Estimated long-term effects of the initial 6 years of the German screening colonoscopy program

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Background: Colorectal cancer is the most common cancer in Germany. Screening colonoscopies have been offered as a primary screening tool in Germany since the end of 2002.

Objective: To estimate the numbers of clinically manifest colorectal cancers prevented by detection and removal of advanced adenomas in the initial 6 years of the program.

Design: Markov model with single-year transitions.

Setting: German screening colonoscopy program.

Patients: Participants in the screening colonoscopy program from 2003 to 2008.

Interventions: Screening colonoscopy with the removal of advanced colorectal neoplasms.

Main Outcome Measurements: The expected numbers of incident colorectal cancers prevented by detection and removal of advanced adenomas.

Results: An estimated total number of 73,024 cases of colorectal cancer might have developed from the removed advanced adenomas and become clinically manifest between 55 and 84 years of age in the absence of screening colonoscopy. This number exceeds the number of colorectal cancers diagnosed in 2002 by 27%. Among prevented cancers, 8%, 43%, and 49% would have occurred at ages 55 to 64, 65 to 74, and 75 to 84 years (median age 74 years), respectively; 60% and 40% would have occurred among men and women, respectively; and 22%, 32%, 25%, and 20% would have occurred within 1 to 5, 6 to 10, 11 to 15, and 16 to 30 years, respectively, after colonoscopy (median 10 years).

Limitations: Diagnoses of advanced adenomas are based on records from a large number of endoscopists and pathology laboratories.

Conclusions: Despite relatively low screening participation, the German screening colonoscopy program is expected to make a major contribution to the prevention of colorectal cancer, even though most of the impact will only be seen in the longer run. (Gastrointest Endosc 2010;72:784-9.)

Colorectal cancer (CRC) is the third most common cause of cancer and the fourth most common cause of cancer death globally, with annual numbers of new diagnoses and deaths exceeding 1 million and 500,000, respectively.1 The incidence has been particularly high in Germany, with an age-adjusted incidence in the German state of Saarland ranking fourth in both men and women in 1998 to 2002 among 225 cancer registries included in the latest volume of Cancer Incidence in Five Continents.2,3 Because of its slow development from detectable and removable precursor lesions, the outcomes with early detection and prevention are much better than for other forms of cancer. Several...
screening options, including fecal occult blood testing, sigmoidoscopy, and colonoscopy, exist and are recommended by expert committees in various countries.4,5

In Germany, an offer of free screening colonoscopies was introduced nationwide as a primary screening tool for CRC in October 2002, and results of screening colonoscopies are documented in a national registry.6,7 For evidence-based decisions about the continuation of this program, it is crucial to timely estimate its effects at the population level. We previously estimated, based on records from the national registry until 2006, that approximately 15,000 additional CRC cases might have become clinically manifest by 2010 in the absence of detection and removal of advanced adenomas at a screening colonoscopy.8 However, most of the effects of the screening colonoscopies will become evident only in the longer run, given the relatively slow development of clinically manifest CRCs from advanced adenomas. By using updated data from the national screening colonoscopy registry, we aimed to derive estimates of the total and age- and sex-specific numbers of CRC that might have become clinically manifest at ages 55 to 84 and that were prevented by detection and removal of advanced adenomas at screening colonoscopy from 2003 to 2008, the initial 6 years of the screening colonoscopy program.

MATERIAL AND METHODS

The German screening colonoscopy program

The setup of the German screening colonoscopy program, introduced in October 2002, was described in detail elsewhere.6,8 Briefly, women and men are entitled to have a first screening colonoscopy from the age 55 on, and a second screening colonoscopy after 10 or more years, provided the first screening colonoscopy was performed before the age of 65. Along with the introduction of the screening colonoscopy offer, a rigorous quality control program was established, and a national registry was set up to document participation rates and reports of screening colonoscopies in a standardized manner. According to recent studies conducted in the screening setting, completeness of screening colonoscopies is high, with the cecum being reached in more than 90% of them.9,10

Participants with detected and removed advanced adenomas

In an initial step, the numbers of participants in the screening colonoscopy program in whom advanced adenomas were detected and removed were estimated by age (a) (55 ≤ a ≤ 84), sex (s = males, females), and calendar year (cy) (2003 ≤ cy ≤ 2008) (denoted as naa,a,s,cy) as naa,a,s,cy = POP,a,s,cy × PART,a,s,cy × PAA,a,s,cy, where POP,a,s,cy, PART,a,s,cy, and PAA,a,s,cy denote the age-, sex-, and calendar year–specific population figures (obtained from the Federal Statistics Office11), the proportion of people participating in the screening colonoscopy program, and the proportion of screening colonoscopy program participants in whom at least 1 advanced adenoma (but no carcinoma) was detected. The latter 2 parameters were obtained from the national screening colonoscopy registry, which included records of 2.82 million participants in the screening colonoscopy program aged 55 to 84 from 2003 to 2008. Advanced adenomas were defined as adenomas with at least 1 of the following features: more than 1 cm in size, tubulovillous or villous adenoma, or high-grade dysplasia. The naa,a,s,cy were then summed over calendar years to obtain the overall age- and sex-specific number of participants in whom at least 1 advanced adenoma (but no carcinoma) was detected at the screening colonoscopy, denoted as Na,a,s. This method for estimating screening colonoscopy–detected carriers of advanced adenomas was preferred over simple enumeration of registered carriers of advanced adenomas in the national registry because it takes into account the fact that the national registry covers only approximately 90% of the German population covered by the statutory health insurance system and, among them, completeness of registration only gradually approached 100% in the initial months of registry setup. Since then, however, registration has been essentially complete because it is a prerequisite for reimbursement. Almost all German citizens not covered by the statutory health insurance system have private insurance, which provides equivalent offers of a screening colonoscopy. The estimation was thus based on the assumption that screening colonoscopy program participation and prevalence of advanced adenomas were similar among those who were covered by the statutory health insurance system and included in the national registry and those who were not. In addition, the number of screening colonoscopy program participants in whom CRC was detected was estimated in a similar manner.

Prevented CRCs

In a second step, the numbers of prevented preclinical CRCs between ages 55 and 84, denoted Pf,a,fy−1,s, were estimated by year after (fy) screening colonoscopy (1 ≤ fy ≤ 30), age a + fy − 1 (55 ≤ a + fy − 1 ≤ 84) and sex (s). This was done consecutively for each year after screening colonoscopy in a Markov type process, as
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Figure 1. Stepwise calculation of the expected number of preclinical CRC cases prevented by detection and removal of advanced adenomas. Parameter definitions: $a$ = age at detection and removal of advanced adenoma, $s$ = sex of screening participants, $f_y$ = year after screening colonoscopy, $N_{a,s}$ = numbers of participants with advanced adenomas detected and removed at age $a$ with sex $s$, $NAA_{a,s}$ = (remaining) screening participants with detected and removed advanced adenomas at the beginning of 2004 in sex $s$ that would have developed from advanced adenomas in $f_y$ at age $a + f_y - 1$ in the absence of screening colonoscopy (ie, prevented preclinical CRC cases).

shown in Figure 1, taking age- and sex-specific death rates (denoted as $d_{a+f_y-1,s}$) and age- and sex-specific transition rates from advanced adenomas to preclinical CRCs (denoted as $t_{a+f_y-1,s}$) into account. The mortality rates were obtained from life tables for the German population for calendar years 2004 to 2006,\textsuperscript{11} and estimates of the transition rates were obtained from a previous study, as described in detail elsewhere.\textsuperscript{12} Estimated annual transition rates were similar in women and men and increased from 2.6% in the age group 55 to 59 to more than 5% in the oldest age groups.

In a third step, the numbers of prevented clinically manifest CRCs between ages 55 and 84 were estimated by year after screening colonoscopy $f_y$ (1 $\leq f_y $ $\leq 30$), age $a + f_y - 1$ (55 $\leq a + f_y - 1 $ $\leq 84$) and sex $s$ by an analogous Markov type process from the numbers of prevented preclinical CRCs (additionally taking their expected onset at various years after screening colonoscopy into account), age- and sex-specific mortality rates, and age- and sex-specific transition rates from preclinical to clinically manifest CRCs. The latter were derived assuming a median sojourn time of preclinical CRC of 3.6 years, corresponding to an annual transition rate of 17.5%, as previously estimated.\textsuperscript{12,13}

Sensitivity analyses were performed to estimate the number of prevented clinically manifest cancers under the following alternative scenarios: (1) 20% lower general mortality, reflecting potential ongoing increase in life expectancy; (2) variation of transition rates from advanced adenomas to preclinical CRC by $\pm 40\%$; (3) variation of annual transition rates from preclinical CRC to clinically manifest CRC by $\pm 40\%$.

These rather extreme sensitivity analyses were performed to depict fluctuations that are not likely to occur, but that are within the realm of possibility for populations of this size and rates based on historical data.

RESULTS

Table 1 shows the average population by sex and age, average annual screening colonoscopy program participation, and average proportion of screening colonoscopy participants in whom advanced adenomas (but no carcinomas) were detected. The average annual participation from 2003 to 2008 ranged from 2.9% to 3.9% in age groups 55 to 59, 60 to 64, and 65 to 69 and was higher among women than among men in these age groups. At older ages, participation was much lower, ranging from 0.3% to 2.3%, and higher among men than among women. The proportion of participants in whom at least 1 advanced adenoma (but no carcinoma) was detected ranged from 3.5% to 10.2%, increased with age, and was substantially higher among men than among women in all age groups.
Overall, 73,024 cases of CRC that might have developed from removed advanced adenomas and become clinically manifest between 55 and 84 years of age were estimated to have been prevented between 2003 and 2008. This number exceeds the total number of CRCs diagnosed in Germany in that age range in 2002 (n = 110,577), the calendar year at the end of which screening colonoscopy was introduced, by 27%.

The estimated number of prevented clinically manifest cancers was slightly increased by 6.6% to 77,878 in sensitivity analyses assuming 20% lower general mortality, ranged from 48,817 to 92,329 in sensitivity analyses assuming 40% lower or higher transition rates from advanced adenoma to preclinical cancer, and from 57,878 to 81,513 in sensitivity analyses assuming 40% lower or higher transition rates from preclinical cancer to clinically manifest cancer, respectively.

As Figure 2 shows, most prevented cancers would have occurred within 15 years after detection and removal of the advanced adenoma. Among prevented CRCs, 22%, 32%, 25%, and 20% would have occurred within 1 to 5, 6 to 10, 11 to 15, and 16 to 30 years, respectively, after the date of colonoscopy (median 10 years). The temporal distributions are very similar for men and women, even though absolute numbers are substantially higher among men than among women in each time window. Overall, a clear majority of prevented cancers, estimated at 60%, would have occurred among men.

Among prevented cancers, 8%, 43%, and 49% would have occurred at ages 55 to 64, 65 to 74, and 75 to 84 years, respectively (median age 74 years) (Fig. 3). Again, the age distribution is very similar among men and women. Looking at time after the date of the screening colonoscopy and age jointly (Fig. 4) illustrates that the protective effect in the younger age groups is essentially restricted to the early years after screening colonoscopy, whereas most of the protective effect in the older age groups is only seen after more than 10 years.

Apart from preventing CRC, colonoscopy screening also contributes to early detection of CRC. Overall, 33,633 cases of CRC were estimated to have been detected at screening colonoscopy from 2003 to 2008, slightly less...
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than half the estimated number of prevented clinically manifest cancers. The age at diagnosis of patients with screening colonoscopy–detected cancers was much lower (median 67 years) than the age of patients with screening colonoscopy–prevented cases.

DISCUSSION

Germany was the first country in the world to offer free colonoscopy as a primary screening to essentially all citizens aged 55 and older. Close monitoring of this program and its expected effects is crucial for decisions as to whether and how this screening offer will be maintained, modified, or extended. We estimate that more than 73,000 cases of CRC that would otherwise have become clinically manifest between ages 55 and 84 were prevented by detection and removal of advanced adenomas in the initial 6 years of the program. This number is far exceeds the annual numbers of CRCs diagnosed in the age range 55 to 84 before the introduction of screening colonoscopy.

The importance of detection and removal of advanced adenomas for CRC prevention is underscored by recent findings of the increasing prevalence of advanced adenomas in younger birth cohorts, which might be related to unfavorable trends in risk factors, such as the increasing prevalence of overweight and obesity in younger generations. According to our analysis, major prevention of CRC is achieved despite relatively low participation rates of approximately 3% to 4% in the age range 55 to 64 years, which, if maintained, would correspond to 30% to 40% participation within the 10-year interval currently recommended for screening. Even much stronger effects would be expected if participation could be increased. So far, CRC screening is offered in an opportunistic manner in Germany, without individual invitation and follow-up of participants. Transition to an organized screening with specific invitation schemes, which is foreseen in the context of the National Cancer Plan initiated in 2008, might further substantially enhance the potential of CRC prevention.

In interpreting our analyses, the underlying assumptions and their impact on the results must be kept in mind. Most critical among these are the transition rates from advanced adenomas to preclinical CRC and from preclinical cancer to clinically manifest cancer. Base case values for both parameters were taken from previous studies. Sensitivity analyses indicated that our estimates of prevented cases of clinically manifest cancer to be rather robust against even major variation in values for these key parameters. In the base case analysis, general mortality was assumed to remain at the level observed in 2004 to 2006. More likely, the long-standing trend of decreasing mortality will continue, albeit the rate of further decrease is uncertain. According to our sensitivity analysis, even a major decrease in general mortality would lead to a rather modest increase in expected numbers of prevented cancers (adding those cancers that would not have become clinically manifest and diagnosed lifetime in the absence of a decrease in mortality).

Our analysis entirely focused on prevention of CRC by detection and removal of advanced adenomas. Additional benefit is to be expected by detection and removal of other, nonadvanced adenomas. Their number exceeds the number of advanced adenomas. Although transition rates to CRC and short-term preventive effects are assumed to be much lower than for advanced adenomas, removal of nonadvanced adenomas may have an impact on the CRC incidence in the longer run.

On the other hand, the number of prevented CRC cases may have been overestimated to some extent in our analyses, given that some proportion of advanced adenomas detected by screening colonoscopy could have become clinically manifest (eg, through bleeding) and removed even in the absence of screening. Furthermore, detection and removal of advanced adenomas will not always eliminate the development of CRC from these lesions because advanced adenomas may recur or may be incompletely removed, synchronous neoplasms may be missed at colonoscopy, and carriers of advanced adenomas may be at increased risk of developing another advanced adenoma or CRC at a different site. Risks of CRC after removal of advanced adenomas can be minimized by surveillance colonoscopy, which is recommended 3 years after polypectomy in Germany. However, colonoscopic surveillance is likely to be less than perfect in the community setting.

Despite major improvement in recent years, approximately half of patients with clinically manifest CRC still die of their disease. Therefore, the prevention of more than 73,000 incident cases through detection and removal of advanced adenomas is expected to be followed by prevention of approximately half of that number of deaths caused by CRC. An additional major impact on the reduc-
tion of CRC deaths is expected with early detection and treatment of CRCs at screening colonoscopies. The 73,000 cases of CRC that were estimated to be prevented by screening colonoscopies from 2003 to 2008 according to our analysis go along with more than 33,000 cases of CRCs that were detected by screening colonoscopy in the same period. With 70% in stage I or II, 24,25 the stage distribution of CRC detected in the German screening colonoscopy program is much more favorable than the stage distribution of CRC seen in clinical settings in Germany where slightly less than 50% of detected cases are stages I or II, 26 suggesting that a substantial (although difficult to quantify) proportion of cancers will have become curable by early detection in screening colonoscopy. On the other hand, some of the screening-detected cancers might not have become clinically manifest during a patient’s lifetime. However, this proportion is likely to be small, given the median age of 67 years of participants with screening colonoscopy–detected CRC. Therefore, overdiagnosis is likely to be limited, but lead time is an additional issue that must be kept in mind.

Our analysis has a number of strengths and limitations. Strengths include the unique national database that enabled us to base our analysis on nearly 3 million records of screening colonoscopies from 2003 to 2008, constituting the vast majority of screening colonoscopies conducted in Germany during those years. On the other hand, despite major efforts of quality assurance in the screening colonoscopy program, the degree of standardization of colonoscopy and histology information, provided by a large number of endoscopists and pathology laboratories, is likely to be less perfect in such a nationwide database than could be achieved in a trial by a few specialized centers with centralized review of all adenomas.

Despite its limitations, our study suggests that screening colonoscopy in Germany is expected to have already made a major contribution to the prevention of CRC in its initial 6 years, even though most of the impact will only be seen in the longer run.

REFERENCES