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Original Research

Expected long-term impact of the German screening colonoscopy programme on colorectal cancer prevention: Analyses based on 4,407,971 screening colonoscopies

Hermann Brenner [a,b,c,*], Lutz Altenhofen [d], Christian Stock [e], Michael Hoffmeister [a]

[a] Division of Clinical Epidemiology and Aging Research, German Cancer Research Center (DKFZ), INF 581, 69120 Heidelberg, Germany
[b] Division of Preventive Oncology, German Cancer Research Center (DKFZ), INF 460, 69120 Heidelberg, Germany
[c] German Cancer Consortium (DKTK), INF 280, 69120 Heidelberg, Germany
[d] Central Research Institute of Ambulatory Health Care in Germany, Berlin, Germany
[e] Institute of Medical Biometry and Informatics, University of Heidelberg, INF 305, 69120 Heidelberg, Germany

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Abstract ***Aim:*** Endoscopy based screening programmes for colorectal cancer (CRC) are being implemented in an increasing number of countries. In Germany, screening colonoscopy at age 55 or older has been offered since the end of 2002. We aimed to estimate the long-term impact of this offer on CRC prevention.

Methods: We estimated numbers of prevented CRC cases by expected age and year of their (prevented) occurrence over four decades (2005–2045) by four state Markov models (non-advanced adenoma, advanced adenoma, preclinical CRC, clinically manifest CRC). Estimates are based on screening colonoscopies reported to the German screening colonoscopy registry in 2003–2012 ($N = 4{,}407{,}971$), transition rates between the four states and general population mortality rates.

Results: Numbers of prevented clinically manifest CRC cases are projected to increase from <100 in 2005 to approximately 6500 in 2015, 12,600 in 2025, 15,400 in 2035 and 16,000 in 2045, compared to approximately 58,000 incident cases observed in 2003. The annual number of prevented cases is expected to be higher among men than among women and to strongly vary by age. The vast majority of prevented cases would have occurred at age 75 or older.

Conclusions: Despite modest participation rates, the German screening colonoscopy programme will lead to substantial reductions in the CRC burden. The reductions will be fully

* *Corresponding author at:* Division of Clinical Epidemiology and Aging Research, German Cancer Research Center, Im Neuenheimer Feld 581, D-69120 Heidelberg, Germany. Tel.: +49 6221 421300; fax: +49 6221 421302.
E-mail address: h.brenner@dkfz.de (H. Brenner).

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disclosed in the long run only and predominantly affect numbers of incident cases above 75 years of age. Screening offers would need to start at younger ages in order to achieve more effective CRC prevention at younger ages.

1. Introduction

Several randomised trials have demonstrated major reduction of distal colorectal cancer (CRC) incidence by screening with flexible sigmoidoscopy [1–4], and observational studies suggest a large potential for even stronger reduction of (proximal and distal) CRC incidence by screening colonoscopy [5–7]. The trials also indicate, however, that it may often take many years until screening effects become fully manifest.

Screening programmes for CRC based on faecal occult blood testing (FOBT), sigmoidoscopy or colonoscopy are being implemented in an increasing number of countries [8]. Germany was one of the first countries introducing colonoscopy as a primary screening offer in October 2002, and it will be of utmost interest to monitor development of CRC incidence in the screening colonoscopy era. It is unclear, however, when to expect which effects of screening colonoscopy on CRC incidence in various age groups. In this article, we aim to estimate and project the numbers of CRC cases prevented (through detection and removal of adenomas) by the German screening colonoscopy programme according to expected age and year of their (prevented) occurrence.

2. Methods

2.1. Data

Our analysis is based on data of the German national screening colonoscopy registry. Details on the German screening colonoscopy programme and the registry have been reported elsewhere [9]. Briefly, men and women aged 55 years or older are entitled to have colonoscopy as a primary screening examination. If the first screening colonoscopy is conducted before 65 years of age, a second screening colonoscopy is offered 10 years later.

Along with introduction of screening colonoscopy in October 2002, a national screening colonoscopy registry was launched to which all screening colonoscopies among members of statutory health insurance (SHI) in Germany (85% of all men and 92% of all women aged 55+ years in Germany) are reported anonymously on a standardised form. Reporting is a prerequisite for physicians' reimbursement by the SHI and is assumed to be close to complete. The registry includes only primary screening examinations (i.e. colonoscopies conducted for surveillance, work-up of symptoms or other screening tests are not included). Findings at colonoscopy are reported, including number, size and histological characteristics of polyps. In case of multiple neoplasms, participants are classified according to the most advanced finding (non-advanced adenoma, advanced adenoma, or cancer). Advanced adenomas are defined as at least one adenoma $\geqslant 1$ cm or at least one adenoma with villous components or high-grade dysplasia.

Approximately 2–3% of eligible people have had a screening colonoscopy each year since the introduction of this screening offer, which corresponds to a cumulative participation rate of approximately 20–30% within the initial 10 years of the screening colonoscopy programme. For this analysis, we used data from 4,408,571 first time screening colonoscopies in 2003–2012 among participants aged 55 years or older. We assumed the same sex and age specific screening participation rates and the same sex and age specific prevalences of neoplasms among non-members of SHI (approximately 15% of men and 8% of women in Germany in the age groups included), the overwhelming majority of whom have private health insurance which provides equivalent (or less restricted) screening offers.

2.2. Statistical analysis

We estimated the numbers of clinically manifest CRCs, by age and year of occurrence, that are expected to be prevented by detection and removal of adenomas at screening colonoscopy. For 2003–2012, the first 10 years of the German screening colonoscopy programme, numbers of participants in whom adenomas were detected were directly available from reported numbers and extrapolated to the total German population as outlined above. For subsequent calendar years, we assumed age and sex specific numbers of participants in whom adenomas are detected to remain at the level observed in 2012.

Prevented case numbers were obtained from four-state Markov models with annual iterations starting at the individual ages of colonoscopy as illustrated in Fig. 1. An overview of input parameters for the models is given in Tables 1 and 2. At each iteration, progression between states was modelled based on previously derived sex and age specific annual transition rates (Table 2) [10,11], accounting for mortality which was obtained from general population life tables for the period 2009/2011. In the base case analysis, age and sex

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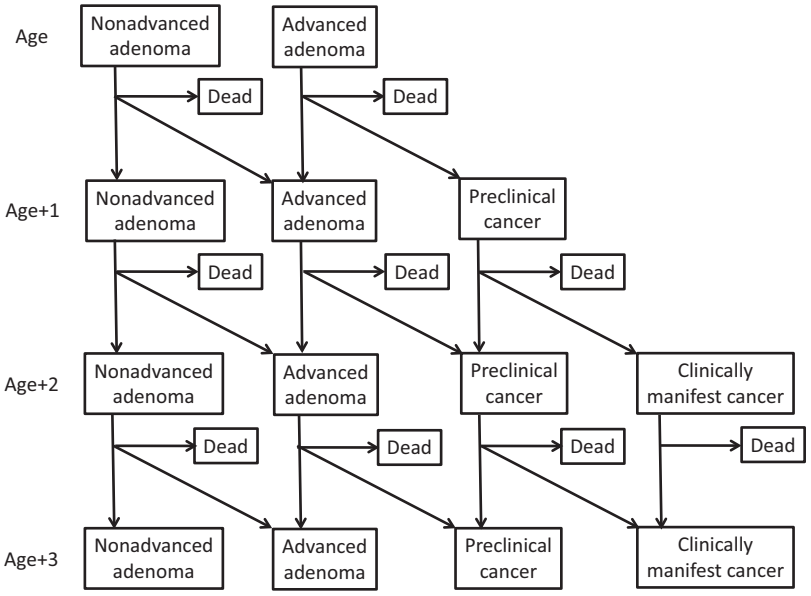

Fig. 1. Schematic presentation of the four-state Markov model for the initial three years after adenoma detection.

Table 1
Overview of data and parameters and their sources for the Markov models.

Data, parameters	Sources; base case analysis	Sensitivity analyses
Sex and age specific numbers of screening colonoscopy participants in Germany in 2003–2045 with non-advanced and advanced adenoma	National screening colonoscopy registry, single calendar years (2003–2012). Extrapolated to German total population Numbers assumed to remain constant at levels observed in 2012 from 2013 to 2045	
Sex and age specific transition rates from non-advanced to advanced adenoma and from advanced adenoma to preclinical cancer	Derived by birth cohort analyses of data from the national screening colonoscopy registry (Ref. [10]; see Table 2) For ages 80+ the same rates as for age group 75–79 are assumed	Upper and lower limits of confidence intervals rather than point estimates of transition rates
Sex and age specific transition rates from preclinical to clinically manifest colorectal cancer	Derived from combination of data from the national screening colonoscopy registry with cancer registry data (Ref. [11]; see Table 2) For ages 85+ same rates as for age group 80–84 are assumed	Upper and lower limits of confidence intervals rather than point estimates of transition rates
Sex and age specific mortality rates	Life table Germany, 2009/2011 Mortality rates assumed to be constant throughout projection period	Life Table Germany, 2009/2011 Mortality rates assumed to decrease by 20% every 10 years (2016–2025, 2026–2035, 2036–2045)

specific mortality rates were assumed to remain constant throughout the projection period. In sensitivity analyses, general population mortality was assumed to decrease by 20% every 10 years (2016–2025, 2026–2035, 2036–2045), the pace of decrease in mortality in Germany in previous decades.

Because detection and removal of adenomas does not provide 100% protection against colorectal adenomas, the expected numbers of cancers that would have developed from the detected adenomas was multiplied by 0.69, the summary estimate of risk reduction by screening colonoscopy derived in a recent meta-analysis of epidemiological studies [7].

3. Results

Table 3 shows the numbers and findings of participants of screening colonoscopy included in the national registry in 2003–2012. Overall, almost 2 million men and more than 2.4 million women were included, slightly more than half of them were between 55 and 64 years of age and less than 10% were 75 years or older at the time of colonoscopy. The total numbers of participants were highest in 2004 to 2006 (approximately 550,000 per year), and gradually decreased in subsequent years to level off at approximately 375,000 per year in 2010 to 2012. Over the years, the proportion of participants in

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Table 2
Sex and age specific transition rates (summary and synopsis of estimates derived and reported in Refs. [10,11]).

Sex	Age	Annual transition rates in %					
		From non-advanced to advanced adenoma		From advanced adenoma to preclinical cancer		From preclinical to clinical cancer[‡]	
		PE	95% CI	PE	95% CI	PE	95% CI
Men	55–59	4.2	3.8–4.6	2.6	2.4–2.9	18.1	16.7–19.5
	60–64	4.0	3.6–4.4	3.1	2.8–3.3	19.2	18.1–20.3
	65–69	4.0	3.6–4.3	3.8	3.5–4.1	21.3	20.3–22.4
	70–74	4.1	3.6–4.6	5.1	4.8–5.5	20.6	19.5–21.7
	75–79	3.7	2.9–4.6	5.2	4.6–5.8	20.1	18.9–21.4
	80+	[*]		[*]		18.2[†]	16.7–19.9
Women	55–59	4.0	3.6–4.5	2.5	2.2–2.7	21.3	19.5–23.4
	60–64	3.6	3.2–4.1	2.7	2.4–3.0	22.5	20.9–24.2
	65–69	3.7	3.2–4.1	3.8	3.5–4.1	21.9	20.6–23.3
	70–74	4.7	4.1–5.3	5.0	4.5–5.4	20.8	19.4–22.2
	75–79	3.7	2.8–4.7	5.6	4.9–6.3	19.2	17.9–20.7
	80+	[*]		[*]		17.3[†]	16.0–18.8

CI, confidence interval; PE, point estimate.
[*] Transition rates for this age group were not specifically derived in Ref. [11], but were assumed to be the same as in age group 75–79 in this analysis.
[†] Transition rates derived in reference 10 pertained to age group 80–84; for this analysis, the same transition rates were assumed for ages 80–84 and 85+.
[‡] Derived by combining data from the national screening colonoscopy registry with German cancer registry data as described in detail in Ref. [11].

Table 3
Participants and findings at screening colonoscopy. German screening colonoscopy registry, 2003–2012.

Sex	Age	Participants	Most advanced finding					
			Non-advanced adenoma		Advanced adenoma		Colorectal cancer	
			N	%	*N*	%	*N*	%
Men	55–59	567,036	97,406	17.2	37,801	6.7	3401	0.6
	60–64	468,912	86,484	18.4	39,465	8.4	4706	1.0
	65–69	464,297	90,502	19.5	43,467	9.4	6291	1.4
	70–74	299,299	60,682	20.3	30,197	10.1	5868	2.0
	75–79	139,834	27,242	19.5	14,780	10.6	3619	2.6
	80+	50,432	9,125	18.1	5,231	10.4	1756	3.5
	Total	1,989,810	371,441	18.7	170,941	8.6	25,641	1.3
Women	55–59	769,572	79,939	10.4	27,932	3.6	2429	0.3
	60–64	570,926	66,356	11.6	26,550	4.7	2865	0.5
	65–69	528,910	67,697	12.8	28,463	5.4	3903	0.7
	70–74	327,492	45,868	14.0	20,186	6.2	3586	1.1
	75–79	157,038	21,609	13.8	10,754	6.8	2505	1.6
	80+	64,223	8445	13.1	4829	7.5	1753	2.7
	Total	2,418,161	289,914	12.0	118,714	4.9	17,041	0.7

the youngest age group (55–59 years) rose from approximately 20% to approximately 40% in 2010–2012. Overall prevalences of non-advanced and advanced adenomas and of colorectal cancer were almost 2-fold as high in men (18.7%, 8.6%, and 1.3%, respectively) compared to women (12.0%, 4.9% and 0.7%, respectively). Prevalences of advanced adenomas and cancer generally increased with age in both men and women (except for advanced adenomas in the oldest age group among men).

As shown in Fig. 2, the annual number of prevented clinically manifest CRCs is expected to steadily increase and to level off only after 2040 according to the base case analysis. The numbers of prevented clinically manifest CRC cases at ages 55+ are projected to increase from less than 100 in 2005 to approximately 6500 in 2015, 12,600 in 2025, 15,400 in 2035 and 16,000 in 2045, compared to approximately 58,000 incident cases observed in 2003. These numbers correspond to approximately 0.2%, 11%, 22%, 27% and 28% of the 58,000 incident CRC cases observed in Germany in 2003, the first year of the period of investigation [12]. As Fig. 3 shows, quite distinct patterns are expected for occurrence of cancers at various ages. It is expected that in the older age groups the full impact of screening colonoscopy will be seen with substantial delay, but

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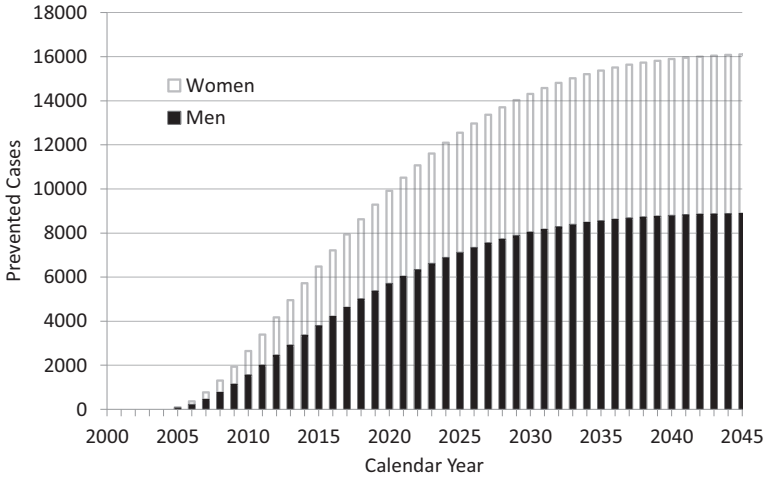

Fig. 2. Expected numbers of prevented cases according to year of occurrence.

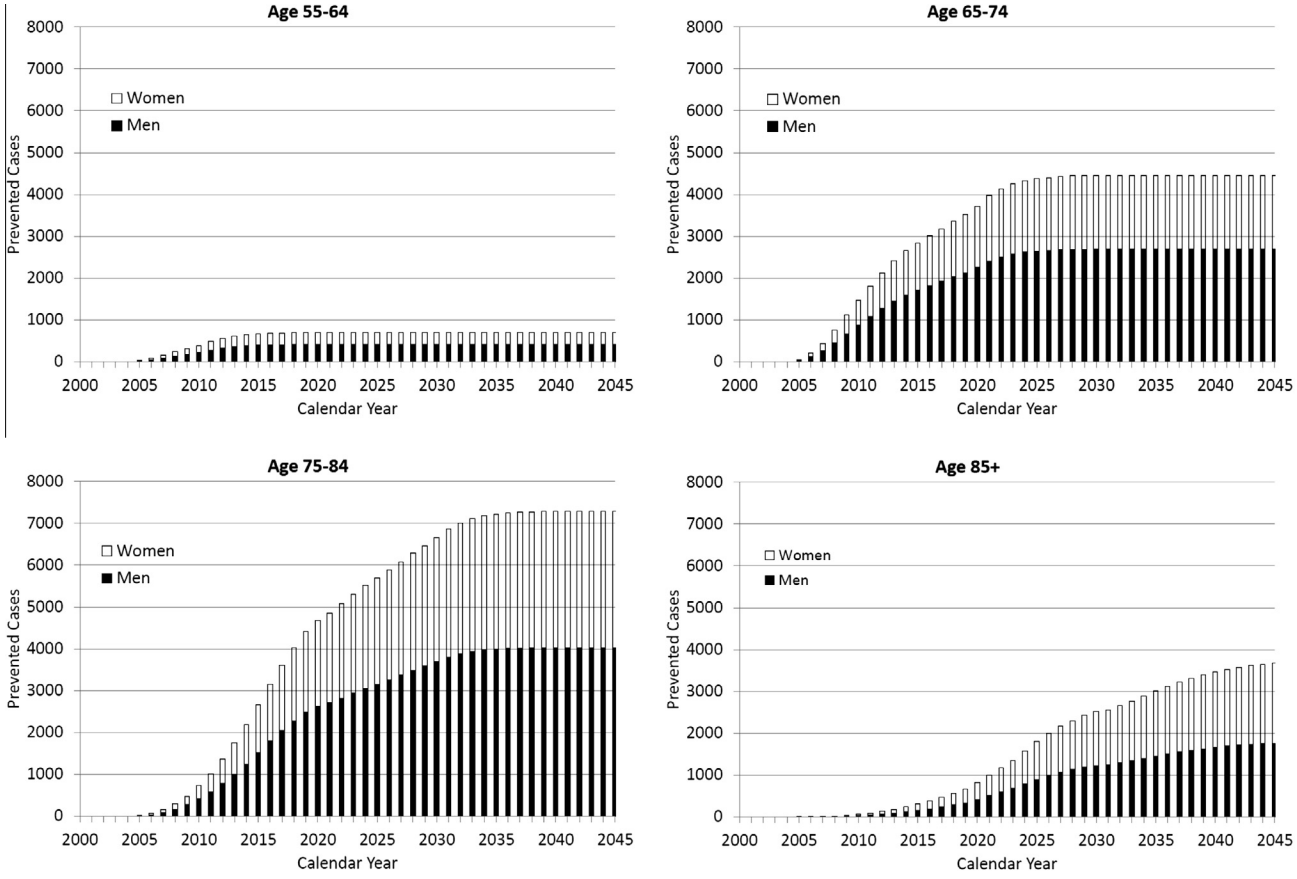

Fig. 3. Expected numbers of prevented cases according to age at diagnosis and year of occurrence.

ultimately will be much stronger than in the younger age groups. In absolute numbers of prevented cases, the impact is expected to be largest in age group 75–84 years, in which a reduction of annual case numbers by more than 3000 in women and more than 4000 in men is expected in the long run. Overall, the impact of screening colonoscopy is expected to be very modest for CRCs diagnosed in age group 55–64. Only in age group 85+ will the expected impact according to prevented absolute case numbers be larger for women than for men in the long run.

Sensitivity analyses assuming continued reduction in mortality rates by 20% per decade suggest that the numbers of prevented CRC cases could even be substantially larger, exceeding 20,000 per year from 2040 onwards, and continuing to rise throughout the projection period

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(Supplementary Fig. 1). Decreasing mortality would have the most pronounced effect on the numbers of prevented cases in age group 85+ (Supplementary Fig. 2), which would be expected to more strongly increase over time to levels approximately twice as high compared with those projected in the base case scenario with constant mortality rates (Fig. 3).

Supplementary Fig. 3 provides results of sensitivity analyses assuming transition rates at lower and upper bounds of the 95% confidence intervals rather than at the point estimates shown in Table 2. These somewhat lower and higher transition rates would result in estimated total annual numbers of prevented CRC of approximately 14,000 and 18,000 rather than 16,000 in the long run.

4. Discussion

In this article, we provide detailed sex and age specific model calculations on the prevention of clinically manifest CRC over a period of four decades from 2005 to 2045. Despite the relatively low annual participation rates in the German screening colonoscopy programme, a major reduction of annual case numbers in the order of up to 16,000 is to be expected in the long run. This number could be even substantially higher in case of ongoing reduction in general population mortality rates. However, most of this reduction will only become manifest in the longer run, and reductions will be strongest in age group 75+, still substantial in age group 65–74 years, and very modest in age group 55–64 years.

The reason for the large time lag of effects on numbers of prevented clinically manifest CRC is the very slow development of CRC from non-advanced and advanced adenoma, which is consistent with results from comparative lesion sequencing [13], with annual transition rates from non-advanced to advanced adenomas around 4% (which corresponds to a mean duration of adenomas in the non-advanced stage of 25 years), and annual transition rates from advanced adenomas to preclinical cancer between around 2.5% at younger ages and around 5–6% at higher ages [10]. As a result, many detected and removed adenomas would have developed into clinically manifest CRC several decades after their detection at screening colonoscopy only (or they would even not have become clinically manifest in a lifetime). This large time lag also explains why removal of adenomas detected by screening colonoscopies, which are mostly conducted between 55 and 70 years of age [9], results in much stronger reduction in the CRC burden at ages 75+ years than at younger ages.

The predicted overall and age specific patterns of reduction in the CRC burden are in agreement with epidemiological observations from the United States, where screening sigmoidoscopy and screening colonoscopy have been offered and increasingly used since the 1980s and the 1990s, respectively [14], and quite substantial decreases in incidence and resection rates of distal and proximal CRC were seen since the 1990s and the first decade of the 21st century, respectively [15–17]. Notably, the decrease in distal cancer incidence was most pronounced in the oldest age groups, whereas no decrease was seen for ages below 50 years for which screening is not generally recommended, and only a modest decrease was seen for age group 50–59 [15]. In agreement with our results, first reductions of CRC incidence and a shift towards earlier stages are meanwhile also seen in Germany [18].

Our model calculations should, however, not be taken as forecasts of changes in CRC incidence or annual numbers of cases over time up to the year 2045. Rather, they exclusively quantify the expected contribution of removal of adenomas detected at screening colonoscopy to the reduction of the CRC burden. Overall changes in incidence and case numbers of CRC will depend on additional factors, such as demographic changes, changes in risk factor profiles and adenoma detection rates, the impact of other screening measures (such as FOBT) or the impact of colonoscopies conducted for other reasons. In Germany, the number of diagnostic colonoscopies exceeds the number of screening colonoscopies [19], and detection and removal of adenomas at diagnostic colonoscopies is likely to have an additional major impact on reduction of CRC cases. Also, some additional impact is to be expected from repeat screening colonoscopies after 10 or more years that were not yet included in the national database in the initial 10 years of the programme. Finally, screening colonoscopy leads to a mostly transient initial increase in numbers of detected CRC which in the long run is compensated by a corresponding reduction of clinically manifesting CRC, except for a small proportion of overdiagnoses of CRC that would not have become clinically manifest in the absence of screening [20].

In our analyses we assumed that detection and removal of adenomas reduces the risk of CRC by 69%, the risk reduction actually observed in case-control and cohort studies according to a recent meta-analysis [7]. This value is also in the range of estimates of maximum clinical incidence reduction obtained by various microsimulation models [21]. Although risk reduction has been shown to vary by subsite of the colon and rectum [7] and according to multiplicity of adenomas, we used this overall estimate to derive the expected total impact of screening colonoscopy. Although close to full protection might be achieved in case of optimal surveillance, less than full protection has to be assumed due to non-adherence or adenoma miss rates at surveillance colonoscopy [22,23].

Our analyses focus on prevented CRC cases. So far, 30–40% of CRC patients eventually die from CRC.

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With ongoing improvement in therapy, these proportions are likely to diminish over time [17]. Given the uncertainties regarding future CRC survival rates, we intentionally refrained from modelling prevented CRC deaths.

Our study has a number of strengths and limitations. A major strength is the use of a national database with complete coverage of members of SHI in Germany including more than 4.4 million records. The main limitation is dependence of our calculations on a variety of assumptions the most critical being the sex and age specific numbers of detected adenomas in the years to come. In our analysis, these numbers were assumed to remain constant at the levels observed in 2012, the most recent year for which they were known. These numbers might change in the future due to a variety of factors, including demographic changes, changes in participation rates in screening colonoscopy, and adenoma detection rates. The biggest impact on numbers of detected adenomas might potentially come from a national law launched in 2013 that requests establishment of an organised screening with targeted invitations of eligible women and men which would be expected to increase participation rates substantially.

As shown in sensitivity analyses, continued reduction in general mortality at the level observed in recent decades in Germany might have a strong impact on prevented numbers of CRC, especially in the older age groups. With continuing decline in mortality, the annual numbers of prevented CRCs will keep increasing beyond 2045, the final year included in our modelling. By contrast, uncertainties in the assumed transition rates would have only relatively small impact on numbers of prevented CRCs given that these transition rates had been estimated at very high levels of precision in previous research.

Notwithstanding the uncertainties in the assumptions made in the modelling, our results demonstrate the large impact screening colonoscopy is expected to have on future numbers of CRC cases. These results, along with previously reported low complication rates (e.g. 0.58 serious complications per 1000 screening colonoscopies, two deaths related to screening colonoscopy in 2005–2008, [9]) should encourage efforts to enhance the still relatively low screening participation rates. Furthermore, the temporal patterns disclosed in our analysis should be kept in mind when monitoring cancer incidence rates as part of the efforts to evaluate the impact of screening colonoscopy at the population level: The so far visible impact of screening colonoscopy is likely just a relatively minor share of the impact on annual case numbers and incidence that can be expected in the long run if current levels of screening colonoscopy participation can be maintained or even increased. We therefore hope that our results will encourage enhancing current efforts in CRC prevention that will pay off over decades to come. Enhanced participation in CRC screening, particularly at younger ages, would make a major contribution to this end. Together with progress in other, less invasive screening methods, such as the shift from guaiac based to immunochemical faecal occult blood tests [24], as well as progress in therapy [25] this could substantially reduce the burden of CRC in the decades to come.

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Conflict of interest statement

None declared.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ejca.2015.03.020.

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