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ORIGINAL ARTICLE

Colorectal cancer screening by colonoscopy and trends in disease-specific mortality: a population-based ecological study of 358 German districts

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Abstract

Purpose Screening for colorectal cancer (CRC) by colonoscopy was implemented in Germany in 2002. Although the procedure has proven to be effective in reducing disease-specific mortality in numerous clinical studies, its effect at the population level is unclear. We performed an ecological study at the level of 358 German districts, testing the hypothesis that a higher participation rate in screening colonoscopy is associated with a stronger decline in CRC mortality from 2001 to 2012.

Methods Information on the use of colonoscopy in each district was extracted from settlement data, used for the remuneration of physicians of the ambulant sector from 2008 to 2011. Yearly mortality rates for each district from 2001 to 2012 were derived from the official mortality statistics. A spatial model was fitted, considering other factors which might influence early detection of CRC (fecal occult blood test (FOBT), diagnostic colonoscopy, material and social area deprivation, and rural-urban disparities).

Results The population-weighted mean annual participation rate during 2008–2011 in screening colonoscopy was 2.0% (range 0.6 to 3.9%). The weighted mean annual percentage change (APC) of CRC mortality was −2.9% (range −7.8 to 1.2%). According to the fully adjusted model, a 1% higher annual participation rate in colonoscopy screening was associated with an additional annual change in CRC mortality rate of −0.34% ($p = 0.015$). Given an annual 2.0% participation rate, colonoscopy screening attributed 23% to the observed decline.

Conclusions Our real-world data from Germany provide first evidence that colonoscopy screening for CRC is effective in reducing disease-specific mortality at the population level.

Keywords Colorectal cancer · Screening · Colonoscopy · Mortality · Epidemiology

Introduction

Colorectal cancer (CRC) is one of the most common causes of cancer-related mortality. In Germany, it is the third leading cause with approximately 13,600 deaths in men and 11,800 deaths in women (2015) [1]. Age-standardized mortality, however, has been decreasing slowly in both sexes since the early 2000s. The same applies to the age-standardized incidence since at least the 1990s. These trends have been attributed in part to intensified and improved screening activities. In particular, the colonoscopy, which was implemented in Germany in October 2002 as part of the statutory screening program, is considered effective in detecting cancerous and precancerous lesions of the colon and rectum at an early stage. Evidence for a protective effect of colonoscopy screening on disease-specific mortality is provided by numerous clinical studies. A Cochrane review on randomized controlled trials (RCTs) estimates the relative risk (RR) of dying from CRC at 0.72 (95% CI 0.65 to 0.79) with flexible sigmoidoscopy, compared with no screening [2]. With respect to a screening endoscopy covering the whole colon, results from RCTs are not yet available. Observational studies suggest an even stronger reduction in distal colorectal cancer mortality, along with a significant reduction in mortality from cancer of the proximal colon [3].

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From an epidemiological perspective, the question arises whether the proven efficacy results in real-world effectiveness. An effective screening should be reflected not only in improved survival which may be influenced by lead time bias [4], but in reduced mortality rates at a population level. Apart from a too low participation rate, there are at least two reasons why this expectation might not—or in part not—be fulfilled. First, even given a high participation in screening, it is possible that the offer is used predominantly by individuals whose risk of dying from colorectal cancer is lower than that of the common population. Second, the conditions under which screening is performed in routine may differ from study settings with respect to information to the target population, resources, training of health professionals, and quality assurance [5]. With respect to the population-based Dutch "bevolkingsonderzoek" for colorectal cancer (BVO), it has been reported recently that screen-detected tumors have a significantly lower T-stage than tumors detected by normal diagnostic colonoscopy [6]. Epidemiological trends in stage-specific incidence rates that are compatible with positive effects of the German colonoscopy screening program have been described by Schnoor et al. [7]. Trends in CRC mortality could not be examined due to the short observation interval since the introduction of screening colonoscopy. Meanwhile, long-term data on CRC mortality are available. However, using these data to make statements on the effectiveness of screening colonoscopy requires particular caution. Effects of early tumor detection on mortality are realized in individuals and should primary be investigated at an individual level. Aggregate data may be confounded by group-level characteristics which are associated with screening use on the one hand and mortality on the other. With regard to investigated question, for example, different levels of health care quality might correlate with both the use of colonoscopy screening and CRC mortality, even if there is no correlation between these variables at the level of individuals (ecological fallacy by cross-level bias [8]). Another concern pertains specifically to a temporal design, relating a time-defined nationwide event (the implementation of a screening intervention) to a nationwide mortality trend. Unlike (overall and stage-specific) incidence rates, which are very sensitive to screening activities, mortality rates are strongly influenced by therapy patterns, changing substantially over time. Any trend change that might be seen in mortality data following the implementation of screening colonoscopy is therefore prone to be confounded by advances in treatment. A practicable way to minimize the potential bias is to compare mortality trends in a large number of regions that are supposed to be similar in the use of treatments, but differ substantially in the extent to which screening colonoscopy is used. Following this approach, we performed an ecological study at the level of 358 German districts to evaluate the relation between the use of preventive colonoscopy and trends in CRC mortality from 2001 to 2012. Other examinations (fecal occult blood test (FOBT), diagnostic colonoscopy) and sociogeographic parameters (material and social area deprivation, and rural-urban disparities), which might result in early detection of CRC or relate to lifestyle or different levels of health care quality as potential confounding group-level characteristics, were considered. We hypothesized that a higher participation rate in screening colonoscopy is associated with a stronger decline in CRC mortality since 2002.

Data and methods

Our analysis covers 15 of 16 German federal states, which comprise 358 of 402 districts at this time. Changes in territorial delimitation of these regions throughout the observation period were offset following Blach et al. [9]. The prevalence of examination and mortality were presented as age- and sex-standardized rates and as age-standardized rates for men and women separately, using the European standard population (ASR [E]) truncated to individuals aged 55 and older. Means over all districts were weighted by size of population in this age group.

The German CRC screening program

Until 2002, when colonoscopy was introduced as a test within the statutory CRC screening program, early detection of CRC in asymptomatic individuals was conducted by a guaiac-based FOBT. Colonoscopy was then established as an alternative method. Holders of the German statutory health insurance aged 55 and older were entitled to opt either for a FOBT (with an interval of 2 years) or a colonoscopy. A second colonoscopy is covered after 10 years if the first has been done before the age of 65. To date, the screening is opportunistic. Personal invitation letters are being planned for the near future.

Use of colonoscopy and FOBT

Information on use of colonoscopy and FOBT was available from 2008 to 2011, provided by the *Zentralinstitut für die kassenärztliche Versorgung in Deutschland* (Zi) [Central Research Institute of Ambulatory Health Care in Germany]. With respect to each district, we obtained the number of inhabitants aged 55 years and older, having had the respective examination and the corresponding number of entitled inhabitants, each stratified by age (5-year age groups) and sex. Numbers are based on settlement data, used for the remuneration of physicians of the ambulant sector. Being limited to holders of the statutory health insurance, the data do not contain examinations of members of a private health insurance, who account for approximately 11.6% of the eligible German population [10]. The incompleteness poses a possible source of bias, since it is known that (1) members of a private health insurance use screening more frequent than statutory policy holders [11] and (2) the percentages of both groups vary markedly between districts. To account for that, we calculated correction factors by which the use of screening colonoscopy differs in both groups. Relating data, stratified by sex and age (55 to 64 years and 65 years and older), derived from the GEDA 2010 Survey ("German Health Update"), and were provided by the Robert Koch Institute; the number of members of a private health insurance aged 55 and older in each district by age and sex was calculated as difference between the number of all inhabitants of this age, provided by official population statistics and respective numbers of individuals on statutory insurance as provided by the Zi. To summarize the use of each examination in each district, we computed average rates from 2008 to 2011.

Mortality trends

Yearly mortality rates for each district from 2001 to 2012 are based on the official mortality statistics, and were provided by the population-based cancer registries of the German federal states. Changes in CRC mortality rates were operationalized as annual percentage change (APC), based on a log-linear regression model [12]. An APC of − 3.0%, for example, means that the mortality rate decreased by 3% every year and by ($1–0.97^{11} \times 100\%$=) 28.5% throughout the observation period of 11 years.

Regression models

The effect of colonoscopy screening use on CRC mortality was estimated using spatial linear regression analyses, each modeling the APC of CRC mortality 2001 to 2012 in the districts as dependent variable. First, a simple regression model was fitted with only the participation rates in screening colonoscopy as an independent variable. Then, a multiple regression analysis with diagnostic colonoscopies and the use of FOBT as additional independent variables was fitted. Finally, a fully adjusted model was fitted involving two sociogeographic parameters that might have a confounding influence on CRC mortality trends. Material and social area deprivation at the district level was operationalized using the German Index of Multiple Deprivation 2006 (GIMD 2006). The index is based on official data reflecting aspects of material and social deprivation in the field of seven domains (i.e., income, employment, education, municipal revenue, social capital, environment, and security deprivation) [13, 14]. Furthermore, we considered rural-urban disparities using a four-level classification, which has been established by the *Bundesinstitut für Bau-, Stadt- und Raumforschung* (BBSR) [Federal Institute for Research on Building, Urban Affairs, and Spatial Development] for the purposes of spatial development. The classification comprises four district types: (1) large independent cities, (2) urban districts, (3) rural districts showing densification, and (4) sparsely populated rural districts.

All regression analyses were performed using sex-standardized rates and for men and women separately. Districts were weighted according to size of population aged 55 and older. To adjust for spatial autocorrelations, we used SAR (Simultaneous Autoregressive) models [15].

Analyses were carried out by means of the statistical software program R [16], using the package "spdep" for spatial modeling [17, 18] and "ggplot2" [19] for visualization. *p*-values were derived from two-sided tests.

Results

Use of colonoscopy and FOBT

The population-weighted mean annual participation rate during 2008–2011 in screening colonoscopy was 2.0%, ranging across districts from 0.6 to 3.9%. Geographical visualization indicates clusters of high participation rates centering around the city states Berlin, Hamburg, and Bremen and in western parts of Bavaria and general low screening use in Hessen and eastern parts of Bavaria (Fig. 1). Participation rates were quite similar in men (2.1%) and women (1.9%), ranging from 0.6 to 4.1% and 0.5 to 3.6%, respectively. Sex- and age-standardized annual frequencies of diagnostic colonoscopies and FOBT were 3.0% [range 0.8 to 6.0%] and 14.4% [range 7.3 to 24.1%], respectively (Table 1).

Mortality trends

The weighted mean annual percentage change of CRC mortality was − 2.9% in the 11-year period from 2001 to 2012, ranging across districts from − 7.8 to 1.2%. Districts showing a relatively strong decline of CRC mortality were located around the city state Berlin and in Schleswig-Holstein. Districts with small declines or increase of CRC mortality revealed no marked regional clustering, but were slightly more frequent in the center of Germany, covering parts of North Rhine-Westphalia, Hesse, Saxony-Anhalt, and Thuringia. In general, the decline in CRC mortality was more pronounced in women than in men (Table 1).

Regression analyses

Results of regression analyses are presented in Table 2. In the simple regression analysis, we found a significant association between participation in screening colonoscopy and decline of CRC mortality. For every additional percentage point in use of screening colonoscopy, the APC decreased by 0.47 percentage points. This unadjusted effect was stronger in men than in women (− 0.54 vs. − 0.35) (Table 2). The overall effect was

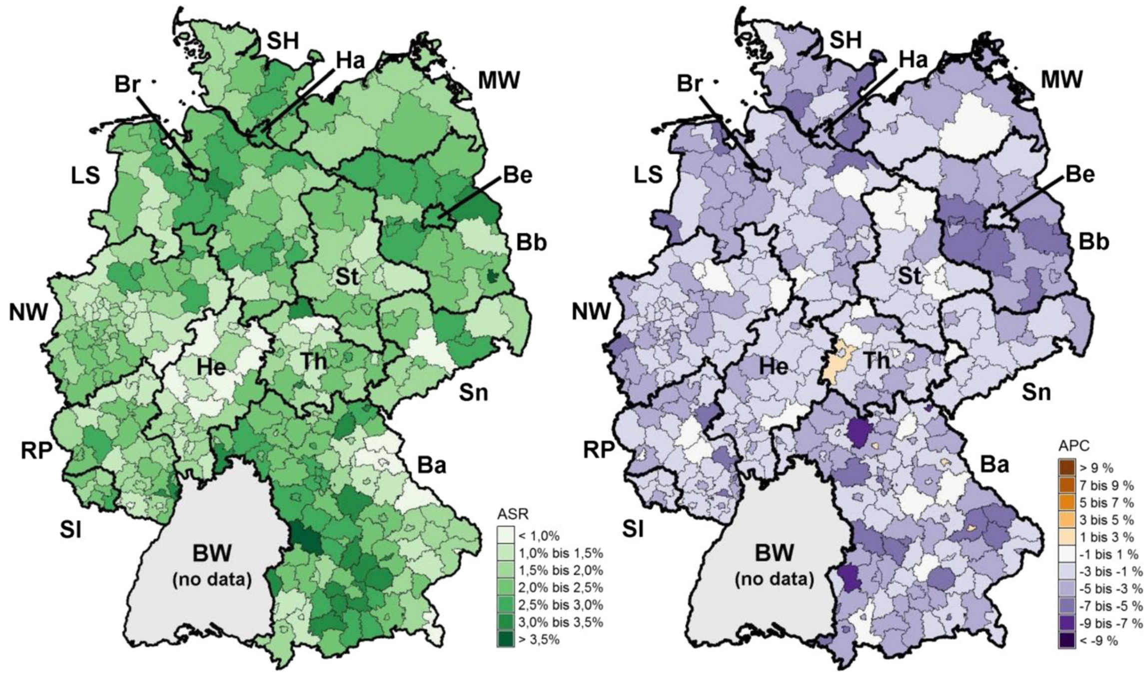

Fig. 1 **a** Use of screening colonoscopies (mean annual participation from 2008 to 2011). **b** CRC mortality trends (annual percentage change of CRC mortality rates from 2001 to 2012). Underlying rates are sex and age standardized, using the European standard population. Abbreviations: Ba, Bavaria; Bb, Brandenburg; Be, Berlin; Br, Bremen; BW, Baden-Württemberg; Ha, Hamburg; He, Hesse; LS, Lower Saxony; MW, Mecklenburg-Western Pomerania; NW, North Rhine-Westphalia; RP, Rhineland-Palatinate; SH, Schleswig-Holstein; Sl, Saarland; Sn, Saxony; St, Saxony-Anhalt; Th, Thuringia

confirmed in the partly adjusted multiple regression analysis, but the effect in men was weaker. The further adjustment for sociogeographic parameters had little impact. In men, however, the effect estimate slightly missed significance.

Discussion

There is good evidence from clinical studies that screening colonoscopy is capable of reducing CRC mortality. Our study indicates that the extent of screening colonoscopy use has an impact on disease-specific mortality at the population level. On average, districts with higher rates of screening colonoscopy showed a larger reduction of CRC cancer mortality than districts with lower screening utilization.

According to the fully adjusted model, 1% higher annual participation rate in colonoscopy screening was associated with an additional annual change in CRC mortality rate of − 0.34%. Assuming an annual 2.0% participation rate as observed for all districts in mean (equivalent to a 20% participation in a 10-year screening round), the additional annual decline was − 0.68% per year. Setting this value in relation to the mean decline in CRC mortality (− 2.9% per year), colonoscopy screening attributed 23% (− 0.68/− 2.9) to the observed

Table 1 Use of screening and diagnostic procedures related to CRC diagnosis and CRC mortality trends from 2001 to 2012 in 358 German districts

	Screening colonoscopy[a] (range); in %	Diagnostic colonoscopy[a] (range); in %	FOBT[a] (range); in %	APC mortality[b] (range); in %
Total	2.0	3.0	14.4	− 2.9
	(0.6–3.9)	(0.8–6.0)	(7.3–24.1)	(− 7.8 to 1.2)
Men	2.1	3.2	12.7	− 2.5
	(0.6–4.1)	(0.9–6.4)	(3.6–26.4)	(− 10.7 to 4.9)
Women	1.9	2.8	16.0	− 3.5
	(0.5–3.6)	(0.7–5.7)	(5.2–27.9)	(− 10.6 to 4.4)

Abbreviations: *FOBT*, fecal occult blood test; *APC mortality*, annual percentage change of CRC mortality

[a] Mean annual use from 2008 to 2011, weighted by size of population

[b] Mean APC mortality, weighted by size of population

Underlying rates are sex and age standardized, using the European standard population

Table 2 Effects of use of screening and diagnostic procedures related to CRC diagnosis on annual percentage change of CRC mortality from 2001 to 2012 in 358 German districts

	Simple regression analysis		Multiple regression analysis		Fully adjusted model[a]	
	β	p value	β	p value	β	p value
Screening colonoscopy	**− 0.47**	**< 0.001**	**− 0.38**	**0.006**	**− 0.34**	**0.015**
Men	**− 0.54**	**< 0.001**	**− 0.38**	**0.027**	− 0.33	0.061
Women	**− 0.35**	**0.034**	**− 0.37**	**0.028**	**− 0.38**	**0.029**
Diagnostic colonoscopy			− 0.16	0.060	− 0.11	0.203
Men			**− 0.28**	**0.009**	**− 0.21**	**0.049**
Women			0.05	0.628	0.04	0.719
FOBT			0.06	0.075	0.06	0.079
Men			0.03	0.351	0.04	0.260
Women			0.04	0.227	0.04	0.253

Abbreviations: *FOBT*, fecal occult blood test

[a] Adjusted for material and social area deprivation (German Index of Multiple Deprivation–GIMD 2006) and rural-urban classification

Significant effects (p value < 0.05) are given in bold

decline, which was 27.7% (1–0.971^{11} × 100%) from 2001 to 2012. Higher participation rates would allow for even higher effects.

As outlined in the "Introduction" section, this estimate may be jeopardized by ecological fallacy. Compared to observational studies using individual data, ecological studies in general hold a stronger risk of bias when causal inferences are in questions. However, considering material and social area deprivation and rural-urban disparities, we adjusted for important confounders, which are hidden in most individual-level observational studies. More specific information, especially straight directed to health-related lifestyle and the quality of health care, would improve the validity of our estimate, but were not available to us. Apart from this pragmatic approach, there are two other aspects that justify the ecological study design. First, if an effect at the individual level exists, it should be reflected at the group level. If an ecological study fails to demonstrate the effect, it would give us strong reason to scrutinize the program. Second, it is plausible that positive effects of a screening program derive from side effects that work independently of the intended mechanism. Wide use of screening, for example, may create an increased awareness for the target disease. This may favor prompt diagnostic workup and treatment not only of screen-detected tumors but also of symptomatic tumors. From the health policy perspective, such a group-level effect would be relevant and attributable to screening, although it is not a direct result of early detection in a strict sense.

True limitations of our study arise from specifics of the available data. First, we had no data on regional use of colonoscopy screening from 2002 (year of introduction) to 2010. We assumed that screening procedures from 2008 to 2011 are sufficiently reliable indicators of screening uptake from the date of implementation. This requirement might be violated in some districts. Most problematic would be districts where uptake of screening colonoscopy was particularly high or low in the first years after introduction. According to the relevant directive on early cancer detection [*Krebsfrüherkennungsrichtlinie* (KFE-RL)], a second screening colonoscopy is remunerated at the earliest 10 years after the first one. A hypothetically high number of colonoscopies in the initial years could—to some extent—favor a low use between 2008 and 2011 and vice versa. The resulting inaccuracy of screening use estimates would lead to an underestimation of their effect on CRC mortality in our analyses.

A second limitation relates to screening activities prior to 2002. Our analysis is based on the assumption that no colonoscopies without diagnostic intention have been performed in that time. This condition is also questionable. Patients who were concerned about CRC and therefore asked their doctor for a colonoscopy might have been offered the examination on the basis of a low-threshold "diagnostic" indication. Widespread and long-standing use of such "gray screening" might rather lead to a low baseline mortality than result in additional mortality reduction after 2001. The possible bias would also result in an underestimation of the effect investigated in our study. Our findings in respect to the FOBT uptake (Table 2) are well compatible with these considerations. In the absence of specific data, it is plausible that the FOBT use prior to the observation period resembles the usage that we observed. If this is the case, we would not expect to find a meaningful influence on CRC mortality decline from 2001 to 2012, although the FOBT is effective.

With restriction to men, we found that diagnostically intended colonoscopies had a significant effect on the change of CRC mortality (Table 2). Against first expectation, the sign of the regression coefficient is negative, indicating an effect that reduces CRC-related mortality. From a theoretical viewpoint, diagnostic colonoscopies should indicate the presence of signs or symptoms that increase the probability of CRC diagnoses and should therefore actually be associated with *higher* disease-specific mortality. There are two aspects that might explain the finding. First, every colonoscopy has, if carried out properly, an inherent preventive potential, since it is not restricted to clarification of conditions causing the presented problem but may reveal other lesions (incidental findings). The possible effects are expected to correlate with CRC mortality in opposite directions. Which one prevails depends on the pre-test probability of the disease. The second aspect, again, relates to regulatory conditions. As mentioned before, a screening colonoscopy is remunerable as such at the earliest 10 years after the first one. However, in the case of an increased risk due to a history of polyps on a prior colonoscopy, earlier re-examinations are recommended in the guidelines. Colonoscopies, which have been performed according to these recommendations between 2008 and 2011, would appear as diagnostic procedures in our data, although initially intended as purely preventive. The potential bias is enhanced by the fact that most of the index examinations would not be caught in our analysis due to the time of conduct. To some extent, these considerations are underpinned by the sex specificity of the finding. An evaluation of the German colonoscopy screening found that multiple (≥ 2) polyps giving reason for a control examinations were found more often in men than in women (21.3% vs. 11.9%) [20].

Finally, it has to be considered that the observation period of the study is too short to reveal the full effect of the intervention. Colonoscopy screening is capable of detecting alterations that might cause death by CRC decades later [21]. In our data, mean time from screening participation (any time from October 2002 to 2011) to 2012 (last year included in the mortality trend analysis) was less than 10 years.

In conclusion, our study showed that the real-world use of screening colonoscopy in Germany has a substantial reinforcing effect on the ongoing decline of CRC mortality. Its ecological design hampers inferences about the effect of the procedure at the individual level, but involves plausible side effects of screening which are relevant from the health policy perspective. The discussed limitations suggest that the true effect at population level is even higher than established in our study.

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Compliance with ethical standards

This article does not contain any studies with human participants or animals performed by any of the authors.

Conflict of interest The authors declare that they have no conflict of interest.

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