Colorectal cancer incidence, mortality, and stage distribution in European countries in the colorectal cancer screening era: an international population-based study

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Summary

Background Colorectal cancer screening programmes and uptake vary substantially across Europe. We aimed to compare changes over time in colorectal cancer incidence, mortality, and stage distribution in relation to colorectal cancer screening implementation in European countries.

Methods Data from nearly 3·1 million patients with colorectal cancer diagnosed from 2000 onwards (up to 2016 for most countries) were obtained from 21 European countries, and were used to analyse changes over time in age-standardised colorectal cancer incidence and stage distribution. The WHO mortality database was used to analyse changes over time in age-standardised colorectal cancer mortality over the same period for the 16 countries with nationwide data. Incidence rates were calculated for all sites of the colon and rectum combined, as well as the subsites proximal colon, distal colon, and rectum. Average annual percentage changes (AAPCs) in incidence and mortality were estimated and relevant patterns were descriptively analysed.

Findings In countries with long-standing programmes of screening colonoscopy and faecal tests (ie, Austria, the Czech Republic, and Germany), colorectal cancer incidence decreased substantially over time, with AAPCs ranging from –2·5% (95% CI –2·8 to –2·2) to –1·6% (–2·0 to –1·2) in men and from –2·4% (–2·7 to –2·1) to –1·3% (–1·7 to –0·9) in women. In countries where screening programmes were implemented during the study period, age-standardised colorectal cancer incidence either remained stable or increased up to the year screening was implemented. AAPCs for these countries ranged from –0·2% (95% CI –1·4 to 1·0) to 1·5% (1·1 to 1·8) in men and from –0·5% (–1·7 to 0·6) to 1·2% (0·8 to 1·5) in women. Where high screening coverage and uptake were rapidly achieved (ie, Denmark, the Netherlands, and Slovenia), age-standardised incidence rates initially increased but then subsequently decreased. Conversely, colorectal cancer incidence increased in most countries where no large-scale screening programmes were available (eg, Bulgaria, Estonia, Norway, and Ukraine), with AAPCs ranging from 0·3% (95% CI 0·1 to 0·5) to 1·9% (1·2 to 2·6) in men and from 0·6% (0·4 to 0·8) to 1·1% (0·8 to 1·4) in women. The largest decreases in colorectal cancer mortality were seen in countries with long-standing screening programmes.

Interpretation We observed divergent trends in colorectal cancer incidence, mortality, and stage distribution across European countries, which appear to be largely explained by different levels of colorectal cancer screening implementation.

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Introduction

Colorectal cancer was estimated to be the second most commonly diagnosed cancer and the second leading cause of cancer death in Europe in 2020, with nearly 520 000 new cases and 245 000 deaths.[1] A large proportion of these cancers are, however, highly preventable. A study in nine European countries found that nearly 20% of colorectal cancer cases were attributable to not adhering to various healthy lifestyle recommendations—namely, having a healthy weight, having high physical activity levels, not smoking, and having low alcohol consumption.[2] In addition to large opportunities for primary prevention by tackling these modifiable risk factors, the long time for development of most colorectal cancers (10–15 years) allows for detection and removal of precancerous lesions and early-stage cancers that can be

Research in context

Evidence before this study

We searched PubMed for studies published up to Sept 25, 2020, reporting changes over time in colorectal cancer incidence, mortality, and stage distribution, as well as colorectal cancer screening strategies in European countries, using the search terms [("incidence" OR "mortality" OR "stage" OR "screening") AND ("colon cancer" OR "rectal cancer" OR "colorectal cancer") AND "Europe*"]. In the past two decades, colorectal cancer screening programmes have started to be extensively implemented in European countries, with large heterogeneity of screening programmes and uptake rates. Previous studies have found large differences in colorectal cancer incidence and mortality trends across European countries, which have been analysed in relation to geographical location and human development levels. Several studies have suggested that differences in access to screening and treatment could help to explain such discrepancies.

Added value of this study

To our knowledge, this is the first study to provide a comprehensive overview and a comparative analysis of the changes in colorectal cancer burden in relation to colorectal cancer screening implementation in European countries, by jointly looking at colorectal cancer incidence, mortality, and stage distribution. We used high-quality population-based data from 21 countries, which allowed us to study changes over time across all European geographical areas, with differing levels of colorectal cancer screening implementation. Furthermore, our detailed analyses of incidence and stage distribution for cancers in the proximal colon, distal colon, and rectum provide insights into potential varying effects of screening by tumour subsite.

Implications of all the available evidence

Our study suggests that the large differences in the colorectal cancer burden across European countries are largely explained by different levels of colorectal cancer screening implementation. While our results are encouraging for countries with screening programmes to maintain and further advance colorectal cancer screening efforts, the limited or lack of progress against colorectal cancer in countries with no screening programmes strongly calls for their implementation. Furthermore, our study shows large potential for achieving even larger reductions in colorectal cancer incidence and mortality in the future through screening if improvements in the detection of precancerous lesions in the proximal colon could be achieved.

successfully treated.[3] Indeed, during the past three decades, several screening tools have been shown to have the potential to considerably reduce colorectal cancer incidence and mortality. These include faecal occult blood tests[4] (faecal immunochemical tests [FITs], currently the most widely used tests, given their better diagnostic performance and acceptance than the traditional guaiac-based faecal occult blood tests [gFOBTs]),[5] flexible sigmoidoscopy,[6–10] and colonoscopy.[7] Based on this evidence, many European countries started to implement colorectal cancer screening programmes targeting the average-risk population (mostly people in the age range 50–74 years).[11] However, the screening strategies vary considerably across countries in timing of implementation, type of screening offered (organised *vs* opportunistic), and primary screening tests, as well as uptake rates.[12] Such heterogeneity of programmes and uptake is likely to result in large differences in colorectal cancer burden across countries.

This study aimed to analyse changes over time in colorectal cancer incidence, stage distribution, and mortality in the first two decades of the 21st century with respect to the colorectal cancer screening programmes that have been implemented in European countries. We placed special focus on potential differences between cancers in the proximal colon, distal colon, and rectum, given suggestions of lower effectiveness of colorectal cancer screening in detecting and removing precancerous lesions at colonoscopy in the proximal colon than in the distal colon and rectum.[7]

Methods

Study design and data sources

In this population-based study, data from 3 078 218 cases of colorectal cancer (codes C18–C20 in the International Classification of Diseases 10th revision [ICD-10]) were obtained from 31 population-based cancer registries in 21 European countries to analyse changes over time in colorectal cancer incidence and stage distribution. Patients were diagnosed from the year 2000 (or the earliest year with available data after 2000) up to the most recent year with available data at the time of analysis (which was 2016 for most countries). Out of the 21 countries, nationwide data were obtained for 16 countries and regional data for five countries. Information on data sources and data quality indicators are provided in the appendix (pp 3–4). The data included patient-level and tumour-level characteristics—namely, sex, year of diagnosis, age at diagnosis, topography, morphology, and, if available, clinical and pathological tumour, node, and metastasis (TNM) information according to the TNM Classification of Malignant Tumours edition in place at the time of diagnosis. Inclusion of colorectal cancer cases followed the International Agency for Research on Cancer and International Association of Cancer Registries rules for reporting multiple primary cancers.[13]

For the 16 countries with nationwide cancer registry data, annual numbers of colorectal cancer deaths were obtained from the WHO mortality database to analyse changes over time in colorectal cancer mortality.[14] Data

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	Years	Cases included in analyses of incidence*	Cases of overlapping or unspecified neoplasms of the colon	Cases with unclassified or unknown stage	Cases included in analyses of stage distribution
Austria	2000–16	81 052	17 293 (21·3%)	15 334	65 718 (81·1%)
Belgium	2004–16	103 521	4234 (4·1%)	10 206	93 315 (90·1%)
Bulgaria	2000–13	60 129	3849 (6·4%)	8051	52 078 (86·6%)
Czech Republic	2000–17	132 917	5532 (4·2%)	12 265	120 652 (90·8%)
Denmark	2002–18	65 211	2113 (3·2%)	7277	57 934 (88·8%)
England	2000–17	578 725	43 253 (7·5%)	27 136†	182 169 (87·0%)†
Estonia	2000–16	13 392	318 (2·4%)	1571	11 821 (88·3%)
Finland	2000–16	45 542	3354 (7·4%)	8055†	34 099 (80·9%)†
France (five regions)	2000–16	45 243	656 (1·4%)	3728†	40 472 (91·6%)†
Burgundy‡	2000–16	12 260	88 (0·7%)	768	11 492 (93·7%)
Calvados	2000–16	6410	144 (2·2%)	610	5800 (90·5%)
Doubs	2000–16	4980	188 (3·8%)	313†	3624 (92·0%)†
Finistere	2000–16	10 602	101 (1·0%)	825	9777 (92·2%)
Isere	2000–16	10 991	135 (1·2%)	1212	9779 (89·0%)
Germany	2000–16	1 080 703§	110 659 (10·2%)§	381 898	435 940 (53·3%)
Ireland	2000–16	38 944	2214 (5·7%)	12 115	26 829 (68·9%)
Italy					
Turin¶	2000–14	11 842	1714 (14·5%)	..	..
Lithuania	2000–12	19 857	1005 (5·1%)	..	..
Netherlands‖	2000–16	206 227	5224 (2·5%)	9008	197 219 (95·6%)
Norway	2000–17	67 992	2598 (3·8%)	5389	62 603 (91·1%)
Portugal**					
North region	2003–12	22 273	4442 (19·9%)	9865	12 408 (55·7%)
South region	2000–16	56 722	12 416 (21·9%)	20 783	35 939 (63·4%)
Slovenia	2000–15	21 878	373 (1·7%)	1835†	16 603 (90·0%)†
Spain					
Basque country	2000–15	29 605	1613 (5·4%)	1572†	11 405 (87·9%)†
Girona	2000–16	8471	1565 (18·5%)	1848†	5808 (75·9%)†
Murcia	2000–12	10 050	1285 (12·8%)	1335†	4531 (77·2%)†
Tarragona††	2000–14	8300	1142 (13·8%)	2606†	3359 (56·3%)†
Sweden	2000–16	102 885	7882 (7·7%)	20 964†	60 023 (74·1%)†
Switzerland					
Bern	2014–16	1884	126 (6·7%)	116	1768 (93·8%)
Eastern and Graubünden-Glarus	2000–16	8020	176 (2·2%)	612	7408 (92·4%)
Ukraine‡‡	2000–16	256 650	12 624 (4·9%)	15 529	241 121 (93·9%)

IARC/IACR=International Agency for Research on Cancer and International Association of Cancer Registries. *Malignant cases according to the international rules for reporting data on cancer incidence and survival of the International Rules for Multiple Primary Cancers (International Classification of Diseases for Oncology, third edition). The exception was England, which reports tumours with different morphology codes at the third digit level as multiple primary ones instead of using the IARC/IACR morphology groups. †Countries or regions for which data on stage were available for only a subset of years (ie, years with >40% of cases with known stage). Years with data were England: 2012–17; Finland: 2000–15; France (Doubs): 2004–16; Slovenia: 2003–15; Spain (Basque country): 2010–15; Spain (Girona): 2002–16; Spain (Murcia): 2006–12; Spain (Tarragona): 2005–14; Sweden: 2004–16. ‡Burgundy comprises the regions Cote-d'Or and Saone-et-Loire. §For Germany, national estimates of colorectal cancer cases diagnosed in 2000–16 were provided by the German Centre for Cancer Registry Data. ¶For Italy (Turin), there was one case with missing data on age at diagnosis that was not considered in the analysis. ‖For the Netherlands, there was one case with missing data on sex that was not considered in the analysis. **For Portugal, there were 175 cases in the northern region and two cases in the southern region with missing data or inconsistent (negative) age at diagnosis that were not considered in the analysis. ††For Spain (Tarragona), there were four cases with missing data on age at diagnosis that were not considered in the analysis. ‡‡For Ukraine, data from the regions Crimea, Donetsk, and Luhansk were not included.

Table 1: **Number of colorectal cancer cases included in analyses of incidence and stage distribution by country or region**

were also extracted from 2000 (or the earliest year with available data after 2000) up to the most recent year with available data at the time of analysis (which was 2017 for most countries), by year, sex, and 5-year age group. Colorectal cancer deaths were considered as those registered with ICD-10 codes C18–C20. Population data were obtained from the national statistical offices of each country or region by year, sex, and 5-year age group (appendix pp 3–4).

To analyse changes over time with respect to colorectal cancer screening implementation, we collected and summarised relevant characteristics of all colorectal cancer screening strategies and uptake rates in the included countries and regions, which were categorised according to timing of implementation (appendix p 1).

This study was approved by the Ethics Committee of the Medical Faculty of the University of Heidelberg (S-84/2019).

Statistical analysis

We calculated age-standardised colorectal cancer incidence and mortality rates (expressed per 100 000 people) in men and women for each country or region and for each calendar year using the 1976 European Standard Population.[15] Average annual percentage changes (AAPCs) for the entire period of investigation were determined by regression analyses defining a best-fitting regression line through the data (appendix p 2).

Incidence rates were calculated for all sites of the colon and rectum combined (C18–C20) and for the subsites proximal colon (caecum to transverse colon, C18·0–C18·4), distal colon (splenic flexure to sigmoid colon, C18·5–C18·7), and rectum (rectosigmoid junction and rectum, C19–C20). Cases of overlapping and unspecific neoplasms of the colon (C18·8–C18·9) were proportionally distributed among proximal and distal colon cancer cases based on the ratio (C18·0–C18·4)/(C18·5–C18·7), by year, sex, and 5-year age group.

Stages I, II, III, and IV were derived from the pathological and clinical TNM information. For Austria, Finland, and Norway, stage at diagnosis had been recorded into slightly different categories and was analysed on the basis of such categorisation (appendix p 1). Cases with unknown stage were excluded from stage-specific analyses, as were the calendar years for which more than 60% of cases did not have complete staging information. Changes over time in stage distribution were descriptively analysed for all colorectal cancer sites combined and by subsite.

Age-specific analyses (0–49, 50–59, 60–69, 70–74, and ≥75 years) were additionally done for all 16 countries for which we had nationwide cancer registry data. We chose these age cutoffs because most colorectal cancer screening programmes in the included countries targeted individuals aged 50–74, 50–69, or 60–69 years.

All statistical analyses were done using SAS version 9.4, except for estimating AAPCs, for which we used the

Joinpoint regression software (version 4.7.0.0) provided by the US National Cancer Institute. Further details on country-specific data and analyses are provided in the appendix (pp 1–2).

Role of the funding source

The sponsor had no role in the study design, data collection, data analysis, interpretation of data, writing of the report, or the decision to submit the paper for publication.

Results

Numbers of colorectal cancer cases included in the analyses are provided in table 1. The relevant characteristics of the colorectal cancer screening strategies and uptake rates in the included countries and regions are shown in table 2 and the appendix (pp 5–6). In countries with long-standing nationwide offers of colonoscopy and faecal tests and more than half of the eligible population up to date with screening—ie, Austria, the Czech Republic, and Germany—age-standardised colorectal cancer incidence rates decreased significantly over time, with AAPCs ranging from –2·5% (95% CI –2·8 to –2·2) to –1·6% (–2·0 to –1·2) in men and from –2·4% (–2·7 to –2·1) to –1·3% (–1·7 to –0·9) in women (figure 1A; table 3). In England and Finland, which also had long-standing screening (gFOBT-based programmes), age-standardised colorectal cancer incidence remained stable or rose during the study period (figure 1A; table 3). In countries where nationwide screening

	Year of programme initiation and termination (if applicable)	Age group, years	Screening interval, years	Percentage of the eligible population who have undergone either a faecal test within 2 years or colonoscopy within 10 years*	Participation rates for organised programmes (year of data collection)
Countries with earlier screening implementation					
Austria†	..	..	..	68·8%	..
gFOBT (opportunistic)	1980	≥40	1	..	NA
Colonoscopy (opportunistic)	2005	≥50	7–10	..	NA
Czech Republic‡	..	..	..	53·5%	..
gFOBT (opportunistic)	2000–09	≥50	2	..	NA
FIT (opportunistic)	2009	50–54	1	..	NA
FIT or colonoscopy (opportunistic)	2009	≥55	2 (FIT), 10 (colonoscopy)	..	NA
FIT or colonoscopy (organised)	2014	50–70	2 (FIT), 10 (colonoscopy)	..	45·2% (FIT) and 54·6% (FIT or colonoscopy; 2016)§
England	..	..	..	66·7%¶	..
gFOBT (organised)	2006–10	60–69	2	..	55·3% (2013)
gFOBT (organised)	2010–19	60–74‖	2	..	Included in above rate
FIT (organised)	2019	60–74‖	2	..	No information
Sigmoidoscopy (organised)	2013–21	55	Once only	..	43·1% (2013–14)
Finland**	..	..	..	34·8%	..
gFOBT (organised)	2004–16	60–69	2	..	66·6% (2014)
FIT (organised)	2019	60–66	2	..	No information
Germany	..	..	..	70·9%	..
gFOBT (opportunistic)	1977–2002	≥45	1	..	NA
gFOBT (opportunistic)	2002–17	50–54	1	..	NA
FIT (opportunistic)	2017	50–54	1	..	NA
gFOBT or colonoscopy (opportunistic)	2002–17	≥55	2 (gFOBT), 10 (colonoscopy; maximum two colonoscopies)	..	NA
FIT or colonoscopy (opportunistic)	2017	≥55	2 (FIT), 10 (colonoscopy; maximum two colonoscopies)	..	NA
FIT (organised)	2019	50–54, ≥55	1 (50–54 years), 2 (≥55 years)	..	No information
Colonoscopy (organised)	2019	≥50 (men), ≥55 (women)	10 (up to two colonoscopies)	..	No information

(Table 2 continues on next page)

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See Online for appendix

For more on the **Joinpoint regression software** see https://surveillance.cancer.gov/joinpoint

	Year of programme initiation and termination (if applicable)	Age group, years	Screening interval, years	Percentage of the eligible population who have undergone either a faecal test within 2 years or colonoscopy within 10 years*	Participation rates for organised programmes (year of data collection)
(Continued from previous page)					
Countries with later screening implementation					
Belgium††	..	..	..	32·7%	..
Wallonia and Brussels					
gFOBT (organised)	2009–2016	50–74	2	..	4·5% (2014)
FIT (organised)	2016	50–74	2	..	No information
Flanders					
FIT (organised)	2013–2014	66–74	2	..	50·3% (2014)
FIT (organised)	2014	56–74	2	..	Included in above rate
Denmark	..	..	..	47·0%	..
FIT (organised)	2014	50–74	2	..	62·6% (2014–16)
Ireland	..	..	..	42·7%	..
FIT (organised)	2012	60–69	2	..	43·1% (2013)
Lithuania	..	..	..	27·7%	..
FIT (organised)	2009‡‡	50–74	2	..	46·0% (2009–12)
Netherlands	..	..	..	24·9%§§	..
FIT (organised)	2014	55–75¶¶	2	..	71·3% (2014)
Slovenia	..	..	..	65·0%	..
FIT (organised)	2009–15	50–69	2	..	50·5% (2011–12)
FIT (organised)	2015	50–74	2	..	Included in above rate

The information was ordered by (i) countries with earlier screening implementation, and countries with later screening implementation; (ii) countries in alphabetical order; and (iii) year of screening implementation. The sources of information provided for each country are listed in the appendix (p 5). Participation rates are calculated as the percentage of people invited who were screened. Among countries with no large-scale screening programmes during the investigation period, developments have taken place in Estonia, Norway, and Sweden. In Estonia, an organised pilot programme with FIT was initiated in the second half of 2016 targeting people aged 60–69 years every 2 years, followed by nationwide rollout. In Norway, in 2012, approximately 140 000 people aged 50–74 years were invited to take part in a randomised trial of either sigmoidoscopy or FIT; also, a nationwide screening programme offering either FIT or colonoscopy is planned for 2021. In Sweden, between 2008 and 2015, an organised screening programme with biennial gFOBT was in place in the counties of Stockholm and Gotland (target age groups 60–69 years), and in 2015, FIT replaced gFOBT. gFOBT=guaiac-based faecal occult blood test. FIT=faecal immunochemical test. NA=not applicable. *Data are from the European Health Interview Survey, 2013–16.[12] †In Austria, an organised programme with annual FIT was implemented in 2003 in the state of Burgenland targeting people aged 40–80 years. ‡In the Czech Republic, a screening programme has been in place since 2000 with enrolment through general practitioners. Quality assurance guidelines (including additional enrolment through gynaecologists) were enacted in 2009, therefore meeting all criteria of an organised programme, only without population-based invitations. In 2014, an organised programme with centralised invitations and reminders was set up to specifically target individuals who had not attended screening spontaneously. §Coverage by examination in the preceding 3 years—ie, number of people who underwent FIT (or colonoscopy) in the past 3 years divided by population in target age group. ¶Data for the whole of the UK. ||In August, 2018, ministers agreed to further include the younger age groups (50–59 years) in the bowel screening programme, which is now being planned by the National Health Service and Public Health England. **In Finland, a randomised, organised health services programme ran between 2004 and 2016 targeting people aged 60–69 years with biennial gFOBT (by 2012, about 22% of the target population had been invited). Furthermore, an organised biennial FIT-based programme was introduced in 2019 in nine municipalities, initially targeting people aged 60–66 years and to be gradually extended to all people aged 60–74 years. ††In Belgium, it has been estimated that about 2–4% of the eligible population also benefit from opportunistic screening. ‡‡In Lithuania, the screening programme was introduced in 2009 in Vilnius and Kaunas (the two largest cities). Since 2012, it has been rolled out to other regions. §§The low proportion of the population up to date with screening measured by the European Health Interview Survey (as compared with participation rates in the organised programme) might be related to the low national coverage of the programme at the time the survey was conducted in the Netherlands (2014). The programme had just been lunched and only about 20% of the eligible population had been invited to screening. ¶¶Individuals aged 55–60 years were not invited in the first 2 years of the programme.

Table 2: **Summary of colorectal cancer screening strategies and utilisation rates in the countries included in the study**

became available more recently (ie, Belgium, Denmark, Ireland, Lithuania, the Netherlands, and Slovenia), age-standardised colorectal cancer incidence either remained stable or increased up to the year screening was implemented. AAPCs for these countries ranged from –0·2% (–1·4 to 1·0) to 1·5% (1·1 to 1·8) in men and from –0·5% (–1·7 to 0·6) to 1·2% (0·8 to 1·5) in women (figure 1B; table 3). Where high screening coverage and uptake were rapidly achieved (ie, Belgium [Flanders], Denmark, the Netherlands, and Slovenia, with regionwide or nationwide invitations since the first rounds and >50% participation rates in the context of organised FIT-based programmes; table 2), age-standardised incidence rates initially increased but then subsequently decreased (figure 1B).

In all countries where no nationwide large-scale screening programmes were available, except Sweden, incidence rates steadily rose, with AAPCs ranging from 0·3% (95% CI 0·1–0·5) to 1·9% (1·2–2·6) in men and from 0·6% (0·4–0·8) to 1·1% (0·8–1·4) in women (figure 2A; table 3). Incidence trends in countries for which data were available for certain regions only

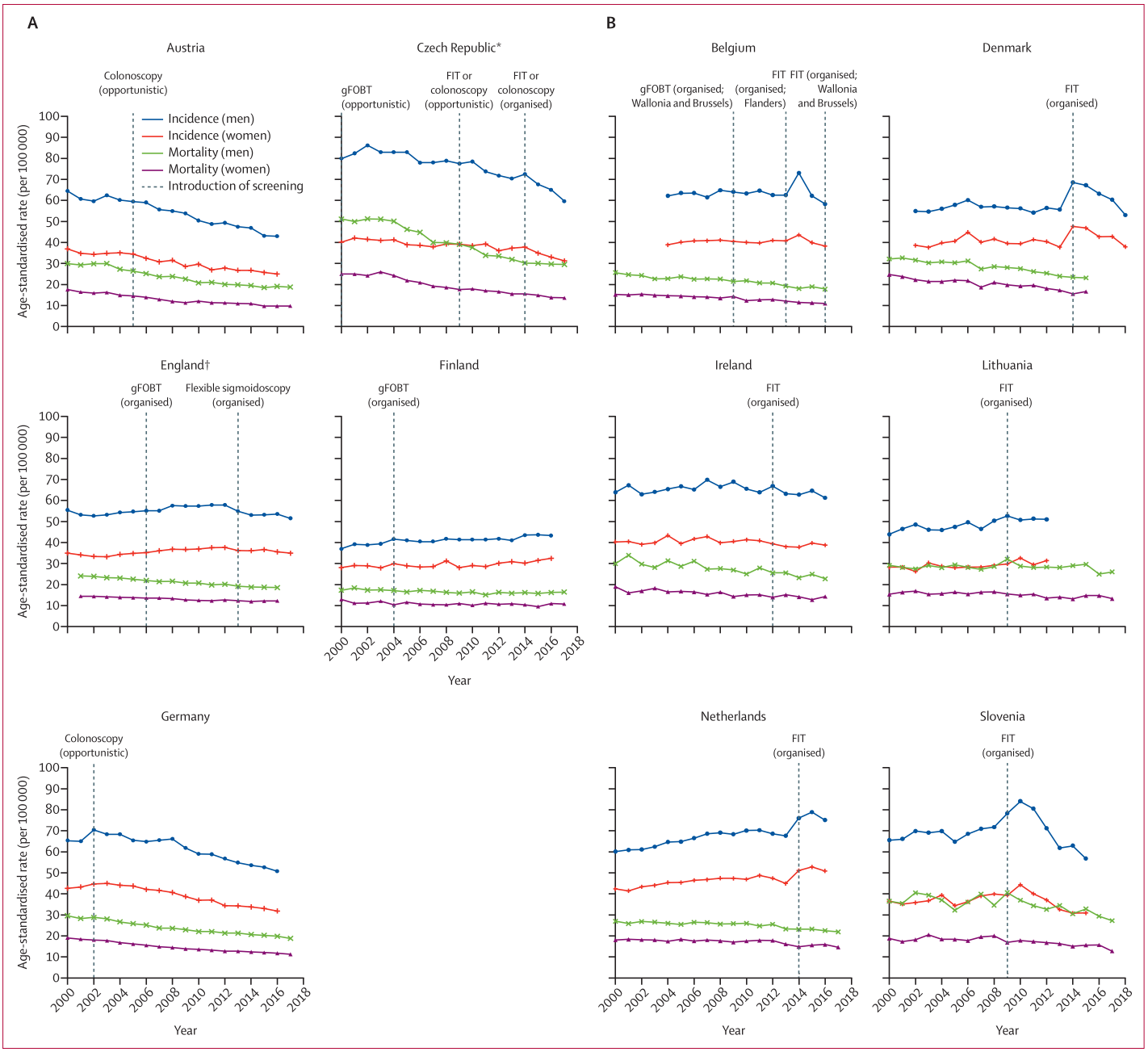


Figure 1: **Changes over time in age-standardised incidence and mortality of colorectal cancer in countries with earlier screening implementation (A) and later screening implementation (B)**
FIT=faecal immunochemical test. gFOBT=guaiac-based faecal occult blood test. *In the Czech Republic, a screening programme was first introduced in 2000; the programme met all criteria of an organised programme in 2009, but no population-based invitations were sent until 2014. †Mortality rates for England include Wales as well.

(ie, France, Italy, Portugal, Spain, and Switzerland) are presented in the appendix (pp 7, 22–26).

The patterns described for countries with large-scale screening programmes were essentially restricted to the distal colon and rectum (appendix pp 10–13), as well as to the screening age groups (appendix pp 8, 27–30). For the proximal colon and for the non-screening ages (particularly 0–49-year-olds), we found either stable or increasing rates over time for most countries, or more modest declines than those observed for the distal subsites and screening ages. For countries with no nationwide large-scale screening programmes, stable or increasing rates over time were found for all three subsites and across all age groups, except for Sweden where rectal cancer incidence slightly declined in women (table 3; appendix pp 8, 14–15, 31–32).

Age-standardised rates of colorectal cancer mortality decreased in all countries apart from Lithuania and

	Incidence								Mortality: colorectum	
	Colorectum		Proximal colon		Distal colon		Rectum		Men	Women
	Men	Women	Men	Women	Men	Women	Men	Women		
Countries with earlier screening implementation										
Austria (2000–16)	−2·5% (−2·8 to −2·2)	−2·4% (−2·7 to −2·1)	−1·2% (−1·8 to −0·7)	−0·9% (−1·3 to −0·4)	−3·0% (−3·4 to −2·6)	−3·5% (−4·0 to −3·0)	−3·0% (−3·4 to −2·5)	−3·1% (−3·6 to −2·5)	−3·2% (−3·5 to −2·9)	−3·5% (−3·9 to −3·1)
Czech Republic (2000–17)	−1·6% (−2·0 to −1·2)	−1·3% (−1·7 to −0·9)	−0·6% (−1·1 to −0·1)	0·3% (−0·1 to 0·7)	−2·1% (−2·7 to −1·5)	−2·1% (−2·6 to −1·6)	−1·9% (−2·3 to −1·5)	−1·9% (−2·5 to −1·4)	−3·8% (−4·2 to −3·4)	−3·9% (−4·3 to −3·5)
England (2000–17)*	−0·0% (−0·4 to 0·3)	0·4% (0·1 to 0·7)	0·8% (0·5 to 1·2)	1·4% (1·1 to 1·8)	0·0% (−0·5 to 0·5)	0·0% (−0·4 to 0·5)	−0·7% (−1·1 to −0·3)	−0·5% (−0·9 to −0·1)	−1·8% (−2·0 to −1·7)	−1·3% (−1·5 to −1·1)
Finland (2000–16)	0·7% (0·5 to 1·0)	0·6% (0·3 to 1·0)	0·6% (0·0 to 1·1)	1·1% (0·5 to 1·7)	1·6% (0·8 to 2·4)	0·8% (0·2 to 1·4)	0·4% (0·2 to 0·7)	−0·1% (−0·5 to 0·4)	−0·7% (−1·0 to −0·4)	−0·7% (−1·3 to −0·2)
Germany (2000–16)	−1·8% (−2·3 to −1·4)	−2·2% (−2·6 to −1·8)	−0·2% (−0·7 to 0·3)	−0·5% (−0·9 to −0·2)	−3·0% (−3·4 to −2·5)	−3·7% (−4·1 to −3·3)	−2·1% (−2·5 to −1·6)	−2·7% (−3·3 to −2·1)	−2·6% (−2·7 to −2·4)	−3·1% (−3·2 to −2·9)
Countries with later screening implementation										
Belgium (2004–16)	0·0% (−0·8 to 0·9)	0·1% (−0·5 to 0·6)	−0·1% (−0·9 to 0·8)	0·8% (0·2 to 1·3)	1·1% (−0·2 to 2·4)	0·8% (−0·2 to 1·9)	−1·0% (−1·6 to −0·3)	−1·6% (−2·2 to −1·1)	−2·0% (−2·3 to −1·7)	−2·1% (−2·4 to −1·7)
Denmark (2002–18)	0·6% (−0·2 to 1·3)	0·5% (−0·3 to 1·2)	1·5% (1·0 to 2·0)	1·3% (0·6 to 2·0)	1·1% (−0·1 to 2·4)	0·5% (−0·5 to 1·5)	−0·6% (−1·3 to 0·2)	−0·4% (−1·4 to 0·5)	−2·3% (−2·7 to −1·9)	−2·5% (−3·0 to −2·0)
Ireland (2000–16)	−0·2% (−0·5 to 0·2)	−0·3% (−0·7 to 0·1)	0·8% (0·3 to 1·3)	0·8% (0·3 to 1·3)	−0·2% (−1·1 to 0·8)	−1·3% (−1·9 to −0·7)	−0·9% (−1·4 to −0·5)	−0·8% (−1·7 to 0·1)	−1·9% (−2·4 to −1·3)	−1·7% (−2·3 to −1·2)
Lithuania (2000–12)	1·2% (0·6 to 1·7)	0·9% (0·2 to 1·7)	1·2% (−0·4 to 2·7)	0·8% (−0·6 to 2·1)	2·3% (0·9 to 3·7)	1·7% (0·3 to 3·1)	0·5% (−0·3 to 1·3)	0·5% (−0·5 to 1·4)	−0·3% (−0·8 to 0·2)	−1·1% (−1·6 to −0·6)
Netherlands (2000–16)	1·5% (1·1 to 1·8)	1·2% (0·8 to 1·5)	1·5% (1·2 to 1·8)	1·5% (1·2 to 1·9)	2·4% (1·9 to 3·0)	1·8% (1·3 to 2·2)	0·5% (0·1 to 0·9)	0·0% (−0·6 to 0·6)	−1·1% (−1·4 to −0·8)	−1·1% (−1·5 to −0·7)
Slovenia (2000–15)	−0·2% (−1·4 to 1·0)	−0·5% (−1·7 to 0·6)	1·4% (0·3 to 2·4)	1·6% (0·4 to 2·8)	−0·3% (−2·1 to 1·4)	−0·5% (−2·2 to 1·2)	−0·9% (−2·2 to 0·4)	−2·1% (−3·5 to −0·8)	−1·5% (−2·2 to −0·7)	−1·6% (−2·3 to −0·9)
Countries with no large-scale screening programmes										
Bulgaria (2000–13)	1·9% (1·2 to 2·6)	1·0% (0·3 to 1·7)	2·7% (1·9 to 3·6)	2·3% (1·4 to 3·2)	1·8% (0·7 to 3·0)	0·7% (−0·4 to 1·8)	1·5% (0·8 to 2·2)	0·3% (−0·5 to 1·1)	0·0% (−0·8 to 0·8)	−1·7% (−2·7 to −0·7)
Estonia (2000–16)	1·1% (0·7 to 1·6)	1·0% (0·5 to 1·6)	1·7% (0·6 to 2·9)	1·8% (0·8 to 2·8)	1·3% (0·4 to 2·2)	0·7% (−0·0 to 1·5)	0·7% (−0·3 to 1·8)	0·6% (−0·2 to 1·4)	0·2% (−0·4 to 0·9)	−0·4% (−1·2 to 0·5)
Norway (2000–17)	0·3% (0·1 to 0·5)	0·6% (0·4 to 0·8)	0·6% (0·2 to 0·9)	1·4% (1·0 to 1·8)	0·5% (0·2 to 0·8)	−0·2% (−0·6 to 0·2)	−0·1% (−0·5 to 0·3)	−0·0% (−0·4 to 0·4)	−1·8% (−2·1 to −1·4)	−1·4% (−1·8 to −1·1)
Sweden (2000–16)	0·1% (−0·2 to 0·4)	0·3% (0·0 to 0·6)	0·2% (−0·2 to 0·5)	1·2% (0·9 to 1·4)	0·5% (−0·2 to 1·2)	−0·1% (−0·7 to 0·6)	−0·3% (−0·6 to 0·0)	−0·5% (−0·9 to −0·1)	−0·9% (−1·2 to −0·7)	−0·7% (−1·0 to −0·3)
Ukraine (2000–16)	1·3% (1·0 to 1·6)	1·1% (0·8 to 1·4)	2·3% (1·9 to 2·7)	2·0% (1·6 to 2·4)	1·4% (1·1 to 1·7)	1·0% (0·7 to 1·3)	0·9% (0·5 to 1·3)	0·8% (0·3 to 1·2)	0·0% (−0·2 to 0·3)	−0·3% (−0·7 to 0·1)

Data are average annual percentage change (95% CI). Time periods shown are for analyses of incidence. For mortality, the time periods were slightly different for some countries: Austria: 2000–17; England: 2001–17; Finland: 2000–17; Germany: 2000–17; Belgium: 2000–16; Denmark: 2000–15; Lithuania: 2000–17; Netherlands: 2000–17; Slovenia: 2000–17; Bulgaria: 2005–15; Norway: 2000–16; and Ukraine: 2000–17. *In analyses of mortality, Wales was also included.

Table 3: **Average annual percentage change in age-standardised incidence and mortality of colorectal cancer in the included countries, by sex**

Bulgaria (in men) and Estonia and Ukraine (both sexes; table 3; figures 1, 2A). Despite the overall declines, we observed differences in the magnitude of the reduction across countries. Overall, the largest decreases in colorectal cancer mortality were found for countries with earlier screening implementation—namely, Austria, the Czech Republic, and Germany (table 3). For countries with no nationwide large-scale screening programmes during the investigation period, such as Norway and Sweden, declines in mortality were much more modest (table 3). Results for specific ages groups are shown in the appendix (p 9).

Among countries with earlier screening implementation, small increases in the proportion of stage I tumours and small decreases in the proportion of stage IV tumours were seen in the Czech Republic after the introduction of FIT and colonoscopy in 2009 and in Germany after the introduction of colonoscopy in 2002 (figure 3A). These patterns were observed in all three subsites (appendix pp 16–17). No changes were seen in England after the introduction of flexible sigmoidoscopy in 2013 (figure 3A; appendix p 16). Detailed TNM staging data were not available for Austria and Finland; analyses of the aggregated staging information available for these countries did not show substantial and sustained changes over time in stage distribution (figure 3A; appendix p 16). For countries with more recent screening implementation, increases in the proportion of stage I colorectal cancers were observed after implementation of organised FIT-based programmes;

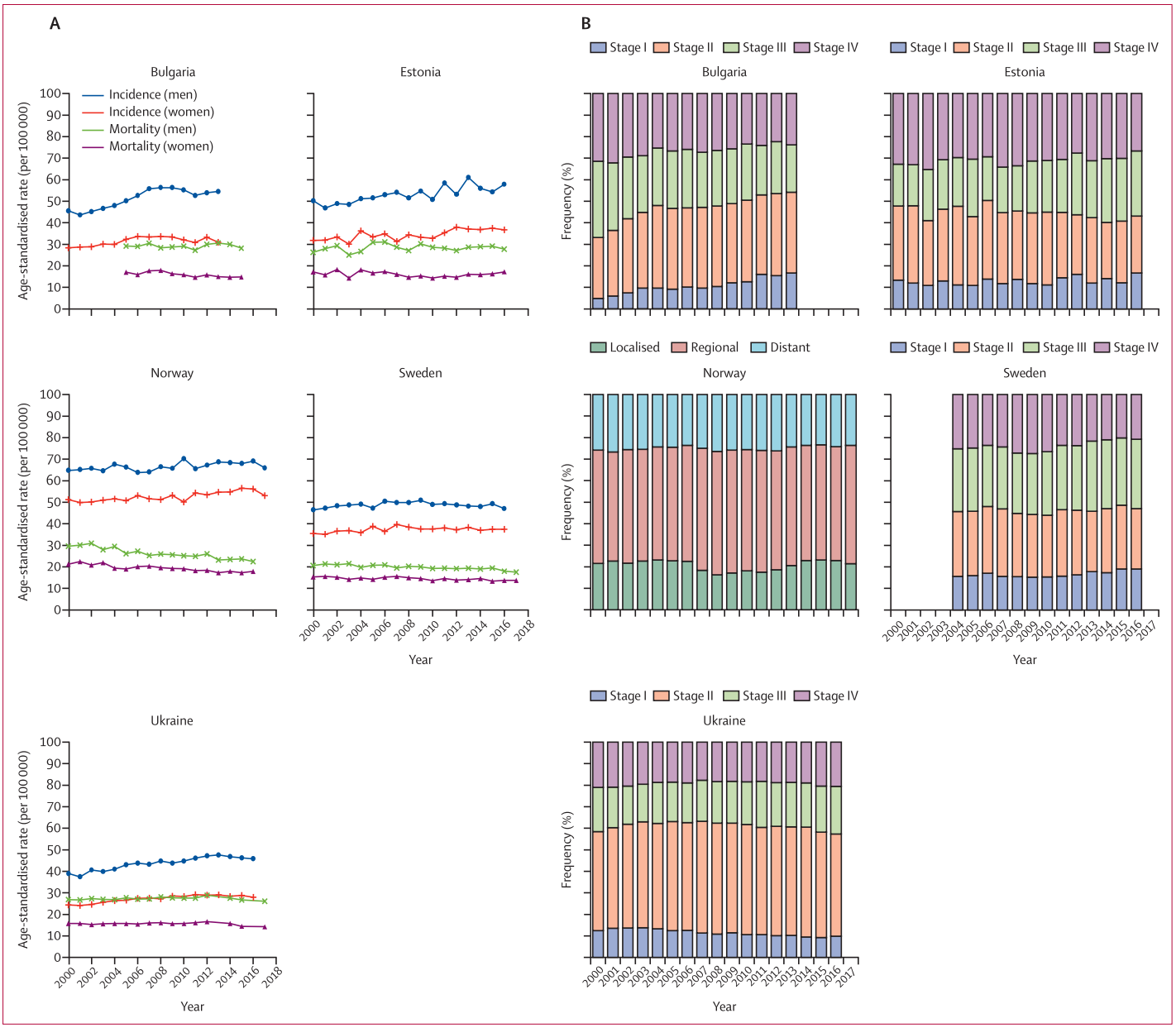


Figure 2: **Changes over time in age-standardised incidence and mortality (A) and stage distribution (B) of colorectal cancer in countries with no large-scale screening programmes during the period of investigation**

this pattern was also seen in all three tumour subsites (figure 3B; appendix pp 18–19).

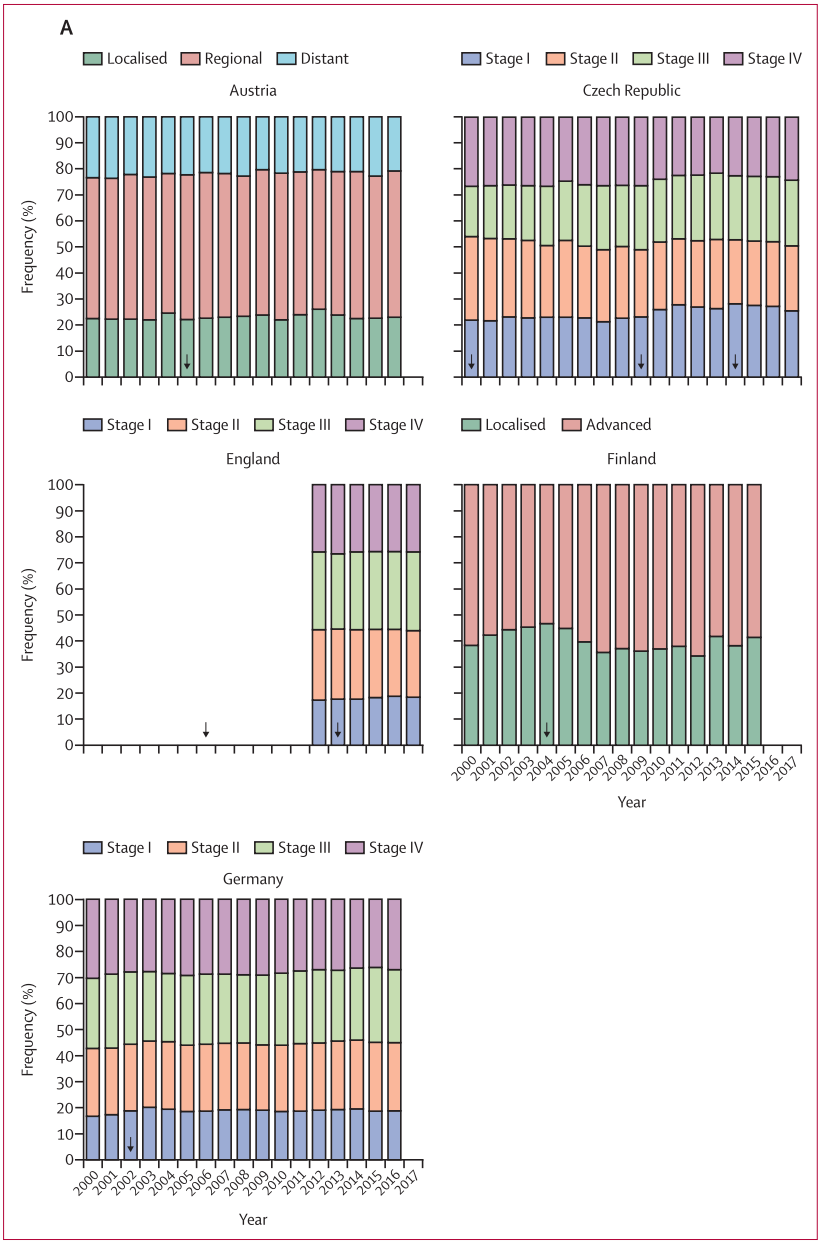
For most countries without large-scale screening programmes, no major or sustained change in stage distribution was observed over time (figure 2B; appendix pp 20–21). Only in Bulgaria—where, in the early 2000s, less than 5% of colorectal cancers were diagnosed at stage I—was a considerable shift towards higher proportions of stage I and II cancers observed. Stage distribution results for countries with regional-level data and for specific age groups are presented in the appendix (pp 33–43).

Discussion

This population-based study, conducted in 21 European countries, found large intercountry differences in colorectal cancer incidence, mortality, and stage distribution in the first two decades of the 21st century. In countries with long-standing screening programmes and wide population coverage, colorectal cancer incidence has decreased substantially in recent years. In countries where screening has been recently introduced and where high coverage and uptake rates were rapidly achieved, we observed an initial increase in colorectal cancer incidence

in the first 1–2 years of screening, which was reversed in subsequent years, as well as an increase in the proportion of stage I colorectal cancers. Conversely, colorectal cancer incidence either remained stable or increased in countries with no large-scale screening programmes during the study period. Moreover, the largest declines in colorectal cancer mortality were seen for countries with long-standing screening programmes.

The ultimate goal of colorectal cancer screening is to reduce colorectal cancer mortality. Significant reductions in colorectal cancer mortality have been shown with gFOBT (15% in intention-to-screen analyses and 25% in per-protocol analyses, in a pooled analysis of randomised, controlled trials [RCTs]),[4] FIT (10–40% in observational studies),[16] flexible sigmoidoscopy (18–30% in intention-to-screen analyses and 38–41% in per-protocol analyses, in RCTs),[6,8–10] and colonoscopy (about 70% in observational studies).[7]



(Figure 3 continues on next page)

Reductions in colorectal cancer mortality could be achieved through detection and removal of malignant colorectal cancers at an early stage, as well as removal of precancerous lesions that would otherwise evolve into cancer—ie, by lowering colorectal cancer incidence. Indeed, reductions in colorectal cancer incidence have also been found in studies with flexible sigmoidoscopy (18–26% in intention-to-screen analyses and 31–35% in per-protocol analyses, in RCTs),[6,8–10] colonoscopy (68% in a meta-analysis of observational studies),[7] and FIT (10–22% in observational studies).[16] Evidence that gFOBT reduces colorectal cancer incidence is scarce; only the US Minnesota trial found a reduction, of 17%.[17] Nevertheless, a study conducted in the context of the organised gFOBT programme in Scotland showed larger declines in colorectal cancer incidence in the screening participant group than in the non-participant group.[18]

Unlike colorectal cancer mortality, on which the effects of screening only become apparent with a long delay, colorectal cancer incidence is influenced immediately after screening implementation. In particular, an initial increase in colorectal cancer diagnoses due to the detection of early-stage asymptomatic cases has been reported in the context of organised regional programmes in Italy and the USA.[19,20] This increase in the first 1–2 years of screening has been shown to be followed by a strong decrease in the incidence of both early-stage and advanced-stage colorectal cancers.[19,20] Thus, the incidence changes and major increases in the proportion of stage I cancers that we found for countries where organised FIT-based screening was implemented during the study period and where high coverage and uptake rates were rapidly achieved (ie, Belgium, after introduction of the Flemish programme; Denmark; the Netherlands; and Slovenia) are concordant with this evidence.[19,20] Of note, the initial increase in incidence, which seems to be largely driven by an increase in the diagnosis of early-stage colorectal cancers, is most likely related to diagnostic anticipation and downstaging rather than overdiagnosis; previous studies done in the context of organised FIT-based programmes that reported similar incidence changes have shown large decreases in mortality in subsequent years.[19,20] It is also worth noting that the decreasing proportion of stage IV colorectal cancers observed after screening implementation might not reflect a decline in incidence of stage IV colorectal cancers.

In Austria, the Czech Republic, and Germany, no such increases in incidence and proportion of early-stage cancers were observed after introduction of screening. It is likely that the type of screening offered in those countries (mostly opportunistic, without a centralised

invitation system) led to a slower increase in screening coverage over time,[21,22] thus preventing such trends from occurring in the first years after screening was introduced. It is also likely that increasing levels of not only screening but also diagnostic colonoscopies (due to increased colonoscopy resources) have played an important role in the declines in incidence.[21] Nevertheless, we cannot disregard some uncertainty around the impact of these opportunistic programmes, given that estimates of screening use were essentially obtained through self-reported data, which are prone to overestimation.[12]

The divergent changes in incidence over time that we found between tumour subsites for countries with screening programmes (particularly those with colonoscopy and FIT-based programmes) are in line with previous evidence suggesting lower effectiveness of colonoscopy on proximal than on distal colorectal cancer incidence.[7] These differing effects might be largely explained by the higher predisposition of the proximal colon for developing serrated precursor lesions, which are more difficult to detect with FIT and at colonoscopy, and evolve more rapidly into cancer than conventional adenomas.[23,24] Despite differences in biology and carcinogenesis between proximal and distal cancers, performing high-quality colonoscopies and including innovative technologies during colonoscopy have been shown to have the potential to substantially reduce proximal colorectal cancer incidence.[25,26]

In concordance with previous evidence,[27] we observed an increase in colorectal cancer incidence rates in individuals younger than 50 years in many countries. These findings call for research to identify underlying factors, awareness among clinicians, and potential adjustment of screening guidelines if current trends are not reversed in the near future.

Declines in colorectal cancer mortality were found for most countries. Reductions in colorectal cancer mortality without apparent declines in colorectal cancer incidence or improvements in stage distribution, as observed for most countries without large-scale screening programmes, suggest that the observed progress in these countries was essentially achieved due to advancements in colorectal cancer diagnosis and treatment (eg, more effective therapy, and improvements in surgical techniques and perioperative care).[3] Yet, the greater declines in colorectal cancer mortality observed in countries with long-standing screening programmes (eg, Austria and Germany) compared with countries with similar colorectal cancer mortality rates in the early 2000s, and with equally high standards of health care but no large-scale screening, such as Norway, suggest that the different magnitudes of mortality reduction are explained by the different levels of screening implementation across countries and progress in reducing colorectal cancer incidence.

Although the described patterns were observed for the large majority of countries according to screening implementation, a few countries did not follow such patterns, or followed them to a lesser extent. Specifically, the apparent lack of or less marked changes in incidence observed for England, Finland, Ireland, and Lithuania than for other countries offering screening might be largely explained by the low coverage and utilisation rates (in Finland, only about 22% of the eligible population had been invited to screening in 2012;[12] in Ireland, invitation coverage was estimated to be only 29% in 2013 due to gradual rollout;[11] and in Lithuania, less than 30% of the eligible population was up to date with screening in 2013–16)[12] and the type of test (gFOBT in England and Finland).

There are also some countries and regions that were analysed as not providing large-scale screening

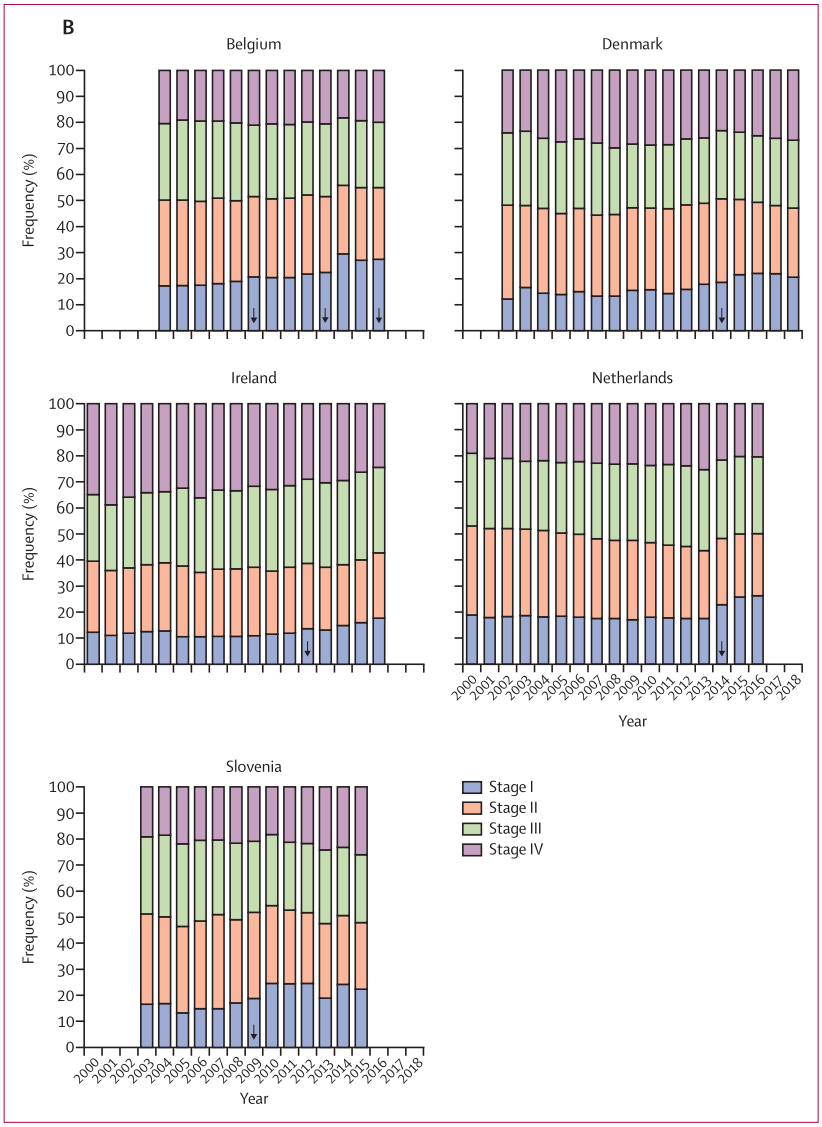


Figure 3: **Changes over time in stage distribution of patients with colorectal cancer diagnosed in countries with earlier screening implementation (A) and later screening implementation (B)**
The arrows indicate the years in which a screening programme was introduced. No staging data were available for Lithuania.

programmes, which started to roll out screening in some areas during the investigation period—namely, Sweden (Stockholm and Gotland) and the southern region of Portugal (Alentejo and Centre). For these, screening use might have, to a certain extent, played a role in the trends observed in later years.

While there are many other factors besides screening and treatment that could influence colorectal cancer incidence (and mortality, in the long run)—in, particular lifestyle-related factors—which need to be kept in mind given the observational nature of our study, a major role of such factors in incidence changes in countries with screening seems unlikely. First, there is no evidence of a profound change towards adoption of low colorectal cancer-risk behaviours in these countries;[28,29] second, even under such a scenario, drastic changes to the extent observed in our study would not be expected.

This study has strengths and limitations that need to be considered. A major strength is its size and geographical representativeness. We used high-quality data from 21 countries to comprehensively analyse, to our knowledge for the first time, changes over time in colorectal cancer incidence, mortality, and stage distribution—by tumour subsite and age group—with regards to colorectal cancer screening implementation. Such extensive analysis allowed us to assess and compare potential population-level effects of screening on colorectal cancer burden across Europe. A major limitation of this study relates to the seemingly different practices in registration of staging data across registries, as seen by the different levels of completeness of stage. Nevertheless, staging information was very complete in most registries (23 of 31 registries had stage information for at least 75% of cases). Another factor that should be considered when analysing stage distribution over time is the likely occurrence of stage migration, especially from stage II to stage III as a consequence of a more exhaustive examination of lymph nodes in the later years of the study period.[30] Furthermore, we were not able to analyse colorectal cancer mortality by tumour subsite because almost all colon cancer deaths had been registered as non-specific sites. Given the subsite differences in incidence trends, such an analysis would have been especially enlightening. Lastly, our study did not allow for comparison of outcomes among participants and non-participants of screening.

In summary, our study shows divergent trends in colorectal cancer incidence and stage distribution, as well as in the magnitude of colorectal cancer mortality reduction across European countries in the first two decades of the 21st century. Our study suggests that screening has contributed substantially to the progress achieved in reducing the colorectal cancer burden, particularly in countries with long-standing screening programmes. These results should encourage these countries to maintain and further advance colorectal cancer screening efforts (eg, by switching from an opportunistic approach to an organised programme if it is not yet in place). Additionally, the low or absence of progress found for countries with no screening programmes strongly calls for their implementation. In the meantime, Estonia (pilot programme in 2016–20) and Norway (starting a nationwide programme in 2021 after completing a screening pilot) have developed efforts to make screening accessible to their populations, and other countries should follow suit if they are to reduce their colorectal cancer burden. Furthermore, improvements in detection of precancerous lesions in the proximal colon could further contribute to colorectal cancer prevention and mortality reduction in the future.

Contributors

HB and RC conceived and designed the study. RC did the literature search. MHa, PI, HDS, NVD, ZV, TA, OM, JM, MCN, AJT, KI, MMä, NM, A-MB, VB, GL, A-SW, MCari, MR, PD, FPo, PMW, CS, SR, IV, VEPPL, MAGE, TBJ, MJB, JR, FAdC, AM, VZ, TŽ, ALdMM, RM-G, MP, JG, MCaru, M-DC, MB, KS, JS, MW, AJ, CH, MMo, and AR prepared the national and regional databases. RC carried out the analysis and drafted the manuscript. All authors contributed to the interpretation of the results and critically revised the manuscript. RC and HB directly accessed and verified the raw data and take responsibility for the integrity and accuracy of the analyses. All authors had full access to all the data reported in the study and accept responsibility to submit the paper for publication.

Declaration of interests

HDS and NVD are employed by the Belgian Cancer Registry, which is financed by regional and federal authorities for collecting data regarding new cancer diagnoses and cancer screening in Belgium, and for disseminating associated epidemiological parameters. FPf reports having received a research grant from Intuitive Surgery, and payment or honoraria from Amgen (for a lecture) and Intuitive Surgery (for a video presentation), outside the submitted work. All other authors declare no competing interests.

Data sharing

Summary statistical data will be available from the corresponding author upon reasonable request with the permission of the contributing cancer registries.

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