Journal Pre-proof

COLORECTAL CANCER MORTALITY IN YOUNG ADULTS IS RISING IN THE USA, CANADA, UK AND AUSTRALIA, BUT NOT IN EUROPE AND ASIA

Claudia Santucci, Paolo Boffetta, Fabio Levi, Carlo La Vecchia, Eva Negri, Matteo Malvezzi, Collaborators

PII: S0016-5085(21)00010-X
DOI: https://doi.org/10.1053/j.gastro.2020.12.070
Reference: YGAST 64017

To appear in: *Gastroenterology*
Accepted Date: 24 December 2020

Please cite this article as: Santucci C, Boffetta P, Levi F, La Vecchia C, Negri E, Malvezzi M, Collaborators, COLORECTAL CANCER MORTALITY IN YOUNG ADULTS IS RISING IN THE USA, CANADA, UK AND AUSTRALIA, BUT NOT IN EUROPE AND ASIA, *Gastroenterology* (2021), doi: https://doi.org/10.1053/j.gastro.2020.12.070.

COLORECTAL CANCER MORTALITY IN YOUNG ADULTS IS RISING IN THE USA, CANADA, UK AND AUSTRALIA, BUT NOT IN EUROPE AND ASIA

Claudia Santucci[1], Paolo Boffetta[2,3], Fabio Levi[4], Carlo La Vecchia[1], Eva Negri[5], Matteo Malvezzi[1]

Collaborators: Paola Bertuccio[5], Greta Carioli[1]

Affiliations

[1] Department of Clinical Sciences and Community Health, Università degli Studi di Milano, Milan, Italy

[2] Stony Brook Cancer Center, Stony Brook University, Stony Brook, New York, USA

[3] Department of Medical and Surgical Sciences, University of Bologna, Bologna, Italy

[4] Department of Epidemiology and Health Services Research, Centre for Primary Care and Public Health (Unisanté), University of Lausanne, Lausanne, Switzerland.

[5] Department of Biomedical and Clinical Sciences "L. Sacco", Università degli Studi di Milano, Milan, Italy

Correspondence to: Matteo Malvezzi, PhD
Department of Clinical Sciences and Community Health
Università degli Studi di Milano,
Via Augusto Vanzetti 5 – 20122 Milan, Italy
Phone: +39 02 503 20 872; fax: +39 0250320866
e-mail: matteo.malvezzi@unimi.it
Author ORCID: 0000-0002-9110-3923

Funding: This research was funded by the Italian Association for Cancer Research (AIRC), grant number IG 2019 - ID. 22987 project, and by “Ministero dell’Istruzione, dell’Università e della Ricerca” (MIUR) with a Scientific Independence of Young Researchers (SIR) 2014 grant, grant number RBSI1465UH. GC was funded by an AIRC scholarship titled to “Laura Dubini”, grant number 22719.

Credit Authorship Contributions

Malvezzi M (Conceptualization: Lead, Formal analysis: Equal; Investigation: Lead; Methodology: Equal; Writing–original draft: Lead; Writing–review & editing: Equal); La Vecchia C (Conceptualization: equal; Supervision: Lead; Writing–review & editing: equal); Santucci C (Formal analysis: Equal; Writing–review & editing: Equal); Bertuccio P (Data curation: lead; Writing–review & editing: Equal); Carioli G (Writing–review & editing: Supporting); Negri E (Conceptualization: equal; Supervision: equal; Writing–review & editing: supporting); Boffetta P (Conceptualization: equal; Supervision: equal; Writing–review & editing: supporting).; Levi F (Conceptualization: equal; Supervision: equal; Writing–review & editing: supporting).

Conflicts of interest: The authors disclose no conflicts.

Keywords: early onset colorectal cancer; mortality; trends; age period cohort; young adults

INTRODUCTION

Rising trends in incidence from colorectal cancer (CRC) in young adults have been reported in the USA and selected countries of Northern Europe and Austral-Asia; corresponding cohort patterns were observed [1-3]. In this work, we examined trends in CRC mortality between age 25 and 49 from 12 selected high-income countries and the EU.

METHODS

We extracted numbers of official certified deaths at age 25-49 for CRC from 1980 to 2017 (or the last available year), using the WHO database [4]. We selected high-income countries with over 20 million population with reliable mortality coverage and the EU as a whole as defined in 2020 (27 countries).

Using the dataset with certified deaths and resident populations, country, sex and calendar year, we calculated the age-standardized (world standard population) mortality rates per 100,000 person-years.

We carried out a joinpoint regression analysis [5] to calculate Estimated Annual Percent Changes (EAPC) and Average Annual percent Changes (AAPC). To disentangle the effects of age, period of death and cohort of birth, we applied an Age Period Cohort (APC) model. Full methods are in supplementary materials.

RESULTS

Figure 1 (panel A) gives rates in the selected countries. The highest rates in 2015-17 (between 3.8 and 3.4/100,000 in men and 3.2 and 2.8/100,000 in women) were in the USA, Canada, Australia and the UK in both sexes, and Russian women. The USA, Canada, and the UK also showed unfavourable trends between 2005 and 2017 in both sexes, Australia only in men; in the same countries AAPCs were between 1.5% and 0.7% in men and between 1.6% and 1.1% in women. All other countries show lower rates in both sexes and favourable or stable trends over the most recent decade.

Considering the whole 1980-2017 period (**Figure 1** panel B and **Supplementary Table 1**), the overall mortality trends were favourable in all included countries in both sexes, except for USA and Korea where they were stable. In men, the AAPCs ranged between -0.2% in the USA and Korea and -1.6% in France, Germany and Italy, while in women the AAPCs ranged from -0.1% in Korea to -2.2% in Australia.

Joinpoint modelling identified significant rising trends for recent calendar years in the USA and Canada in both sexes and the UK women in the 2000s with EAPCs between 1.1 and 2.6%. There was also a rising trend in Australian men (1.9%). In Germany and the EU in both sexes and UK and Japanese men, there was a flattening of the previous favourable trends in the 2000s.

APC (**Figure 1** panel C) shows favourable period effects over the most recent quinquennia in all countries and both sexes, except for Russia and Poland, and UK women which had a plateau after the declining trends seen until the early 2000s. A common cohort pattern with descending effects up to those born in the 1950s or 1960s, with a trough and a subsequent rise in effects, was observed in the USA in both sexes, and in men in Canada and Australia. In women in Canada, France, Germany, Australia, UK and EU, effects either reached a plateau or a slowdown in the falling trend. The remaining examined countries displayed declining risks for successive recent cohorts.

DISCUSSION

In recent years trends in incidence for CRC in young adults have been rising in the USA, and selected European and Asian countries [1-3]. In particular rises in CRC cancer incidence under the age of 50 were recorded since the 1990s in both males and females in the USA and a cohort pattern showed that recent cohorts of birth shared the same risk of developing CRC as those born in 1890; a similar pattern was also seen in Canada [1, 6]. In the EU, rises in incidence were reported for young adults aged 20 to 39 years in France, Germany, Poland and the UK, but not Italy [3].

This mortality analysis confirms the trends reported for incidence in the USA and Canada, and to a lesser degree in the UK particularly in women and Australia mainly in males. Rising cohort patterns observed in incidence [1, 3, 6] are confirmed by mortality data for the USA, and to a lesser degree Canada, Australia and limited to the last few cohorts in France and UK, only in men. Although a comparison of incidence and mortality analyses should take into account the lag between the two indicators (estimated in 5-10 years), our results suggest that the increase in incidence in the young include also advanced and aggressive CRC, at least in countries that showed the strongest trend in incidence.

Overweight and obesity are recognized risk factors for colorectal cancer and the prevalence patterns recorded in the studied countries are coherent to the recorded CRC mortality trends; the USA, Canada, Australia and UK are the countries examined with the highest and fastest rising prevalences in overweight/obesity [7]. Alcohol is also confirmed risk factor in early onset colorectal cancer, and among the countries that did not display a rising trend in mortality from these neoplasms, France and Italy had the greatest fall in total alcohol consumption since at least the 1960s with Germany and Spain showing similar falls in consumption since the 1980s, Canada and the USA did not have these falls in consumption[8].

As a result of these rising trends in incidence in young onset colorectal cancer, the American Cancer Association updated its guidelines on screening, recommending that subjects at average risk should start screening at 45 years instead of 50. In Europe, screening programs have mostly been implemented from the early 2000s, differently from the USA where they have been recommended since the 1980s.

In conclusion, the rising trends in young adult colorectal cancer are confirmed by mortality data in the USA, Canada, Australia and the UK, but not in other selected countries. Due to their cohort nature, a smaller increase in overweight and obesity and declining alcohol drinking in some European countries may, at least in part explain the observed trends [7, 8].

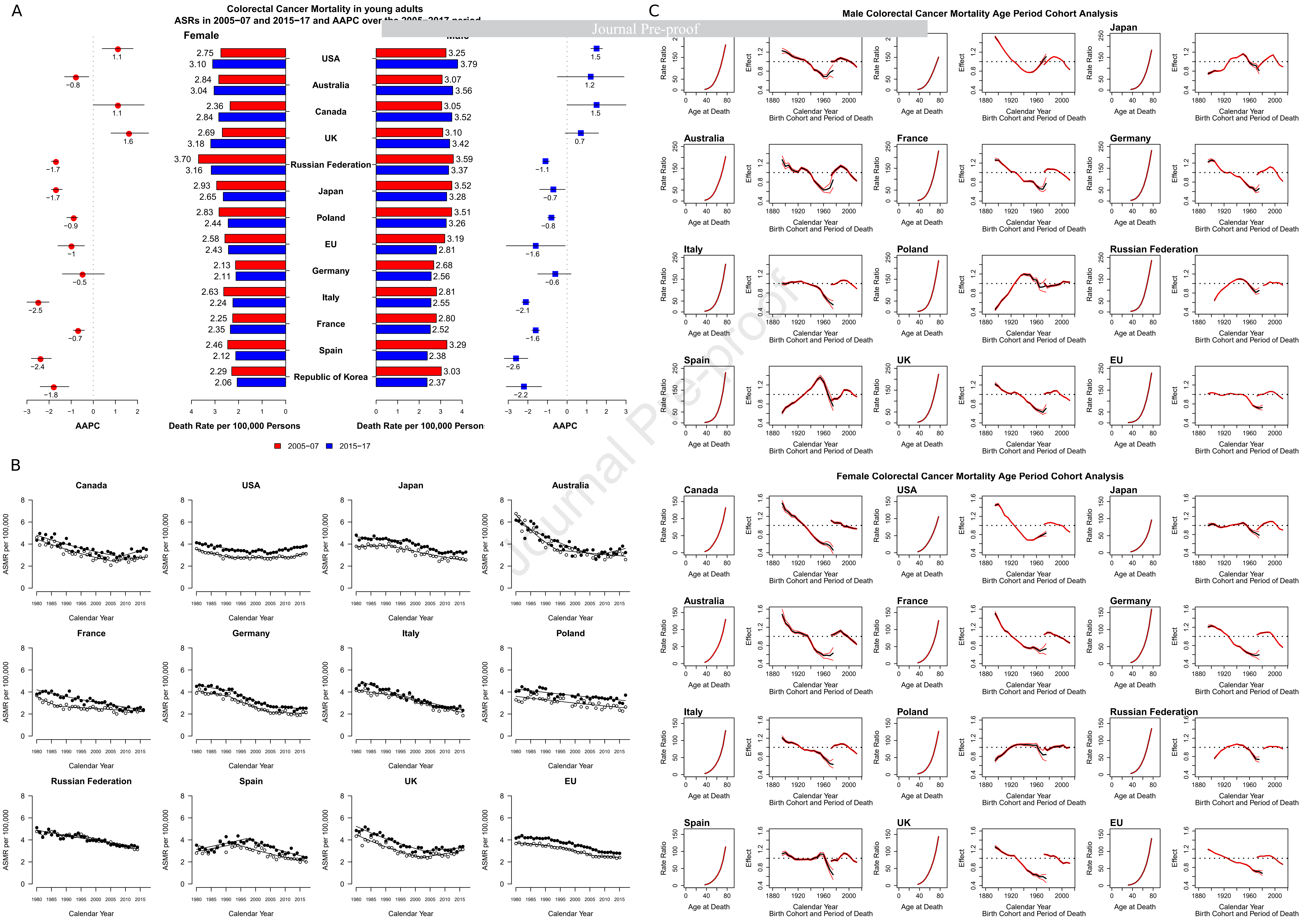
REFERENCES

1. Siegel RL, Fedewa SA, Anderson WF, et al. Colorectal Cancer Incidence Patterns in the United States, 1974-2013. J Natl Cancer Inst 2017;109.
2. Sung JJY, Chiu HM, Jung KW, et al. Increasing Trend in Young-Onset Colorectal Cancer in Asia: More Cancers in Men and More Rectal Cancers. Am J Gastroenterol 2019;114:322-329.
3. Vuik FE, Nieuwenburg SA, Bardou M, et al. Increasing incidence of colorectal cancer in young adults in Europe over the last 25 years. Gut 2019;68:1820-1826.
4. World Health Organization Statistical Information System. WHO mortality database: Estimated coverage of mortality data. Geneva: World Health Organization. Available at: https://wwwwhoint/healthinfo/statistics/mortality_rawdata/en/ (Last accessed August 2020).
5. National Cancer Institute. Joinpoint Regression Program, version 4.1. Volume 2015.
6. Heer EV, Harper AS, Sung H, et al. Emerging cancer incidence trends in Canada: The growing burden of young adult cancers. Cancer 2020.
7. Collaborators GBDO, Afshin A, Forouzanfar MH, et al. Health Effects of Overweight and Obesity in 195 Countries over 25 Years. N Engl J Med 2017;377:13-27.
8. Holmes AJ, Anderson K. Convergence in National Alcohol Consumption Patterns: New Global Indicators. Journal of Wine Economics 2017;12:117-148.

Author names in bold designate shared co-first authorship.

FIGURE LEGENDS

Figure 1 (panel A) Bar plots of male and female age-standardized mortality rates from colorectal cancer among young adults aged 25-49 years per 100,000, in 12 countries and the EU as a whole, in 2005-2007 (red) and 2015-2017 (blue), and the corresponding AAPC (males in blue and females in red, with 95% confidence intervals) for the period from 2005 to the most recent available year. (Panel B) Trends in age-standardised (25-49 years) mortality rates for colorectal cancer (males: full circles, females: empty circles) and corresponding joinpoint models (lines) for 11 selected countries and the EU as a whole, over the period 1980-2017. (Panel C) APC analysis of colorectal cancer mortality (top panel: men, bottom panel: women) in 11 selected high-income countries worldwide and the EU as a whole. Age estimates are expressed as average age-specific (35-39 to 75-79 years) mortality rates per 100,000 persons; birth cohort (1890-99 to 1970-89) and period of death (1970-74 to 2010-14) effect estimates are expressed as relative multiplicative effects against their weighted average set to unity. Effect estimates are in black, approximate 95% confidence interval limits in red.


A
Colorectal Cancer Mortality in young adults
ASRs in 2005−07 and 2015−17 and AAPC over the 2005−2017 period
Female
Male
USA
Australia
Canada
UK
Russian Federation
Japan
Poland
EU
Germany
Italy
France
Spain
Republic of Korea
2.75
3.10
2.84
3.04
2.36
2.84
2.69
3.18
3.70
3.16
2.93
2.65
2.83
2.44
2.58
2.43
2.13
2.11
2.63
2.24
2.25
2.35
2.46
2.12
2.29
2.06
3.25
3.79
3.07
3.56
3.05
3.52
3.10
3.42
3.59
3.37
3.52
3.28
3.51
3.26
3.19
2.81
2.68
2.56
2.81
2.55
2.80
2.52
3.29
2.38
3.03
2.37
1.1
−0.8
1.1
1.6
−1.7
−1.7
−0.9
−1
−0.5
−2.5
−0.7
−2.4
−1.8
1.5
1.2
1.5
0.7
−1.1
−0.7
−0.8
−1.6
−0.6
−2.1
−1.6
−2.6
−2.2
AAPC
Death Rate per 100,000 Persons
Death Rate per 100,000 Persons
AAPC
2005−07
2015−17
B
Canada
USA
Japan
Australia
France
Germany
Italy
Poland
Russian Federation
Spain
UK
EU
ASMR per 100,000
Calendar Year
C
Male Colorectal Cancer Mortality Age Period Cohort Analysis
Female Colorectal Cancer Mortality Age Period Cohort Analysis
Canada
USA
Japan
Australia
France
Germany
Italy
Poland
Russian Federation
Spain
UK
EU
Rate Ratio
Age at Death
Effect
Calendar Year
Birth Cohort and Period of Death

SUPPLEMENTARY METHODS

We extracted numbers of official certified deaths at age 25-49 years for colorectal cancers (according to the 10th Revision of the International Classification of Disease [1], ICD-10 codes: C17-C21 and C26) considered all together, in selected countries worldwide, since 1980 up to 2017 (or the last available year), using the WHO database [2].

From the same WHO database [2], we also extracted estimates of the resident populations, based on official censuses, for all countries considered except for the USA and Canada, for which we retrieved data from the Pan American Health Organization (PAHO) [3].

We selected high income countries with over 20 million population analysed data for 12 high income countries with reliable mortality coverage (Canada, the USA, Japan, Korea, Australia, France, Germany, Italy, Poland, the Russian Federation, Spain, and the UK) and the EU as a whole (as defined in 2020 without the UK).

Using the dataset with certified deaths and resident populations, country, sex and calendar year, we derived age-specific rates for five age groups (25-29, 30-34, 35-39, 40-44, 45-49 years), and calculated the age-standardized mortality rates per 100,000 person-years, using the world standard population [4].

We carried out a joinpoint regression analysis [5] over the period 1980-2017. We thus identified the time point(s), called 'joinpoints', when a change in the linear slope (on a log scale) of the temporal trend occurred, by testing from zero up to a maximum of four joinpoints. As a summary measure, we also obtained the estimated annual percent change (EAPC) for each identified linear segment, and the weighted average EAPC (AAPC) over the entire study period [6, 7].

To disentangle the effects of age, period of death and cohort of birth, we applied an age period cohort (APC) model to quinquennial age-standardized rates from 1970-74 to 2010-14. Age groups were limited to those between 35 (35-39 years) and 79 (75-79 years) years.

Cohorts were defined according to their central year of birth, hence the earliest possible cohort is that of 1895 corresponding to 75-79 year olds who died in the 1970-74 quinquennium. The age effects are interpretable as mean age-specific death rates per 100,000 persons over the analysed period, the period and cohort effects are expressed in relative terms against their weighted average set to unity [8, 9].

No ethics committee approval was necessary because we only considered public data. For all statistical analyses, we used the software R version 3.4.1 (R Development Core Team, 2017), in particular, the package "apc" [8], SAS version 9.4 (SAS Institute Inc., Cary, NC, USA), SEER*Stat (seer.cancer.gov/seerstat) version 8.3.6, and Joinpoint Regression Program version 4.11.

SUPPLEMENTARY REFERENCES

1. World Health Organization. International Statistical Classification of Disease and related Health Problems: 10th revision. Geneva: World Health Organization, 1992.
2. World Health Organization Statistical Information System. WHO mortality database: Estimated coverage of mortality data. Geneva: World Health Organization. Available at: https://wwwwhoint/healthinfo/statistics/mortality_rawdata/en/ (Last accessed August 2020).
3. Pan American Health Organization (PAHO).Health Information Platform for the Americas. Available at: http://wwwpahoorg/data/indexphp/en/indicators/demographics-core/308-poblacion-nac-enhtml (Last accessed August 2020).
4. Doll R, Smith PG. Comparison between registries: age-standardized rates. Vol. IV. IARC Sci Publ No. 42. In: Waterhouse JAH, Muir CS, Shanmugaratnam K, Powell J, Peacham D, Whelan S, eds. Cancer Incidence in Five Continents. Lyon: IARC, 1982:671-675.
5. National Cancer Institute. Joinpoint Regression Program, version 4.1. Volume 2015.
6. Kim HJ, Fay MP, Feuer EJ, et al. Permutation tests for joinpoint regression with applications to cancer rates. Stat Med 2000;19:335-51.
7. Clegg LX, Hankey BF, Tiwari R, et al. Estimating average annual per cent change in trend analysis. Stat Med 2009;28:3670-82.
8. Decarli A, Vecchia CL, Malvezzi M, et al. An R package for fitting age, period and cohort models. Epidemiology, Biostatistics and Public Health 2014;11 doi 10.2427/9977.
9. Malvezzi M, Bertuccio P, Edefonti V. Age Period Cohort Analysis of Cancer Mortality Data: Methods and Application to Italian Male Mortality Data for Gastric Cancer and Cancers of the Oral Cavity and Pharynx. BMSCE 2009;3:97-105.

Supplementary Table 1. Joinpoint analysis for colorectal cancer in young adults aged 25-49 years, from 1980 to 2017 (according to data availability), by country and sex.

	Males									Females										
Country	**Years**	**EAPC1**	**Years**	**EAPC2**	**Years**	**EAPC3**	**Years**	**EAPC4**	**AAPC**	**Years**	**EAPC1**	**Years**	**EAPC2**	**Years**	**EAPC3**	**Years**	**EAPC4**	**Years**	**EAPC5**	**AAPC**
Canada	1980-2008	-1.8*	2008-2017	2.6*					-0.8*	1980-2005	-2.3*	2005-2017	1.1*							-1.2*
USA	1980-1998	-1.3*	1998-2001	2.8	2001-2004	-3.2	2004-2017	1.5*	-0.2	1980-1992	-2*	1992-2012	0.1	2012-2017	2.6*					-0.3
Japan	1980-1998	-0.5*	1998-2009	-2.4*	2009-2017	0.2			-0.9*	1980-1991	0.2	1991-2017	-1.7*							-1.1*
Republic of Korea	1985-2001	1.9*	2001-2017	-2.2*					-0.2	1985-1997	2.8*	1997-2017	-1.8*							-0.1
Australia	1980-2007	-2.6*	2007-2017	1.9					-1.4*	1980-1994	-4.6*	1994-2017	-0.8*							-2.2*
France	1980-2016	-1.6*							-1.6*	1980-1987	-3.9*	1987-2016	-0.7*							-1.3*
Germany	1980-1992	-1.1*	1992-2006	-3.1*	2006-2017	-0.4			-1.6*	1980-1991	-1.1*	1991-2005	-3.6*	2005-2017	-0.5					-1.8*
Italy	1980-1982	6.5	1982-2016	-2.1*					-1.6*	1980-1996	-1*	1996-2016	-2.5*							-1.9*
Poland	1980-2017	-0.8*							-0.8*	1980-2017	-0.9*									-0.9*
Russian Federation	1980-2014	-1.1*							-1.1*	1980-1982	-5*	1982-1985	3.5	1985-1988	-3.4	1988-1995	0.1	1995-2014	-1.7*	-1.2*
Spain	1980-1997	1.6*	1997-2017	-2.6*					-0.7*	1980-1993	1.7*	1993-2017	-2.4*							-1*
UK	1980-2003	-2.4*	2003-2016	0.7					-1.3*	1980-2002	-2.8*	2002-2016	1.6*							-1.1*
EU	1980-1991	-0.4*	1991-2005	-1.6*	2005-2008	-3.7	2008-2015	-0.7*	-1.2*	1980-1995	-0.8*	1995-2007	-2.3*	2007-2015	-0.6					-1.3*

EAPC: estimated annual percent change. *Significantly different from 0 ($p<0.05$)