

Self-Reported Lower Gastrointestinal Endoscopy Use and Changes in Colorectal Cancer Mortality Rates in European Countries

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INTRODUCTION: To quantify the association of self-reported lower gastrointestinal endoscopy use measured in 2004/05 with colorectal cancer (CRC) mortality changes over 2004–2015 in Europe.

METHODS: An ecological analysis was performed using endoscopy utilization data from the Survey of Health, Aging, and Retirement in 11 European countries in 2004/05 and CRC mortality data from the World Health Organization Mortality Database over 2004–2015. Mortality trends were compared through annual mortality changes from joinpoint regression models. Cross-national variations in mortality trends with respect to endoscopy use were tested for statistical significance by negative binomial regression models.

RESULTS: The proportion of respondents who reported having had an endoscopy within 10 years varied widely across countries, from 6.1% to 25.1%. Large disparities in CRC mortality trends were also observed, with annual mortality change ranging from a decline of 3.3% to an increase of 0.9% for men and from a decline of 3.3% to a decline of 0.6% for women. Endoscopy uptake was negatively associated with the magnitude of annual mortality change over 2004–2015 (rate ratio for a 10-year mortality change per 10% higher endoscopy use, 0.88; 95% confidence interval, 0.82–0.94).

DISCUSSION: This analysis provides quantitative evidence on the contributions of endoscopy use to CRC mortality declines in European countries over the past decade. A considerable fraction of protection is likely to be delivered through endoscopic removal of adenomas and sessile serrated lesions. With many European countries having recently implemented CRC screening programs, an increase in endoscopy use and a subsequent reduction in CRC mortality would be expected.

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INTRODUCTION

With approximately 500,000 cases and more than 240,000 deaths every year, colorectal cancer (CRC) is the second leading cause of cancer morbidity and mortality in Europe (1). Screening for adenomas and cancers through a range of tests, especially lower gastrointestinal endoscopy (colonoscopy and sigmoidoscopy), has been demonstrated to be effective in reducing CRC incidence and mortality (2,3) and is recommended to average-risk population by several guidelines (4–7).

Utilization of lower gastrointestinal endoscopy for screening varies across European countries. Some countries, e.g., Austria and Germany, offer colonoscopy as a primary screening test through a nationwide opportunistic screening program, whereas in many other countries, such as the Netherlands and Denmark,

colonoscopy is used to follow-up positive results of fecal occult blood test (FOBT) (8,9). In Piedmont, Italy, CRC screening is delivered through once-only sigmoidoscopy (8,9). In addition to screening, lower gastrointestinal endoscopy is commonly used for diagnostic workup of abdominal symptoms and for surveillance of bowel diseases. According to data from a large survey conducted in 2004–2005, uptake of lower gastrointestinal endoscopy varied widely across European countries (10).

Large disparities in the trends of CRC incidence and mortality between European countries have been observed over the past decades (11,12). Although studies have demonstrated that the widespread use of screening, especially colonoscopy screening, could explain a large proportion of CRC mortality declines in the United States during the past few decades (13–16), the association

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between cross-national variation in endoscopy use and variation in CRC mortality changes in Europe has not been well analyzed. It remains unclear whether and to what extent endoscopy use in the general population has contributed to the declines in CRC mortality observed in European countries. We therefore performed an ecological analysis to quantify the association of self-reported lower gastrointestinal endoscopy use measured in 2004/05 with CRC mortality change in the subsequent decade among 11 European countries.

METHODS

Data sources

Country-specific data on lower gastrointestinal endoscopy use and CRC mortality in Austria, Belgium, Denmark, France, Germany, Greece, Italy, the Netherlands, Spain, Sweden, and Switzerland were used to perform this ecological analysis.

Estimates of colonoscopy and sigmoidoscopy use in the general population were based on data from the Survey of Health, Aging, and Retirement in Europe (SHARE). SHARE is a multidisciplinary and cross-national panel database covering 27 European countries and Israel and collects extensive information on health, socioeconomic status, and family networks of the elderly (www.share-project.org) (17). Data on colonoscopy and sigmoidoscopy uptake were available from the first wave of SHARE conducted in 2004–2005 among the aforementioned 11 European countries (data collected over May–October 2004 in Austria, Denmark, Germany, Greece, Italy, the Netherlands, Spain, and Switzerland; over May–December 2004 in Sweden; over October–November 2004 in France; and over January–July 2005 in Belgium) (18). Respondents aged 50 years and older were asked whether they had ever undergone lower gastrointestinal endoscopy (colonoscopy or sigmoidoscopy), and if so, when the most recent examination was performed (survey question: “Have you ever had a sigmoidoscopy or colonoscopy? If so, about how long ago did you have the most recent one?”). Colonoscopy and sigmoidoscopy were not differentiated (response options: “Yes, I had one of these tests less than 10 years ago”/“Yes, I had one of these tests 10 or more years ago”/“No, I never had any of these tests”). Indication for endoscopy use was not ascertained. The proportions of individuals who reported endoscopy use within the past 10 years, which were weighted to be representative of the population of each country in terms of age and sex and age-standardized to the European standard population, were directly extracted from a previous publication of our group (10).

Numbers of deaths from CRC and corresponding population sizes were extracted for the 11 countries from the World Health Organization Mortality Database (https://www.who.int/health-info/mortality_data/en/), which provides official national mortality data obtained from member states and serves as a central source of global mortality monitoring (19). Mortality data were reported annually by member states from their national vital registration system and the World Health Organization provided tools and standards to support countries in developing their registration and vital statistics system. Data on cause of death were coded according to *International Classification of Disease (ICD)*. In this study, we extracted annual sex- and age-specific data in 5-year age bands (except for 95+ and in a few cases 85+) for people aged 50 years and older over the period of 2004–2015. Complete data for Switzerland and France were available up till 2013 and 2014, respectively. CRC death was defined as any death

with a code of C18-21 by *ICD, Tenth Revision* or B093-B094 by *ICD, Ninth Revision* (for Greece during 2004–2013).

Statistical analysis

Annual CRC mortality rates of each country were estimated from the numbers of deaths and population sizes and were age-standardized to the European standard population using the direct method to enable comparison across countries (20). Overall mortality changes were derived from the age-standardized rates in year 2004 and 2015 (or the last year with available data). Average annual mortality changes over the study period were obtained from joinpoint regression models. A series of connected regression lines were fitted to the logarithms of the age-standardized CRC mortality rates over time for each country, and then, the annual percentage changes obtained from each regression line were weighted to obtain the average annual percentage change. Analyses were separately performed for men and women.

Cross-national variations in CRC mortality change over the period of 2004–2015 with respect to lower gastrointestinal endoscopy use were tested for statistical significance by negative binomial regression models of CRC death counts to account for overdispersion. The logarithm of person-years at risk, computed as the product of population size and time at risk, was used as offset. A regression model was fitted with calendar year modeled as a continuous variable and age and sex included as covariates. An interaction term between lower gastrointestinal endoscopy uptake rate and calendar year was included to test the differences in CRC mortality change over time with respect to endoscopy use. Analyses were then repeated with additional adjustment for the random effects of country by adding random intercept and random slope for country in the models. Associations between endoscopy uptake and CRC mortality change were quantified by rate ratios (RRs) and their 95% confidence intervals (CIs). The model fitted in our analyses can be expressed as:

$$\begin{aligned} \log(\text{death count}) = & \beta_0 + \beta_1 \left(\frac{\text{uptake} - \text{mean value of uptake}}{10} \right) \\ & + \beta_2(\text{year} - 2004) + \beta_3 \left(\frac{\text{uptake} - \text{mean value of uptake}}{10} \right) \\ & \times (\text{year} - 2004) + \beta_4 \text{female} + \beta_5 \text{age group}_2 + \dots + \beta_{11} \\ & \text{age group}_8 + \log(\text{person-years}). \end{aligned}$$

Estimated CRC mortality change over 2004–2015 for an endoscopy uptake rate of 2%, 5%, 10%, 15%, and 20% was estimated from the regression model with random intercept and slope effects of country.

SAS version 9.4 (SAS Institute, Cary, NC) was used to perform most of the analyses and to plot the figures. Joinpoint regression analysis was performed with Joinpoint Regression Program (21). A 2-sided *P* value of <0.05 was considered statistically significant.

RESULTS

Figure 1 displays the lower gastrointestinal endoscopy uptake rates among the 11 European countries obtained from the SHARE. The response rate for this survey ranged from 70% in Sweden to 93% in Greece (10). A total of 18,139 respondents aged 50 years and older who did not report CRC diagnosis were involved in this analysis. In 2004–2005, the proportion of respondents who reported colonoscopy or sigmoidoscopy use within the

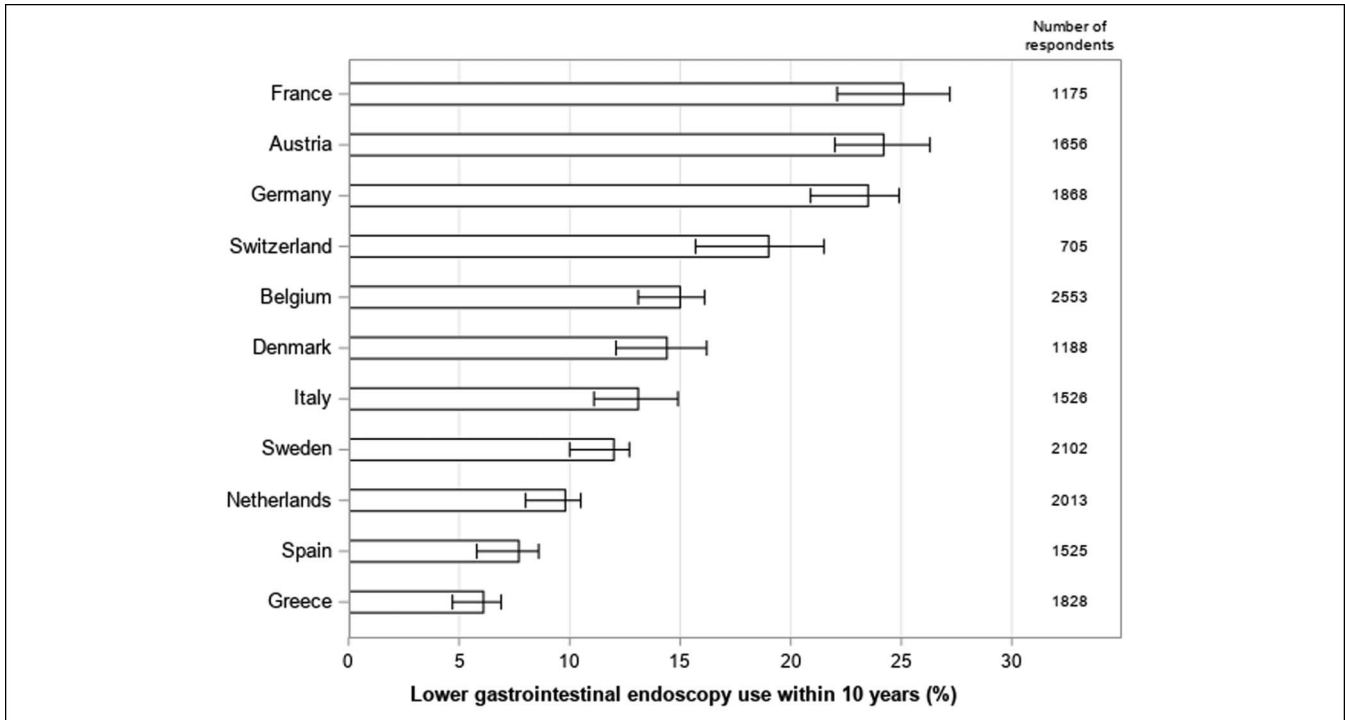


Figure 1. Lower gastrointestinal endoscopy use within the past 10 years among people aged 50 years and older in 11 European countries, 2004/05. Error bars represent the 95% confidence interval for lower gastrointestinal endoscopy use.

past 10 years varied widely across countries, from 6.1% (95% CI, 4.7%–6.9%) in Greece to 25.1% (95% CI, 22.1%–27.2%) in France. The average uptake rate was 15.4%.

Trends in CRC mortality rates among the 11 countries over 2004–2015 are separately shown in Figure 2a–c for countries with high, medium, and low endoscopy uptake rate, respectively. Substantial and continuous declines in CRC mortality rates were observed for both sexes in the 3 countries with the highest endoscopy uptakes of >20% (Figure 2a). Over the study period, age-standardized CRC mortality rates fell by 19.5%–32.0% among men and 18.6%–34.2% among women in Germany, Austria, and France, representing an average annual mortality decline of between 1.9% and 3.3% (Table 1).

Except Denmark and Belgium, countries with an endoscopy uptake rate of 10%–20% had smaller decreases in CRC mortality rates over 2004–2015 when compared with high uptake

countries (Figure 2b) and the average annual percentage change ranged from –0.5 to –1.6 for men and from –0.6 to –1.5 for women (Table 1). The estimated reductions in Denmark and Belgium were in fact higher than those of France but were either comparable or lower than those of Germany and Austria (Table 1).

Mortality trends among the Netherlands, Spain, and Greece, the countries with the lowest endoscopy utilization (less than 10%), varied between men and women (Figure 2c). In this group, decreases among women were more pronounced than among men, and the average annual mortality changes were comparable with those of the medium uptake countries. CRC mortality rates among men remained relatively stable over the study period or even increased slightly (Table 1). Overall, countries with a higher endoscopy uptake rate tended to have higher reduction in CRC mortality over 2004–2015 for both men and women,

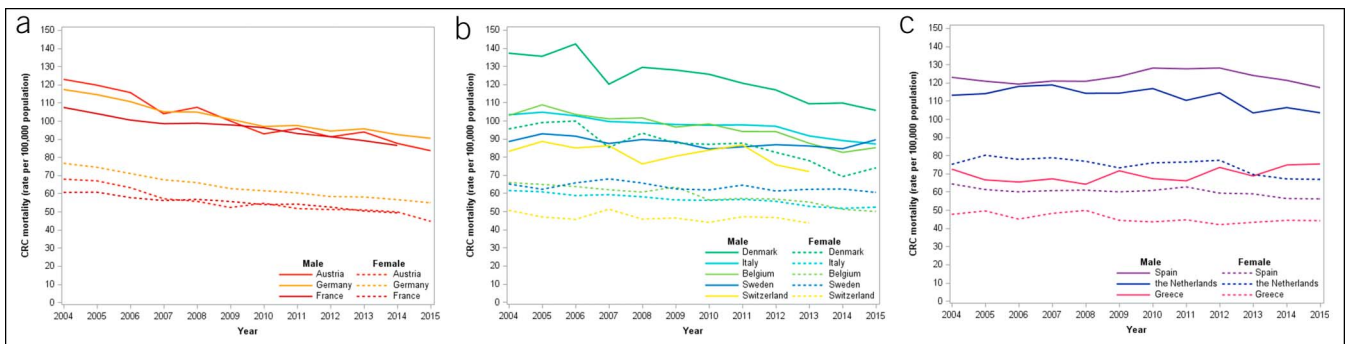


Figure 2. Trends in colorectal cancer (CRC) mortality in men and women aged 50 years and older, by country. (a) Countries with high endoscopy uptake rate. (b) Countries with medium endoscopy uptake rate. (c) Countries with low endoscopy uptake rate.

Table 1. Change in CRC mortality rates among men and women aged 50 years and older in 11 European countries, 2004–2015

Country ^a	Male					Female				
	Endoscopy use within 10 yr	ASR in 2004 ^b	ASR in 2015 ^b	Change in ASR over 2004–2015 (%)	Average annual percentage change (%) ^c	Endoscopy use within 10 yr	ASR in 2004 ^b	ASR in 2015 ^b	Change in ASR over 2004–2015 (%)	Average annual percentage change (%) ^c
France	27.4	107.4	86.4 ^d	–19.5 ^d	–1.9	23.1	60.6	49.3 ^d	–18.6 ^d	–2.0
Austria	24.1	122.9	83.6	–32.0	–3.3	23.7	67.8	44.6	–34.2	–3.3
Germany	23.6	117.3	90.4	–22.9	–2.3	23.4	76.6	54.8	–28.4	–3.0
Switzerland	19.4	83.1	71.9 ^e	–13.5 ^e	–1.4	18.8	50.5	43.5 ^e	–14.0 ^e	–1.0
Belgium	13.6	102.8	85.1	–17.3	–2.2	16.3	65.9	49.9	–24.2	–2.4
Denmark	14.3	137.2	105.6	–23.0	–2.4	14.4	95.4	73.9	–22.5	–2.8
Italy	13.1	103.2	87.1	–15.6	–1.6	13.0	61.5	52.2	–15.0	–1.5
Sweden	12.0	88.4	89.5	1.2	–0.5	12.2	65.1	60.4	–7.2	–0.6
The Netherlands	9.3	113.0	103.4	–8.5	–1.0	10.5	75.1	66.8	–11.0	–1.6
Spain	7.9	123.0	117.3	–4.6	–0.4	7.3	64.3	56.1	–12.8	–1.3
Greece	5.5	72.4	75.3	4.0	0.9	6.7	47.6	44.1	–7.3	–1.1

ASR, age-standardized rate; CRC, colorectal cancer.
^aCountries are ordered by endoscopy uptake rates among the total population (males + females).
^bEstimates were age-standardized to the European standard population.
^cObtained from joinpoint regression models.
^dASRs in 2014 (as the last year with available data) were used.
^eASRs in 2013 (as the last year with available data) were used.

while countries with lower uptake rate had a much smaller reduction or even an increase (Figure 3a,b).

Table 2 demonstrates the associations between lower gastrointestinal endoscopy use and the temporal trends in CRC mortality rates estimated by the negative binomial regression models. The temporal trend in CRC mortality varied across different endoscopy uptake rates. A negative association was identified between endoscopy use and the magnitude of annual mortality change over 2004–2015 (RR, 0.989; 95% CI, 0.985–0.993), and this association remained essentially unchanged after controlling for the random effects of country (RR, 0.987; 95% CI, 0.985–0.990 in the random intercept model and RR, 0.987; 95% CI, 0.981–0.994 in the random intercept and slope model). When examining the magnitude of CRC mortality change over 10 years, the rate ratio per 10% higher endoscopy use became 0.880 (0.860–0.901) and 0.879 (95% CI, 0.822–0.940) in the models that added random intercept and random intercept and slope for country, respectively.

As illustrated by the estimated CRC mortality change obtained from the regression model (Figure 4), a higher endoscopy uptake was associated with greater CRC mortality declines over 2004–2015. The reduction would become smaller with decreasing endoscopy uptake, and when endoscopy uptake dropped to 2%, a theoretical mortality increase would be expected.

DISCUSSION

In this analysis, we quantified the impact of lower gastrointestinal endoscopy use on CRC mortality changes over 2004–2015 among 11 European countries. In 2004–2005, the proportion of respondents who reported having had an endoscopy within 10 years varied widely across countries. Large cross-national disparities also existed in CRC mortality trends over the study

period, with average annual percentage change ranging from –3.3 to 0.9 for men and from –3.3 to –0.6 for women. Results from regression models indicate that endoscopy uptake was negatively associated with the magnitude of mortality change over 2004–2015 (RR for a 10-year mortality change per 10% higher endoscopy use, 0.879; 95% CI, 0.822–0.940). A decline in CRC mortality trend was more pronounced with higher colonoscopy/flexible sigmoidoscopy uptake.

The potential effect of endoscopy utilization in reducing CRC mortality is likely to primarily come from the uptake of endoscopy, especially colonoscopy for screening purpose, either as a primary screening test or as a follow-up for positive FOBT results. As a large proportion of CRC cases develop slowly from pre-cancerous lesions, detection and removal of these lesions at screening could effectively prevent them from progressing to cancers and eventually reduce cancer mortality (22). The reduction in mortality is also realized through the detection of cancer and initiation of treatment at an earlier and more curable stage. Studies have constantly reported more favorable stage distributions and higher survival among patients detected by screening, including screening colonoscopy, than among those detected after symptoms develop (23–27). In addition, the improvement since 2004/5 in quality of lower gastrointestinal endoscopy is likely to enhance its preventative effect. In our study, countries with a long-standing and well-functioning CRC screening mechanism tended to have relatively greater reduction in CRC mortality. For example, Austria and Germany were among the first European countries to introduce CRC screening, where screening by FOBT has been offered for more than 4 decades. In addition in these 2 countries, screening colonoscopy has been introduced as an alternative primary screening modality

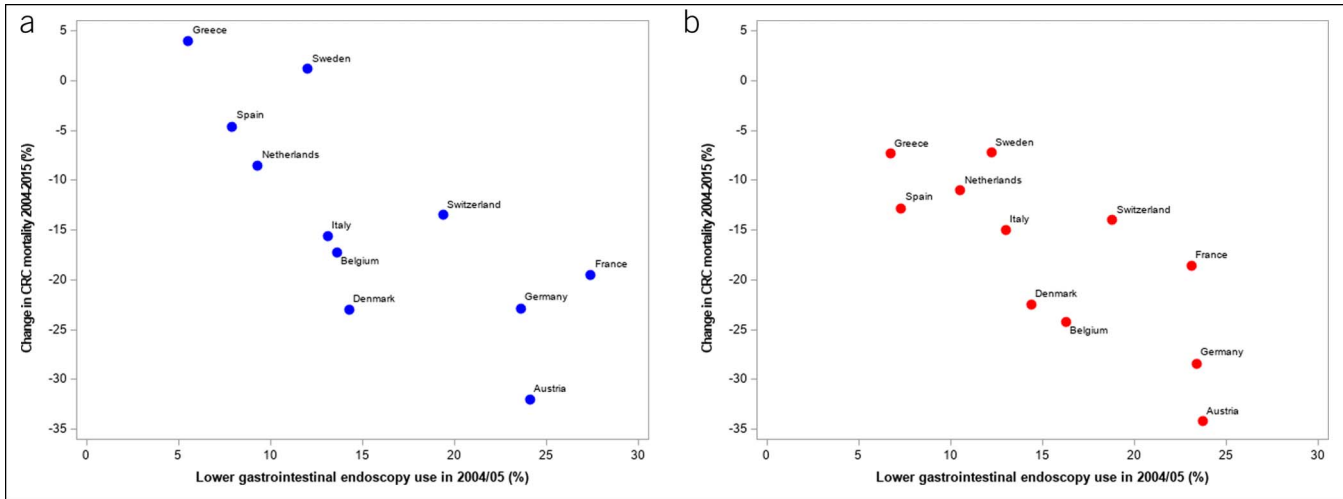


Figure 3. Lower gastrointestinal endoscopy use in 2004/05 and change in colorectal cancer (CRC) mortality over 2004–2015. (a) Male. (b) Female. Estimates for France and Switzerland were changes over 2004–2014 and 2004–2013, respectively.

since 2005 in Austria and 2002 in Germany (9,28,29) and has been performed with steadily improving quality (30,31). In contrast in the Netherlands, fecal immunochemical test-based screening program started in 2014 and the rollout is ongoing (8,9,32). In keeping with these developments, much larger decline in CRC mortality occurred in Austria and Germany over the past decade, although the 3 countries had comparable mortality rates for both sexes in the reference year 2004.

It is worth noting that the preventive effect of sigmoidoscopy/colonoscopy comes through removal of lesions destined to develop into CRC or treatment of CRC at an early stage. In most endoscopies when no such lesions are detected, no preventive effects are provided. Nevertheless, the evaluation of the impact of endoscopy screening on CRC mortality is meaningful for countries where endoscopy is widely used for primary CRC screening and largely represents screening coverage. In countries with FOBT-based screening programs, the number of eventual colonoscopic examinations should be considered together with the extent of FOBT use to enable a complete picture of the protective effects of CRC screening. Nonetheless, the relatively low uptake of endoscopy in most of the countries in our analysis represents primarily the lack of screening program in 2004/05, in particular in Greece, the Netherlands, and Sweden (8).

Although colonoscopy/flexible sigmoidoscopy use in 2004/5 was found to be associated with a trend of downward CRC mortality, multiple factors other than screening would have also contributed to the decline in mortality observed in many of the

European countries examined over the decade in question. For example, the adoption of total mesorectal excision of rectal tumors, adjuvant chemotherapy for high-risk colon cancer, neoadjuvant radiotherapy for rectal cancer, and other improvements in best available treatment procedures is believed to be 1 major contributing factor to the progress in CRC survival (33–35). The change in risk or protective factors, such as reduced tobacco consumption and regular use of aspirin, might also partially explain the declines in CRC mortality in some countries (36–38). In Denmark, although CRC screening was implemented in 2014 and endoscopy use in 2004/05 was at an average level, a considerable reduction in CRC mortality was identified, which might be related to a larger than average decline in smoking prevalence (38) in addition to a much higher mortality rate in the reference year of 2004. Changes in specific CRC risk factors might also explain the increases in CRC mortality observed in men in Sweden and Greece. For example, 1 potential explanation can be the unfavorable trends in obesity, whose prevalence has strongly increased in the recent decades (39,40). Further studies are warranted to determine the specific reasons for the change in mortality in a specific country.

A substantial variation in the absolute CRC mortality was also identified across the countries, which might reflect the cross-national differences in multiple CRC influencing factors, such as dietary factors, socioeconomic status, and the adoption of preventive measures. To understand the degree of protection each factor can provide, further studies comparing the impact of each

Table 2. Rate ratios (RRs) and 95% confidence intervals (CIs) for colorectal cancer mortality from negative binomial regression models

	Adjusted for age and sex		Adjusted for age, sex, and country (random intercept)		Adjusted for age, sex, and country (random intercept and slope)	
	RR (95% CI)	P	RR (95% CI)	P	RR (95% CI)	P
Annual mortality change over 2004–2015, per 10% higher endoscopy uptake	0.989 (0.985–0.993)	<0.0001	0.987 (0.985–0.990)	<0.0001	0.987 (0.981–0.994)	<0.001
10-yr mortality change over 2004–2015, per 10% higher endoscopy uptake	0.892 (0.857–0.928)	<0.0001	0.880 (0.860–0.901)	<0.0001	0.879 (0.822–0.940)	<0.001

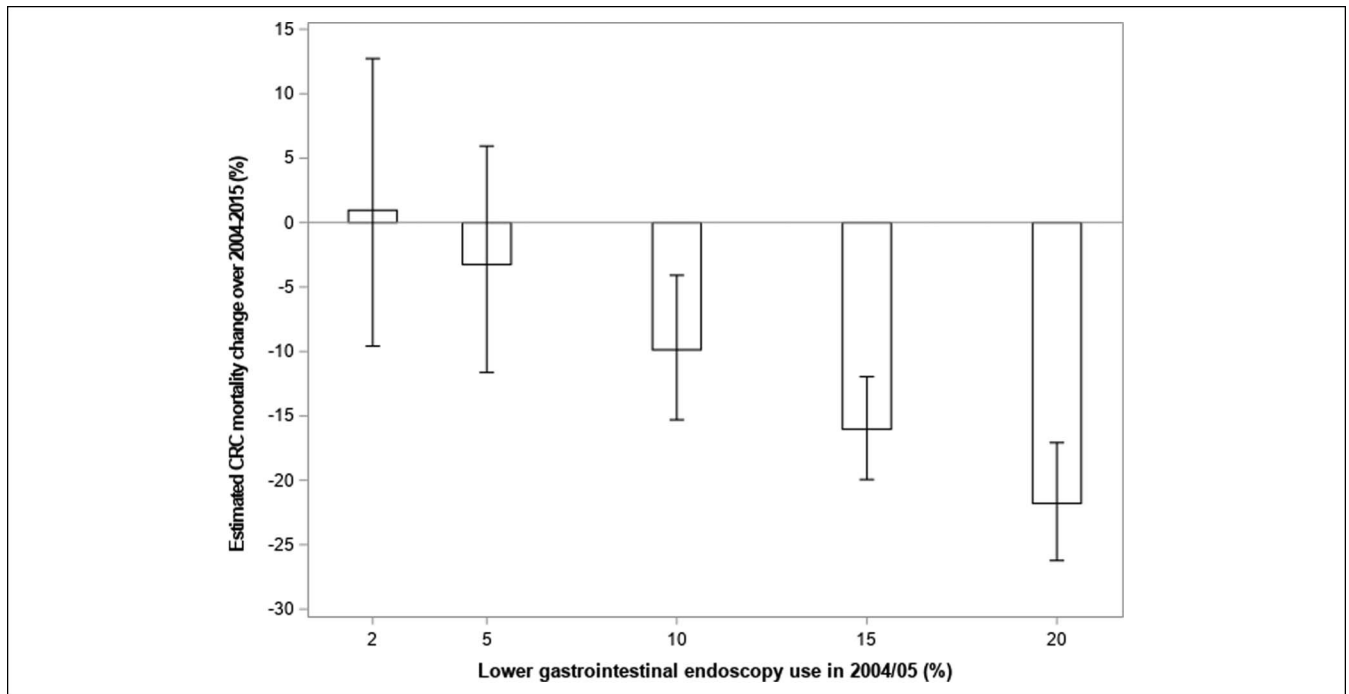


Figure 4. Estimated colorectal cancer (CRC) mortality change over 2004–2015 for different endoscopy uptake rates in 2004/05. Error bars represent the 95% confidence interval for estimated CRC mortality change.

factor simultaneously, for instance the calculation of population attributable fraction, are needed.

This analysis is one of the first attempts to quantitatively evaluate the impact of lower gastrointestinal endoscopy use in the general population on CRC mortality trends in European countries. Previous studies have evaluated the impact of FIT-based screening programs in Italy or multiple modalities in the United States (41,42). One of the major strengths of our study is the use of nationally representative data on both endoscopy utilization and CRC mortality rates. Although no specific validation of self-reported endoscopy use was available in SHARE, high validity of self-reported lower gastrointestinal endoscopy use has been demonstrated in other questionnaire studies of similar study populations from Europe (43,44). Some limitations should also be noted when interpreting the results from this study. First, given that some countries introduced CRC screening programs over the study period, the cross-national variation in endoscopy use might not stay stable and the same as in the reference year. However, considering it takes a few years for the screening practice to have a substantial effect on mortality (45), the influence should be limited. A further limitation relates to the use of FOBT-based CRC screening program in a number of European countries (8,9). In these countries, as colonoscopy use correlates with the number of FOBT-positives, a low sigmoidoscopy/colonoscopy uptake rate does not necessarily translate into a low adherence to screening or lack of protection against CRC mortality. Nevertheless, in our study, the observed low endoscopy uptake rates back in 2004/05 in some countries most likely reflect a lack of screening program and low utilization of screening tests. Furthermore, the setup of the questionnaire did not allow us to distinguish between sigmoidoscopy and colonoscopy; however, the overall effects of sigmoidoscopy and colonoscopy combined on CRC mortality should be similar to the effects as if all these endoscopies are

colonoscopy examinations, considering that the majorities of CRC are distal, and studies have consistently shown much weaker effects of colonoscopy for proximal cancers (35). Finally, although the overall change in age-standardized mortality rates over 2004–2015 in Switzerland and France was not comparable with those of other countries because of missing data for the recent years, the estimation of average annual percentage changes enabled a complete cross-national comparison.

In summary, this ecological analysis provides an assessment of cross-national variations in CRC mortality trends over 2004–2015 in 11 European countries according to cross-national variations in lower gastrointestinal endoscopy use. Endoscopy uptake was found to be negatively associated with the magnitude of mortality changes, with larger reduction occurring in countries with higher uptake. Although multiple factors might have contributed to the disparities in mortality trends, our data support suggestions that a considerable fraction of protection against CRC mortality is delivered through endoscopy use, especially screening endoscopy use. Our study provides quantitative evidence of the potential of further enhancement of CRC screening. Improved colonoscopy techniques and practices such as better bowel preparation and longer withdrawal times are likely to contribute to even higher levels of CRC prevention. With many European countries having recently developed or implemented their CRC screening program, an increase in endoscopy use and further reduction in CRC mortality would be expected.

CONFLICTS OF INTEREST

Guarantor of the article: Hermann Brenner, MD, MPH.

Specific author contributions: H.B. and C.C.: conceived and designed the study. C.C.: contributed to the data analysis, data interpretation, and manuscript drafting. C.S.: contributed to data analysis, data interpretation, and critical revision of the manuscript.

M.H. and H.B.: contributed to data interpretation and critical revision of the manuscript, and all authors read and approved the final draft submitted.

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Potential competing interests: None to report.

Study Highlights

WHAT IS KNOWN

- ✓ Lower gastrointestinal endoscopy use and CRC mortality trends vary widely across European countries.
- ✓ Experience from the United States over the past decades suggests that the widespread use of colonoscopy, including screening colonoscopy, is a major contributing factor to the declining CRC mortality.
- ✓ It is unclear whether the cross-national variation in CRC mortality change in Europe can be explained by the cross-national variation in lower gastrointestinal endoscopy use.

WHAT IS NEW HERE

- ✓ This analysis for the first time quantifies the association of colonoscopy/sigmoidoscopy use with CRC mortality changes among 11 European countries.
- ✓ The temporal trend in CRC mortality varied with different colonoscopy/sigmoidoscopy uptake rates.
- ✓ Colonoscopy/sigmoidoscopy uptake was negatively associated with the magnitude of CRC mortality changes over 2004–2015, with more pronounced declines occurring in countries with higher colonoscopy/sigmoidoscopy uptake.

TRANSLATIONAL IMPACT

- ✓ These data serve as quantitative evidence for the benefit of colonoscopic screening and suggest that a further increase in the use of such screening may lead to still more benefit.

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