Prevention, Early Detection, and Overdiagnosis of Colorectal Cancer Within 10 Years of Screening Colonoscopy in Germany

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BACKGROUND & AIMS: **Screening colonoscopy was introduced in Germany in October 2002. We aimed to quantify its effects on prevention, early detection, and overdiagnosis of colorectal cancer (CRC) in the 10 years since its introduction.**

METHODS: **We analyzed data from more than 4.4 million screening colonoscopies (conducted on individuals 55–79 years old from 2003 through 2012) available through the national screening colonoscopy registry. CRCs prevented, detected earlier than they would have been without screening, and overdiagnosed (cancers detected at screening colonoscopy that would not have become clinically manifest during the patient's lifetime) were estimated by Markov models. Model parameters included sex-specific and age-specific findings at screening colonoscopy; mortality; rates of transition from nonadvanced to advanced adenoma, advanced adenoma to preclinical cancer, or preclinical cancer to clinically manifest cancer; and protection from screening colonoscopy.**

RESULTS: **Overall, approximately 180,000 CRCs (1/28 screening colonoscopies) were estimated to have been prevented, and more than 40,000 CRCs (1/121 screening colonoscopies) were detected earlier than they would have been without screening, compared with approximately 4500 overdiagnoses (1/1089 screening colonoscopies). Almost all CRCs prevented or detected earlier than they would have been without screening resulted from screening colonoscopies performed on individuals up to 75 years old (97% and 89%, respectively), whereas 28% of overdiagnoses occurred from screening colonoscopies of individuals older than 75 years old.**

CONCLUSIONS: **On the basis of a 10-year analysis of data from a national registry in Germany, screening colonoscopies have large potential for prevention and early detection of CRC, with low risk of overdiagnosis.**

Keywords: Adenomas; Colon Cancer; Colorectal Neoplasms; Tumor.

Colorectal cancer (CRC) is one of few cancers for which effective screening options are established. Randomized controlled trials have shown reduction of CRC mortality by annual or biennial fecal occult blood test screening[1–3] and reduction of both CRC incidence and mortality by screening sigmoidoscopy.[4] Although long-term results from randomized controlled trials for screening colonoscopy are not available yet, observational studies suggest even stronger reductions of CRC incidence and mortality,[4] and screening colonoscopy has been recommended for CRC prevention and early detection by expert panels for more than 10 years.[5–8] Germany was one of the first countries in the world to introduce colonoscopy as a primary screening offer. Timely estimation of its impact on prevention and early detection but also on potential overdiagnoses of CRC is crucial for decisions regarding maintenance or eventual adaptation and optimization of screening colonoscopy in Germany and for informing decisions on introduction, maintenance, or adaptation of CRC screening offers in other countries. In this article, we aim for a comprehensive, joint, and detailed analysis of prevented, early detected, and overdiagnosed CRCs by screening colonoscopy according to sex and age in the initial 10 years of the German screening colonoscopy program.

Methods

German Screening Colonoscopy Program

The offer of screening colonoscopy was introduced in Germany in October 2002 as an alternative to fecal occult

Abbreviations used in this paper: CRC, colorectal cancer; SHI, statutory health insurance.

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blood testing (which has been offered since 1977) for women and men aged 55 years or older covered by Statutory Health Insurance (SHI). If the first screening colonoscopy is conducted when younger than 65 years of age, a second screening colonoscopy is offered 10 years later. Close to 90% of older adults in Germany are covered by SHI, and the vast majority of those not included have private health insurance that provides equivalent screening offers in most cases.

National Screening Colonoscopy Registry

Along with introduction of screening colonoscopy, a national registry was built up,[9–11] to which all screening colonoscopies among people covered by SHI are reported anonymously on a standardized form (no such registry exists for privately insured people). Reporting is virtually complete, because it is a prerequisite for physicians' reimbursement by SHI funds. The registry includes only primary screening examinations (ie, it does not include colonoscopies conducted for surveillance, work-up of symptoms, or other screening tests). Findings at colonoscopy are reported, including number, size, and histologic characteristics of polyps. In case of multiple neoplasms, only the most advanced finding (nonadvanced adenoma, advanced adenoma, or cancer) is recorded. Advanced adenomas are defined as at least 1 adenoma $\geq$1 cm or at least 1 adenoma with villous components or high-grade dysplasia. Within the initial 10 years of this screening offer, approximately 22% of eligible women and 20% of eligible men covered by SHI had a screening colonoscopy. For this analysis, we used data from 4,407,971 first-time screening colonoscopies in 2003–2012 among participants aged 55 years or older included in the national screening colonoscopy registry.

Statistical Analysis

We first derived numbers of participants of screening colonoscopy aged 55–80 years in 2003–2012 by sex, single year of age, and most advanced finding at colonoscopy. Next, for each sex and each single year of age, we derived the probability of having a CRC prevented or early detected and for having a CRC overdiagnosis, denoted $Prob_{prev}$, $Prob_{early}$, and $Prob_{over}$, respectively, as

$$Prob_{prev} = (P_{non} \times C_{non} + P_{adv} \times C_{adv}) \times RR,$$

$$Prob_{early} = P_{CRC} \times C_{CRC}, \text{ and}$$

$$Prob_{over} = P_{CRC} \times (1 - C_{CRC}),$$

where P_{non}, P_{adv}, and P_{CRC} denote the sex- and age-specific prevalences at screening colonoscopy of nonadvanced adenoma, advanced adenoma, and CRC, respectively, C_{non}, C_{adv}, and C_{CRC} denote the sex- and age-specific probabilities of developing clinically manifest CRC during lifetime of carriers of nonadvanced adenoma, advanced adenoma, and CRC, respectively, and RR denotes the relative reduction of CRC risk by screening colonoscopy. In this approach, overdiagnoses are defined as cancers detected at screening colonoscopy that would not have become clinically manifest during lifetime without screening colonoscopy. Early detected cancers are defined as the complementary group of cancers detected at screening colonoscopy in which screening colonoscopy led to earlier detection of the disease that would otherwise become clinically manifest later in life.

RR was assumed to be 69% on the basis of a recent meta-analysis.[4] P_{non}, P_{adv}, and P_{CRC} were directly obtained from the screening colonoscopy registry. C_{non}, C_{adv}, and C_{CRC} were derived by 4 state Markov models, with annual iterations starting at the specific age of colonoscopy up to a maximum age of 100 (variation of this upper age limit by $\pm$5 years had very little impact on the results). At each iteration, progression between states (carriage of nonadvanced adenoma, advanced adenoma, preclinical cancer, clinically manifest cancer) was modeled on the basis of previously derived sex- and age-specific annual transition rates.[11,12] These estimates had been derived at very high levels of precision by birth cohort analyses by using the German national screening colonoscopy registry and by combining CRC prevalence estimates from the German national screening colonoscopy database and from national cancer incidence data (Table 1).[11,12] For each iteration and each transition, we accounted for mortality that was obtained from general population life tables for the year 2010.[13] Because estimates of sex- and age-specific transition rates were available up to age groups 75–79 (transition rates from nonadvanced adenoma to advanced adenoma and from advanced adenoma to preclinical cancer) or 80–84 (transition rates from preclinical to clinically manifest cancer) only, available transition rates for these age groups were assumed to also apply at older ages. To account for uncertainties in the assumed transition rates, sensitivity analyses were carried out in which all transition rates were varied between the lower and upper ends of the 95% confidence intervals that are shown in Table 1 for each sex and all age groups.

Finally, we calculated cumulative numbers of prevented and early detected CRCs and of overdiagnoses from age 55 on up to various ages between 55 and 80 years for each sex. Sex- and age-specific numbers to be added up were obtained by multiplying sex- and age-specific numbers of screening colonoscopy participants with sex- and age-specific estimates of $Prob_{prev}$, $Prob_{early}$, and $Prob_{over}$. To derive estimates for the total German population, the numbers of screening colonoscopy participants included in this analysis were determined by multiplying sex- and age-specific numbers of registered screening colonoscopy participants covered by SHI with the inverse values of the sex- and age-specific SHI coverage proportions during the period of investigation.