007	−0.80 (−1.70–0.11)	1995–2007	0.69 (−0.05–1.43)
	Colorectal cancer	2002–2007	1.00 (−1.93–4.03)	1994–2007	**0.63 (0.12–1.14)**
Sweden	Colon cancer	1988–2007	**0.97 (0.15–1.80)**	1988–2007	0.05 (−0.22–0.31)
	Rectal cancer	1988–2007	0.93 (−0.04–1.92)	1998–2007	**0.86 (0.02–1.72)**
	Colorectal cancer	1988–2007	**0.95 (0.22–1.68)**	2000–2007	**1.08 (0.25–1.91)**
The Netherlands	Colon cancer	1989–2007	−0.16 (−0.82–0.49)	2002–2007	**3.50 (2.17–4.85)**
	Rectal cancer	1997–2007	**3.10 (1.64–4.58)**	1989–2007	**1.02 (0.74–1.29)**
	Colorectal cancer	1998–2007	**1.90 (0.81–3.00)**	2003–2007	**2.86 (0.87–4.88)**
United Kingdom	Colon cancer	1988–2007	0.02 (−0.59–0.63)	2002–2007	0.92 (−0.22–2.07)
	Rectal cancer	1988–2007	**1.76 (1.02–2.50)**	1988–2007	**0.34 (0.13–0.55)**
	Colorectal cancer	2001–2007	**3.05 (0.42–5.75)**	1992–2007	0.00 (−0.21–0.21)
United States	Colon cancer	2004–2007	−2.60 (−7.88–2.98)	2001–2007	**−3.52 (−4.41 to −2.62)**
	Rectal cancer	1988–2007	**3.98 (3.37–4.59)**	1988–2007	**−1.92 (−2.22 to −1.62)**
	Colorectal cancer	1988–2007	**2.86 (2.51–3.20)**	1998–2007	**−3.10 (−3.41 to −2.77)**

NOTE: Values in bold represent statistical significance ($P < 0.05$).
Abbreviation: CI, confidence interval.
[a]APC refers to the latest period before 2007.

increasing incidence from 1988 till after 1995, followed by a decline till the early 2000s, with an increase again in the latest time period up till 2007. We suggest several possible reasons for this: first, there are only three prefectures represented in the Japanese data and therefore it may not be representative of the country on the whole. Second, it is possible that the early launch of screening for colorectal cancer in Japan may play a role in the initial decline of colorectal cancer incidence even among the younger population (since 1992, a screening program based on fecal immunochemical test was initiated in Japan for average risk individuals at 40 years of age; ref. 16). In addition, Japan has one of the lowest rates of obesity in the world (17), which also differs with many other developed regions in the world.

Although young-onset colorectal cancer was shown to be on the rise in our study, the risk factors leading to this have yet to be fully elucidated. It is probable that a myriad of genetic variants displaying variable penetrance maybe involved (18), rather than a rise in well-defined hereditary colorectal cancer syndromes (19). However, it is unlikely that genetic changes can solely explain these trends given the relatively short timeframe and the diverse geographic distribution involved. Other factors, such as the global pandemic of obesity (20), may play a role in the rise of young-onset colorectal cancer. Obesity has been implicated as an important risk factor for the development of various cancers including colorectal cancer (21), possibly related to its effects on hyperinsulinemia (22) and alterations in the gut microbiota (23). A systematic review showed that each 5 kg/m^2 increment in body mass index (BMI) was associated with an 18% increased risk of colorectal cancer (24). Recently, a risk score validated in Asian subjects for predicting advanced neoplasia was shown to have better risk stratification with the inclusion of BMI (25) as a factor. Other lifestyle changes involving diet, exercise, alcohol consumption, and smoking could also play a significant role (26). Previously, a prospective longitudinal study on the effects of increased dietary quality showed that it was associated with a lower risk of colorectal cancer incidence for men regardless of baseline BMI (27). Italy is unique in our study, where the APC of those ages <50 years are consistently lower than those ages ≥50 years. Being the only region from southern Europe, it may imply that distinct lifestyles and dietary patterns such as the Mediterranean diet may confer certain protective benefits (28), leaving age as an unmodifiable risk factor, which could be one of the explanations of why the colorectal cancer rates in Italy were steadily rising relative to younger age groups. On the other side of the coin, adopting a more westernized diet and lifestyle with higher consumption of red and processed meats may increase the risk of

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Table 4. Cancer trends of females across 12 countries/regions

		Age < 50 years		Age ≥ 50 years	
Country/region	**Cancer**	**Latest period**	**APC (95% CI)[a]**	**Latest period**	**APC (95% CI)[a]**
Australia	Colon cancer	1988–2007	0.57 (−0.13–1.27)	1993–2007	−0.28 (−0.60–0.05)
	Rectal cancer	1988–2007	**1.89 (1.26–2.53)**	1995–2007	**−0.46 (−0.82** to **−0.10)**
	Colorectal cancer	1988–2007	**1.41 (0.97–1.85)**	1993–2007	**−0.35 (−0.61** to **−0.08)**
Brazil	Colon cancer	1988–2007	**6.90 (2.84–11.12)**	1988–2007	**3.55 (1.54–5.60)**
	Rectal cancer	1988–2007	**6.30 (1.27–11.59)**	1988–2007	**7.53 (4.63–10.50)**
	Colorectal cancer	1988–2007	**6.98 (4.05–9.99)**	1988–2007	**4.65 (2.89–6.44)**
Canada	Colon cancer	1988–2007	1.29 (−0.22–2.83)	2001–2007	−1.71 (−3.69–0.32)
	Rectal cancer	1988–2007	**4.15 (2.69–5.62)**	1988–2007	**1.12 (0.65–1.58)**
	Colorectal cancer	1988–2007	**2.88 (1.67–4.09)**	2002–2007	**−2.04 (−3.57** to **−0.48)**
China (Hong Kong)	Colon cancer	1988–2007	**1.25 (0.17–2.33)**	1998–2007	**−2.43 (−3.83** to **−1.02)**
	Rectal cancer	1988–2007	**3.69 (2.55–4.84)**	1988–2007	**2.75 (1.97–3.52)**
	Colorectal cancer	1988–2007	**1.77 (0.88–2.68)**	1994–2007	**−0.80 (−1.32** to **−0.28)**
China (Shanghai)	Colon cancer	1988–2007	0.86 (−0.31–2.04)	2001–2007	−1.61 (−3.58–0.41)
	Rectal cancer	1988–2007	**1.87 (0.85–2.91)**	2002–2007	−3.27 (−7.21–0.85)
	Colorectal cancer	1988–2007	0.77 (−0.09–1.64)	2002–2007	**−2.74 (−5.38** to **−0.03)**
Germany	Colon cancer	1988–2007	−0.84 (−3.86–2.27)	1988–2007	0.14 (−0.42–0.70)
	Rectal cancer	1988–2007	**3.65 (0.14–7.30)**	1988–2007	**2.06 (1.39–2.75)**
	Colorectal cancer	1988–2007	0.38 (−1.64–2.44)	2000–2007	**−2.13 (−3.80** to **−0.44)**
Italy	Colon cancer	1988–2007	−0.06 (−0.72–0.60)	1988–2007	**1.63 (1.37–1.90)**
	Rectal cancer	1988–2007	0.17 (−0.76–1.12)	1988–2007	**0.89 (0.62–1.15)**
	Colorectal cancer	1988–2007	0.16 (−0.44–0.75)	1988–2007	**1.20 (1.00–1.40)**
Japan	Colon cancer	1988–2007	0.03 (−0.73–0.79)	1994–2007	**1.58 (1.10–2.06)**
	Rectal cancer	1988–2007	−0.80 (−1.70–0.11)	1995–2007	0.69 (−0.05–1.43)
	Colorectal cancer	2002–2007	**4.63 (0.51–8.91)**	1994–2007	**1.26 (0.86–1.65)**
Sweden	Colon cancer	1988–2007	0.65 (−0.31–1.62)	2000–2007	**1.59 (0.52–2.67)**
	Rectal cancer	1988–2007	0.93 (−0.04–1.92)	1998–2007	**0.86 (0.02–1.72)**
	Colorectal cancer	1988–2007	**0.98 (0.28–1.69)**	1997–2007	**0.95 (0.32–1.58)**
The Netherlands	Colon cancer	1991–2007	−0.10 (−0.52–0.32)	2001–2007	**2.02 (1.00–3.05)**
	Rectal cancer	1997–2007	**3.10 (1.64–4.58)**	1989–2007	**1.02 (0.74–1.29)**
	Colorectal cancer	1992–2007	**0.72 (0.27–1.16)**	2001–2007	**1.91 (1.36–2.46)**
United Kingdom	Colon cancer	2003–2007	**6.97 (0.26–14.12)**	2003–2007	0.97 (−0.72–2.69)
	Rectal cancer	1988–2007	**1.76 (1.02–2.50)**	1988–2007	**0.34 (0.13–0.55)**
	Colorectal cancer	2003–2007	**5.61 (0.78–10.67)**	2002–2007	0.70 (−0.50 to 1.92)
United States	Colon cancer	1988–2007	**1.88 (1.35–2.41)**	2000–2007	**−2.94 (−3.62** to **−2.26)**
	Rectal cancer	1988–2007	**3.98 (3.37–4.59)**	1988–2007	**−1.92 (−2.22** to **−1.62)**
	Colorectal cancer	1988–2007	**2.56 (2.11–3.03)**	1998–2007	**−2.68 (−2.94** to **−2.42)**

NOTE: Values in bold represent statistical significance ($P < 0.05$).
Abbreviation: CI, confidence interval.
[a]APC refers to the latest period before 2007.

colorectal cancer (29, 30). A high intake of animal fat was shown to increase the risk of colon cancer (31). This may well be the case observed from the data in Brazil. Of interest, discrepancies in interregional cancer incidence rates in jurisdictions with similar economic development and cultural background were noted, that is, North American, Australia, and European countries. This would suggest that "westernization" as a risk factor is an overgeneralization, and further work is needed to elucidate the individual components driving this increased risk of cancer. Recently, a study from Murphy and colleagues suggested that early life exposures accumulated throughout the life course may increase cancer risk (32). Because of limitations of our study design and the available datasets, many of these unanswered questions would require further research.

Recently, the American Cancer Society has updated their guidelines providing a qualified recommendation to lower the age of screening for average risk adults to 45 years of age from 50 years (33). This change in screening policy is debatable as it will inevitably shift resources to a younger population, while the majority of patients are still those above the age of 50 years and much more likely to benefit from screening. However, the fact that screening colonoscopy and polypectomy for premalignant lesions can effectively disrupt the adenoma-carcinoma sequence, and will likely lead to cost savings in the long run cannot be overstated. With a predilection of these lesions in the distal colon and rectum, the efficacy and cost effectiveness of performing flexible sigmoidoscopy should be an idea worth visiting (34). Lower cost guaiac-based or immunochemical-based stool tests could also be a viable entry test as a more economic and safer alternative for younger adults. Ultimately, the choice of age criterion and screening modalities will need to be region-specific, and will be dependent on local incidence rates of young-onset colorectal cancer, and individual governments' resource prioritization policies, as adopting a screening program will incur potential opportunity costs. Although it would be premature at this juncture to advocate for earlier screening in individuals with average risk around the world, raising awareness and conducting cost-effective analyses in the future would be a way forward to address this problem.

Our study has several limitations. Further delineation of patient characteristics for young-onset colorectal cancer cannot be achieved with the available dataset, and therefore we could not assess the epidemiologic risk factors and possible causal relationships involved. It is known from other studies that proximal colon cancers may behave more aggressively with a significantly higher all-cause mortality relative to patients with distal colon or rectal

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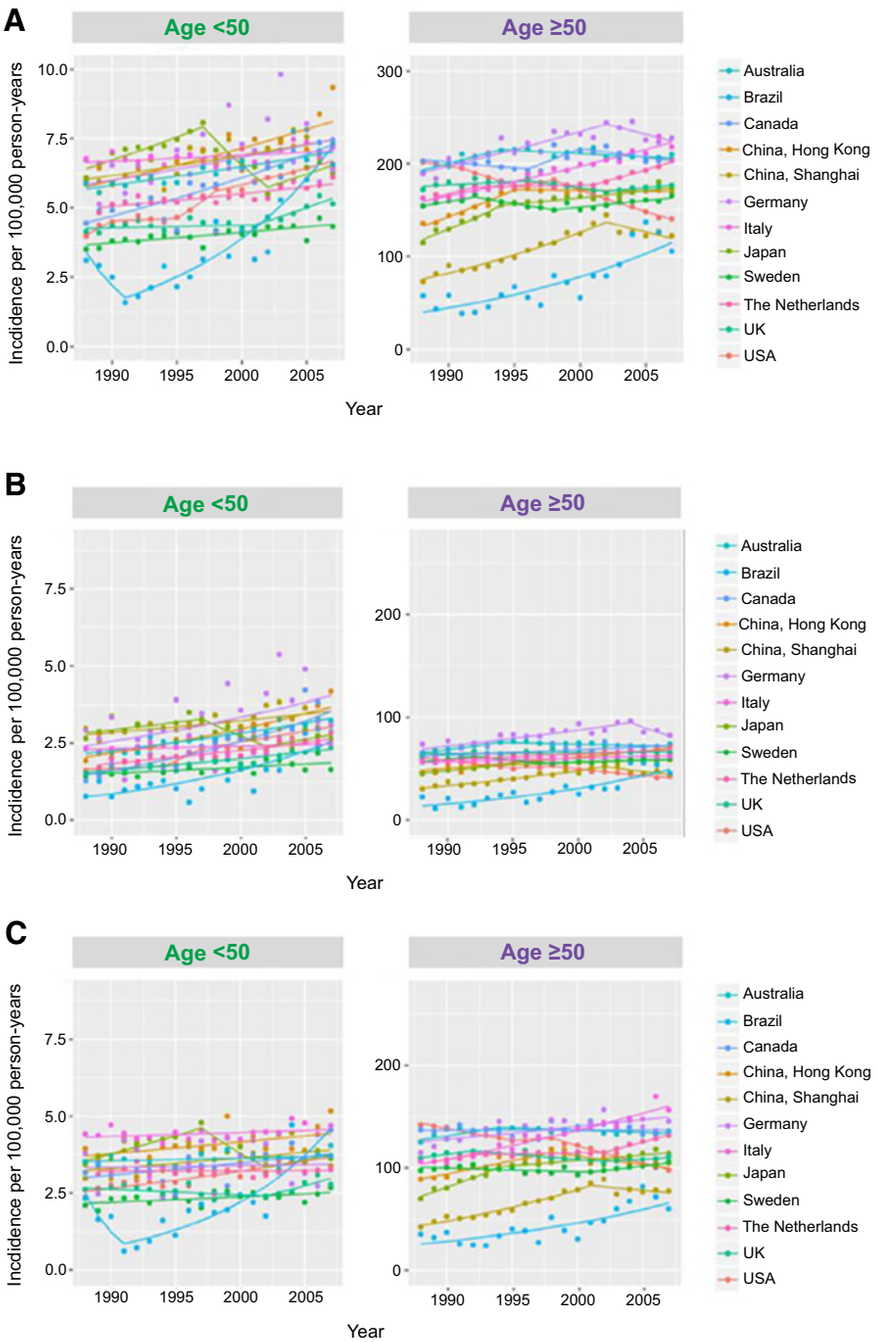

Figure 1.
Graphs depicting colorectal cancer incidence rates from 1988 to 2007. **A,** Trends of colon cancer. **B,** Trends of rectal cancer. **C,** Trends of colorectal cancer.

cancer (35). However, due to the limitations of the datasets it was not possible to separate colon cancers into these respective anatomic distributions for analysis. Regarding all similar studies using global data, concerns over data completeness, comparability, and validity will invariably be present. Another limiting factor is that we only analyzed data from 1988 to 2007. Although the latest data available are from more than a decade ago, we believe that secular trends would become even more apparent with time. Also, capturing data from earlier on may theoretically add more information with regard to the cancer incidence trends. However, when this is balanced against the possibility of bias with incomplete datasets, which would require missing data imputations, difficulties in comparing regions with different time periods, together with data suggesting that these secular trends are recently emerging, we opted to keep this study design. Another limiting factor is that we only included 12 jurisdictions with developed economies in our analysis. Again, wider coverage theoretically has the advantage of having a larger sample size and drawing more robust conclusions, but this may also include datasets that are of lower quality with missing categories thus affecting results. The

IARC has strongly recommended this approach, or making appropriate adjustments before comparing rates, which may also introduce other difficulties in the methodology. Thus, we have chosen to use our predefined criteria to impartially select representative regions from across the globe. Despite of these limitations, we believe that the central tenet raised in our study holds true and conveys the important message that young-onset colorectal cancer is on the rise globally, at least in developed regions.

Conclusion

Although still relatively uncommon, increasing incidence of young-onset colorectal cancer is an emerging global problem with significant ramifications on healthcare policies in the near future. Discrepancies in interregional cancer incidence rates in jurisdictions with similar economic development and cultural background, differential trends in the incidence of colon and rectal cancer, and intraregional differences with regard to anatomic distribution of colorectal cancer highlight the many important clinical questions that necessitate further research. Hopefully, future insights will lead to improved risk stratification, possibly by adopting a more individualized approach to screening. Cost-effective studies for these strategies would also be essential to allow policymakers to make better informed decisions in this regard.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: R.N. Lui, K.K.F. Tsoi, J.J.Y. Sung
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Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): K.K.F. Tsoi
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): R.N. Lui, K.K.F. Tsoi, J.M.W. Ho, C.M. Lo, F.C.H. Chan, J.J.Y. Sung
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