Generational shifts in colorectal cancer incidence in seven high-income countries: a population-based study

Marzieh Araghi, PhD[1], **Isabelle Soerjomataram, PhD**[1], **Aude Bardot, MSc**[1], **Jacques Ferlay, ME**[1], **Citadel Cabasag, PhD**[1], **David S. Morrison, MD**[2], **Prithwish De, PhD**[3], **Hanna Tervonen, PhD**[4], **Paul M. Walsh, PhD**[5], **Oliver Bucher, MSc**[6], **Gerda Engholm, MSc**[7], **Christopher Jackson, FRACP**[8], **Carol McClure, PhD**[9], **Ryan R. Woods, MSc**[10], **Nathalie Saint-Jacques, PhD**[11], **Eileen Morgan, PhD**[12], **David Ransom, MD**[13], **Vicky Thursfield, Grad Dip**[14], **Bjørn Møller, PhD**[15], **Suzanne Leonfellner, BN**[16], **Marianne G. Guren, PhD**[17], **Freddie Bray, PhD**[1], **Melina Arnold, PhD**[1]

[1]Section of Cancer Surveillance, International Agency for Research on Cancer, 150 Cours Albert Thomas, Lyon, France

[2]Information Services Division (ISD), NHS National Services Scotland Meridian Court/South Gyle, Scotland, United Kingdom

[3]Analytics and Informatics, Cancer Care Ontario, 620 University Ave., Toronto, Canada

[4]Cancer Institute New South Wales, Alexandria, Australia

[5]National Cancer Registry Ireland, Cork Airport Business Park, Kinsale Road, Cork, Ireland

[6]Department of Epidemiology and Cancer Registry, Cancercare Manitoba, Winnipeg, Canada

[7]Danish Cancer Society, Strandboulevarden, Copenhagen, Denmark

[8]Cancer Society of New Zealand, Wellington, New Zealand

[9]Prince Edward Island Cancer Registry, Charlottetown, Canada

[10]BC Cancer Agency, Vancouver, Canada

[11]Nova Scotia Health Authority Cancer Care Program, , Halifax, Canada

[12]Northern Ireland Cancer Registry, Queen's University Belfast, Belfast, Northern Ireland

[13]Western Australia Cancer and Palliative Care Network Policy Unit Health Networks Branch, Department of Health, Western Australia, Australia

[14]Victorian Cancer Registry, Cancer Council Victoria, Melbourne, Australia

Correspondence to: Marzieh Araghi, Section of Cancer Surveillance, International Agency for Research on Cancer, 150 Cours Albert Thomas, Lyon, 69372 CEDEX 08, France, Telephone: +33 4 72 73 84 28, araghim@fellows.iarc.fr.

[15]Institute of Population-Based Cancer Research, Cancer Registry of Norway, Norway

[16]Provincial Epidemiology Service, Fredericton, New Brunswick, Department of Health, Province of New Brunswick, New Brunswick, Canada

[17]Oslo University Hospital, Dept. of Oncology and K.G. Jebsen Colorectal Cancer Research Center, Oslo, Norway

Abstract

Background—Overall colorectal cancer (CRC) incidence rates are in decline in many high-income countries, yet recent analyses in the U.S. and elsewhere have reported increasing risks among younger generations. Here, we examined generational changes in colon and rectal cancer incidence rates across seven high-income countries.

Methods—Data on colon and rectal cancer incidence were obtained from 21 population-based cancer registries from Australia, Canada, Denmark, Norway, New Zealand, Ireland and the U.K. for the earliest available year until 2014. Age-period-cohort (APC) modeling was used to assess trends by age group, period and birth cohort.

Findings—An overall decline or stabilization in the incidence of colon and rectal cancer was observed in all studied countries. In the most recent 10-year period however, steep increases were seen in both colon and rectal cancer incidence rates among younger persons (ages <50 years), with the largest increases for colon cancer in Denmark (3.1% per year) and for rectal cancer in Norway (4.0%). This coincided with a decrease in incidence at older ages (50-74 years) in all countries. Trends in CRC incidence in the young were mainly driven by increases in distal (left-sided) tumours of the colon. In all countries, we observed strong non-linear cohort effects were observed, which were more pronounced for rectal than colon cancer.

Interpretation—A considerable increase in the incidence of CRC in younger persons under age 50 can be observed across seven high-income countries included in this study. Strong birth cohort effects imply that a changing distribution and prevalence of risk factors that may exert particular influence on earlier stages of carcinogenesis is affecting recent generations. Evidently future studies are needed to determine the root causes of the upsurge of colorectal cancer incidence among younger persons that aid potential preventive and early detection strategies.

Introduction

Colorectal cancer (CRC) is the third most common cancer worldwide, with an estimated 1.8 million new cases and 881,000 associated deaths in 2018.[6] While the incidence of CRC is increasing rapidly in emerging economies, rates have been stabilising or declining

in many highly-resourced settings, including the U.S., Australia, New Zealand and several Western European countries.[7,8] Such declines, driven by rates at ages >50, have largely been attributed to the implementation of screening for premalignant polyps,[9] though other risk factors may have contributed.[2]

Despite observed declines in overall CRC incidence, several recent studies have reported increasing CRC rates in adults younger than 50 years – an age group that is typically not targeted by organized screening.[1–5] In Australia, colon cancer incidence rates in the 20-29 age range increased by 9.3% per annum from 2004 to 2014. Similarly, rectal cancer incidence increased by 7.1% every year from 1993 to 2014.[3] In the U.S., those born circa 1990 were found to have double the risk of colon cancer and quadruple the risk of rectal cancer, relative to their counterparts born around 1950.[2] This recent rise in CRC incidence at ages<50 years may imply a role for specific lifestyle factors, including diet or increasing rates of obesity.[10]

In this study, we characterized and comprehensively assessed time trends in CRC incidence by tumour subsite, tumour location, age at diagnosis, and year of birth using data from seven high income countries (Australia, Canada, Denmark, Ireland, New Zealand, Norway, and the U.K.). By means of age-period-cohort modelling, we analysed time trend by period of diagnosis and year of birth (birth cohort) in order to increase our understanding of factors that affect the population regardless of age at a given time (e.g., changes in medical practice), versus those that vary in generations of individuals as they age (e.g., changing prevalence and distribution of known or putative risk factors).

Methods

Study Design and Data Sources

The second phase of the International Cancer Benchmarking Partnership (ICBP SURVMARK-2) aims to measure international differences in cancer survival, across seven high-income countries with similar access to health care; (1) Australia [New South Wales, Western Australia, Victoria], (2) Canada [Alberta, British Columbia, Manitoba, New Brunswick, Newfoundland, Nova Scotia, Ontario, Prince Edward Island, Saskatchewan], (3) Denmark, (4) Ireland, (5) New Zealand, (6) Norway and (7) the U.K. [England, Northern Ireland, Scotland, and Wales]. According to the ICBP SURVMARK2 data specification protocol, data on primary cancers of the colon and rectum were obtained from 21 population-based cancer registries for cases diagnosed in the period 1995-2014 (with the exception of Australia and Denmark: 1995-2012, and Ireland: 1995-2013). In order to investigate long-term trends, the *Cancer Incidence in Five Continents* (CI5) database was used, to expand these data series going back in time for Australia: (from) 1983, Denmark: 1978, and Norway: 1953.[11] Cases were stratified by tumour subsite as follows: colon (the International Classification of Diseases, 10th edition (ICD-10) codes C18.0, C18.2-C18.9), proximal (right) colon (C18.0, C18.2-C18.4), distal (left) colon (C18.5-C18.7), rectum (C19-C20). Malignant neoplasms of the appendix (C18.1) were excluded, as their aetiology is different to other CRC tumours and changes in the classification of the behaviour of these tumours may render the trends unreliable. The data submitted from registries included information on patient- and tumour-level data including topography, histology, morphology

and basis of diagnosis. Datasets were quality-checked and harmonized according to a pre-defined protocol. As incidence trends were similar in males and females (appendix pp 3-4), results are presented for both sexes combined.

Statistical Analysis

Age-standardized incidence rates (ASIR) were calculated for three age groups (0-49 years, 50-74 years, 75+ years) and all ages combined, using the world standard population and presented per 100,000 person-years.[12] For the detailed assessment of trends among younger people, these were further stratified by age (20-29 years, 30-39 years, and 40-49 years). Joinpoint regression analysis was used to identify magnitude and direction of temporal trends by anatomic sub-site, and age for varying time periods. This method uses a statistical algorithm to define a best-fitting regression line through incidence data across time to estimate the annual percent change (APC) and average annual percent change (AAPC) (with 95% confidence intervals).[13] Trends in incidence rates were quantified by AAPC and the corresponding 95% confidence interval over the most recent 10-year period of available data (Australia: 2003-2012; Canada/ New Zealand/ Norway/U.K.: 2005-2014; Denmark: 2003-2012; Ireland: 2004-2013). Two-sided P values were considered to indicate statistical significance when they were less than 0.05.

Observed trends (in 5-year intervals for age and period, and 10-years for birth cohort) were presented as rates *versus* birth cohort by age, and rates *versus* calendar period by age, with the identification of quasi-parallelism between age-specific curves providing an indication of their effects on the temporal pattern. Assuming CRC incidence rates were constant within the 5-year age classes and 5-year periods of diagnosis, an age-period-cohort (APC) model was fitted and goodness-of-fit was evaluated by comparing the deviance for each sub model.[14,15] The APC model assumes a linear dependency among age, period, and cohort (*cohort = period – age*). To solve the non-identifiability problem of the full APC model, the general method of setting constraints on the parameters was used.[16] Both period and cohort effects are presented as incidence rate ratios (IRR) relative to their respective medians (with respect to the number of cases for the period and cohort variable). The model analysis and presentation was performed using *APCfit* in Stata, which uses the splines to estimate each of the three effects that are then combined to give estimated rates.[17] The default number of internal knots (five) for each of the spline bases for the three variables (age, period and cohort) was used.

Results

Overall, the incidence of colon cancer in the most recent five year period varied between 24.5 in Norway and 19.0 per 100,000 person-years in the U.K. Rectal cancer incidence was somewhat lower, but showed similar geographical patterns, with the highest and lowest rates observed in the same countries: Norway (13.6) and the U.K. (10.9) (Table 1). Of the 402,376 CRC patients diagnosed during the last five years of available data across countries, 66% were diagnosed with colon cancer and 34% were diagnosed with rectal cancer. An overview of the number of CRC cases diagnosed throughout the study period by sex, age, tumour

subsite, year of diagnosis and year of birth by country is provided in the supplementary material (appendix p 1).

While overall trends in colon cancer incidence stabilized and subsequently decreased in Australia, New Zealand, Canada, and to a lesser extend in the U.K. and Ireland, rates continued to rise in Denmark and Norway (Figure 1). As for recent trends, in the most 10-year period, colon cancer incidence rates for all ages decreased by 1.8% per annum in New Zealand and by 1.3% in Canada, but stabilized in Australia and Ireland and increased in Denmark (Figure 2, appendix p 2). Trends for rectal cancer were similar to colon cancer, except for the U.K., where incidence rates declined by 1.2% every year, similar to decreases observed in Australia and Canada (Figure 2, appendix p 2). No significant changes were observed for rectal cancer in the remaining countries.

Incidence trends by age group showed diverging patterns (Figures 1 & 2, appendix p 2). In younger persons aged 0-49 years, colon cancer incidence rates increased in all countries except Norway over the most recent 10-year period (AAPC: Denmark +3.1%; New Zealand +2.9%; Australia +2.9%, U.K. +1.8%; Ireland +0.8%; Canada +0.7%, $p < 0.05$ for all, except Ireland and Canada, Figure 2), with increases more pronounced in females than males (appendix pp 3-4). In this age group, increasing incidence trends were specially seen for tumours occurring in the distal (left) colon (appendix p 8). Similar increases were also observed for rectal cancer across all countries, except Ireland and Denmark (AAPC: Norway +4.0%; Canada +3.4%, New Zealand +3.0%; Australia +2.6%, U.K. +1.4%; p < 0.05 for all, except Norway and New Zealand). Sub-analyses showed that observed increases for both colon and rectal cancer were most pronounced amongst those aged 20-29 years and were driven by increasing incidence rates of rectal and left-sided colon cancer (Figure 3, appendix p 9).

In the 50-74 age group, colon cancer incidence rates decreased significantly in New Zealand (-3.4% per year) and showed downward trends in Canada (-1.9%), Australia (-1.6%) and Ireland (-1.1%), while rates stabilized or slightly increased in Denmark, the U.K. and Norway. Similarly, decreases or a levelling off of rectal cancer incidence rates were observed in this age group across all countries. In the elderly (ages 75 and over), colon cancer incidence rates increased in Norway and Denmark but were stable elsewhere; whereas rectal cancer incidence decreased or stabilized in all countries (Figures 1 & 2, appendix p 2).

To explore period and cohort effects, age-specific colon and rectal cancer rates are presented by year of birth (birth cohort) and period of diagnosis in all countries (appendix pp 10-11). The parallelisms in the lines are more apparent for birth cohorts than across period of diagnosis and therefore indicative of strong generational effects. Uniform increases in incidence rates of colon and rectal cancer are seen in successive birth cohorts (Australia: those born between 1970-1985, Canada: 1975-1990, Denmark & New Zealand: 1970-1980, Norway: 1930-1980, Ireland: 1980-1990, and the U.K.: 1970-1980), affecting those aged of 20-39 years in the most recent period. In contrast, rates seem to stabilize for those aged 50+ that were born from 1950 onward.

On the basis of the full APC model and a parameterization that allocates drift to birth cohort, an increasing trend in the IRRs can be seen in successive generations for both colon and rectal cancer across all countries (appendix pp 12-13), with more pronounced patterns for rectal relative to colon cancer. For example, compared with those born circa 1925, generations born around 1990 in Norway had a twofold increase in the age-specific risk of colon cancer (IRR = 2.0, 95% CI = 1.6–2.5) and a fivefold increase in the risk of rectal cancer (IRR = 5.1, 95% CI = 4.0– 6.6). Similar trends were observed for recently born cohorts in the U.K., Australia, Canada and New Zealand (appendix pp 5-6). In Ireland and Denmark, increases in IRRs of colon and rectal cancer in younger cohorts did not reach statistical significance.

Discussion

Despite a general decline or stabilization in colon and rectal cancer incidence rates for all ages and at ages 50 years and over, the phenomenon of an increase in incidence in adults below the age of 50 can be observed across several high-income countries, with the rate of change as much as 3.1% per year in Denmark (for colon cancer) and 4.0% per year in Norway (for rectal cancer) over the most recent 10-year period. Our results underscore the presence of strong (non-linear) cohort effects, pointing towards significant upward trends in CRC risk for those born after 1990 in all seven countries under study.

The increasing incidence of CRC in individuals aged below 50 years is in line with previous studies investigating CRC trends at the national level.[1–5] In the U.S., Siegel and colleagues[2] showed that age-specific CRC risk for recent birth cohorts has declined to the levels seen among generations born circa 1890. Similarly, increasing incidence of CRC in young patients has been reported in studies from Australia,[3] Canada,[4] and Norway.[5] The parallelism of the incidence rates by cohort and the strong significance of non-linear cohort effects in the APC model across countries likely reflects differentials in the changing prevalence and distribution of risk factors in recent generations of men and women.

Such factors may include lifestyle-related risk factors, including population-level changes in excess body weight, consumption of red and processed meat, cooking meats at high temperatures, high fat intake, physical activity, dietary fibre intake, alcohol consumption, and cigarette smoking.[18] Recent evidence also suggests that antibiotic use, which alters the gut microbiome, may also be associated with a rise in paediatric inflammatory bowel diseases that may eventually increase the risk of CRC.[19] Site-specific effects have been reported for some of these factors that may selectively promote tumorigenesis proximally (high fat consumption), distally (high consumption of processed meat) or the entire colon albeit not the rectum (obesity and low levels of physical activity).[20] This study confirmed that the increasing trends among those aged 20-29 years was more pronounced for distal colon and rectal tumours– a finding that has also been previously been reported among those aged <50 years in USA.[2]

Obesity has become a global pandemic over the past 40 years and compared to older generations, younger populations across the world may experience longer lasting effect of excess adiposity across their life span.[21] In the U.S., the risk of obesity-related cancer

has been found to be increasing in younger birth cohorts.[21] Young-onset CRC may also be a result of cumulative exposure to excess weight over the lifetime of recent birth cohorts.[22] Moreover, the complex epigenetic interactions between dietary intake and obesity, on the one hand, and CRC risk on the other can be explained when different components of unhealthy diet such as high–glycaemic load carbohydrate are assessed separately.[23] A recent study found that exposure to high-fat and low-fibre diets initiates inflammation and proliferation in the colonic mucosa.[24] The marked alterations in the incidence rates of CRC between generations of Asian immigrants in the U.S. and U.K. suggest that Western dietary and lifestyle factors may play a pivotal role in the aetiology of the disease.[25,26]

In persons aged 50 years and older, we observed a declining incidence of colon and rectal cancer in most of the countries studied, which may be due to interventions leading to removal of adenomatous polyps.[27] In several countries, it is recommended for those aged 50-74 years and older to participate in routine population-based screening activities other than considered at high-risk (e.g. patients with a history of familial polyposis, hereditary nonpolyposis CRC, or ulcerative colitis).[28] The fact that routine screening is largely confined to individuals within this age range may partly explain the age-related disparities in secular trends in CRC incidence rates.

Indeed, where population-based screening has started earlier, for example in Australia, Canada, and the U.K. (2006), observed overall decreases of CRC seem to be more pronounced.[29] On the other hand, in Ireland (2012), Denmark (2014), Norway (only pilot programme, 2012), and New Zealand (2017), where screening started later, rates within the age range of 50-74 years remain more stable.[30] Controversies persist as to the role of screening for sporadic cancers in younger populations. Some studies have identified distinctive tumour sites, more advanced stage at diagnosis and histologic features in young-onset CRC.[31–35] For example, patients below age 50 less often presented with more proximal colon tumours (age < 50 years, 24% vs age 50 years, 43%) and had fewer rectal tumours (age < 50 years, 39% vs age 50 years, 27%).[35] Patients with young-onset CRC were also more likely to present with greater spread of disease, with 22% having distant-stage CRC with worst prognosis, relative to patients with later-onset disease.[36–38] Moreover, poorly differentiated histologic features and mucinous and signet ring cell features are more common in younger-onset disease - characteristics that are also associated with bad prognosis.[39,40]

Furthermore, the proportion of high microsatellite instability (MSI-H) among young CRC cases ranges from 19.7% to 41.0% depending on the age of onset, which has been further associated with poor prognosis.[41] Given the low CRC rates at younger ages, the cost of population screening per life year gained is high and not presently considered cost-effective.[42] Nonetheless, in view of the recent trends, the American Cancer Society adopted screening guidelines recommending CRC screening from the age of 45 years.[43] Multiple studies have reported strong associations of cancer history among first-degree relatives in younger onset CRC.[44] One in every 6 patients with young onset CRC cases has been reported to present with at least one pathogenic cancer susceptibility gene mutation.[45] For example, mismatch repair gene variants linked to Lynch syndrome seems to be much more common than previously reported. As such, screening for genetic susceptibility in primary

care through ascertainment of family history may identify high risk individuals who may require referral.

While the incidence of CRC in adults under age 50 years remains low when compared to older age groups, the observed increases are of clear concern and highlight the need for action to counteract the rising burden of CRC in this age group. Some genetic components may play a role; these however cannot fully explain the rapid changes in cancer incidence we reported here. For this reason, primary prevention is a key course of action, and therefore raising awareness of the public and clinicians with respect to a balanced and healthy diet, and maintenance of an ideal weight and lifestyle from an early age are critical measures to control the future burden. National level programs to promote healthy diets and physical activity might be the most efficient approach to ensure population level changes.[46] In addition, educational and preventive programs that provide information on symptoms and high-risk populations, as well as additional screening for high risk patients with inflammatory bowel disease or a genetic predisposition to CRC, are needed. Further research is warranted to identify the risk factors for young-onset cancer. Finally, development and validation of risk prediction models could aid clinicians to identify the presence of high risk adenomatous polyps in younger populations.[47]

The strengths of this study include the use of high quality and the most up-to-date cancer incidence data, and a comprehensive assessment of time trends in the incidence of CRC by subsite across seven high-income countries. The longer time series in some countries, such as Norway, enabled cohort analyses of those born from 1870 to 1995. Our study also has limitations. The calculation of birth cohorts from period and age may cause a linear dependency between the time components and a non-identifiability of their linear slopes.[16] As the solution presented is entirely dependent on our choice of allocation of the overall time trend (drift), caution should be applied when interpreting the results. We did not have access to individual-level data on risk factors and screening to examine trends of CRC over time across age groups, in relation to temporal changes in those factors.

In conclusion, the rise of colon and rectal cancer incidence rates among young adults is now evident in a number of high-income countries. This is paralleled by ongoing incidence declines in adults older than 50 years. These results highlight the future need for studies that determine the underlying causes for rapidly altering trends and identify potential preventive and early detection strategies that arrest the escalating rates of young-onset colorectal cancer.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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Research in context

Evidence before this study

We searched PubMed for studies containing the terms "young adult", "colorectal cancer", "incidence trends", and "birth cohort" to identify previous studies on colorectal cancer (CRC) incidence with a focus on age- or cohort-specific trends. The final search date for all previous papers published in English was January 03, 2019. Previous studies have shown CRC incidence rates at ages <50 have been rising in the U.S.[1,2] and other high-income countries including Australia,[3] Canada,[4] and Norway.[5] Data from the Surveillance, Epidemiology, and End Results (SEER) database covering the period 2000-2013 showed that U.S. CRC rates decreased at ages >55 years, but increased for younger adults aged 20-54 years (with the steepest rise in adults aged 20-29).[2] The increase in incidence rates was more pronounced for rectal than colon cancer.

Added value of this study

There are currently no other studies that comprehensively address and compare age-specific trends and cohort effects in CRC incidence across high-income countries. In this study, we used long-term data from the high quality population-based cancer registries in Australia, Canada, Denmark, Ireland, New Zealand, Norway, and the U.K. to assess CRC incidence trends by age and period of diagnosis, and by birth cohort. While marked declines or stabilizations in colon and rectal cancer incidence rates were observed for all ages combined and among older ages in all countries, the incidence rates increased among younger age groups (<50 years). Our results confirm that generational effects were more pronounced for rectal than colon cancer in all countries.

Implications of all the available evidence

These findings suggest that the epidemiology of colorectal cancer is changing, with risk increasing in successive generations born towards the end of the 20th century in high-income countries in different world regions. Research into risk factors such as obesity is warranted to identify the main drivers behind the upsurge in colorectal cancer among recent generations. Sustained monitoring of trends is key to successful cancer control as these findings also have important implications for policy and early detection programs. There is an acute need for innovative approaches to promote sustainable and healthy dietary behaviours to reduce obesity.
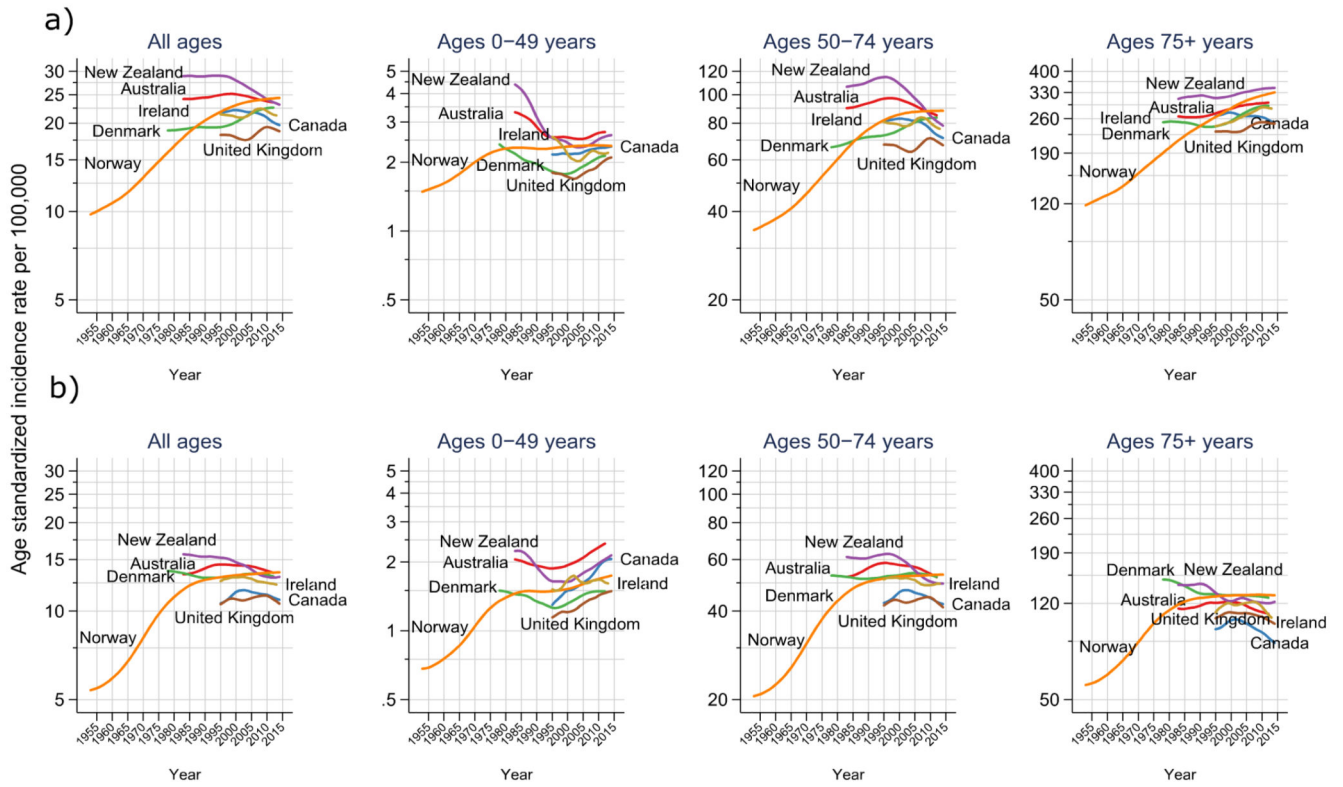
Figure 1.
Long-term trends in age-standardized incidence rates of colon (a) and rectal (b) cancer in four age groups (all ages, 0-49 years, 50-74 years, 75+ years) by country
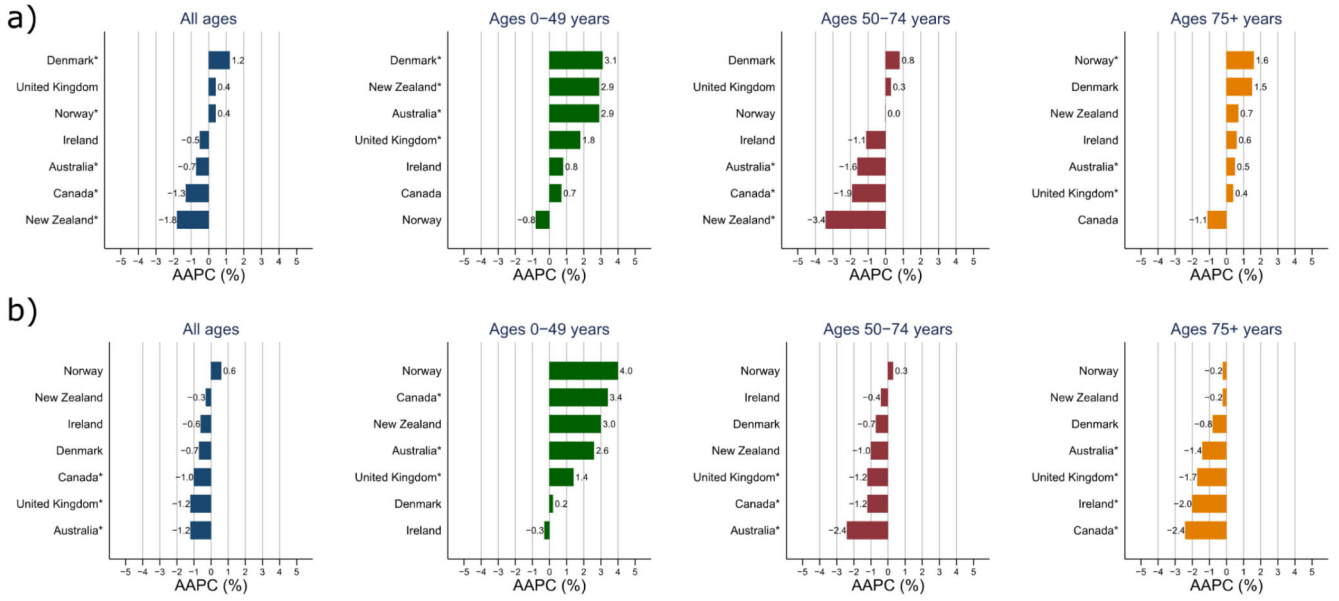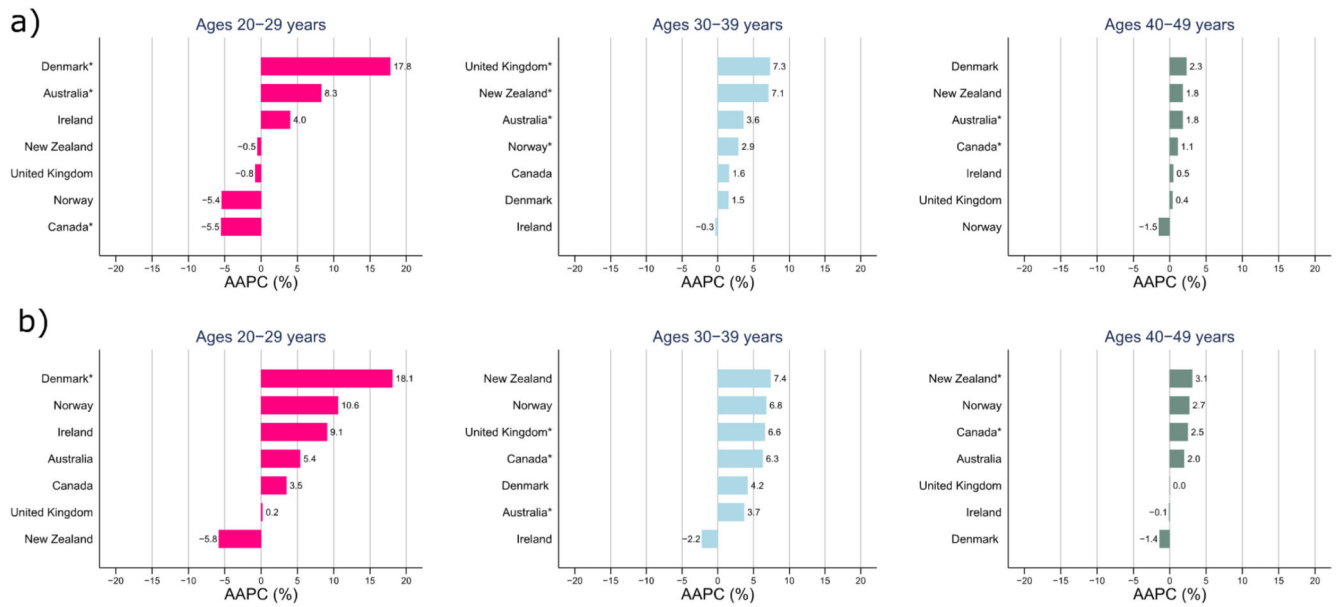
Figure 2.
Average annual percent change (AAPC) in colon (a) and rectal (b) cancer incidence in four age groups (all ages, 0-49 years, 50-74 years, 75+ years) for the most recent 10-year period
*Statistically significant ($p < 0.05$)

Figure 3.
Average annual percent change (AAPC) in colon (a) and rectal (b) cancer incidence in young age groups (20-29 years, 30-39 years, 40-49 years) for the most recent 10-year period
*Statistically significant ($p < 0.05$)

Table 1

Absolute number of cases and age standardised incidence rates (ASIR), by age, cancer site and country of the last five years of the study period[a]

Age groups	Countries	Colon Cancer		Rectal Cancer	
		Cases	ASIR [b]	Cases	ASIR [b]
All ages	Australia	32,875	23·4	16,759	13·4
	Canada	53,450	20·0	26,424	11·0
	Denmark	13,764	22·6	7,343	13·0
	Ireland	7,973	21·6	4,225	12·3
	New Zealand	9,870	23·2	4,945	13·0
	Norway	13,051	24·5	6,460	13·6
	United Kingdom	135,553	19·0	69,684	10·9
0-49 years	Australia	1,851	2·7	1,646	2·3
	Canada	2,913	2·3	2,560	2·0
	Denmark	548	2·1	384	1·4
	Ireland	474	2·2	354	1·6
	New Zealand	517	2·6	426	2·1
	Norway	543	2·3	445	1·9
	United Kingdom	5,963	2·0	4,280	1·4
50-74 years	Australia	16,426	85·0	9,946	52·0
	Canada	27,583	72·8	16,176	42·7
	Denmark	7,359	83·5	4,506	52·1
	Ireland	4,179	78·6	2,580	48·9
	New Zealand	4,730	78·8	2,922	49·4
	Norway	6,295	88·0	3,754	53·1
	United Kingdom	65,253	69·1	39,501	42·7
75+ years	Australia	14,598	301·2	5,167	108·4
	Canada	22,954	256·1	7,688	87·6
	Denmark	5,857	293·9	2,453	125·7
	Ireland	3,320	286·8	1,291	111·5
	New Zealand	4,623	346·7	1,597	121·6
	Norway	6,213	343·4	2,261	129·1
	United Kingdom	64,337	250·0	25,903	102·2

[a]The last five years of the study period: Australia: 2008-2012, Canada: 2010-2014, Denmark: 2008-2012, Ireland: 2009-2013, New Zealand: 2010-2014, Norway: 2010-2014 and United Kingdom: 2010-2014

[b]Age standardised incidence rate using the world population standard per 100,000 (ASIR)