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Original Contribution

Sojourn Time of Preclinical Colorectal Cancer by Sex and Age: Estimates From the German National Screening Colonoscopy Database

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The sojourn time of preclinical colorectal cancer is a critical parameter in modeling effectiveness and cost-effectiveness of colorectal cancer screening. For ethical reasons, it cannot be observed directly, and available estimates are based mostly on relatively small historic data sets that do not include differentiation by age and sex. The authors derived sex- and age-specific estimates (age groups: 55–59, 60–64, 65–69, 70–74, 75–79, and $\geq$80 years) of mean sojourn time, combining data from the German national screening colonoscopy registry (based on 1.88 million records) and data from population-based cancer registries (population base: 37.9 million people) for the years 2003–2006. Estimates of mean sojourn time were similar for both sexes and all age groups and ranged from 4.5 years (95% confidence interval: 4.1, 4.8) to 5.8 years (95% confidence interval: 5.3, 6.3) for the subgroups assessed. Sensitivity analyses indicated that mean sojourn time might be approximately 1.5 years longer if colorectal cancer prevalence in nonparticipants of screening colonoscopy is 20% lower than prevalence in participants or 1 year shorter if it exceeds the prevalence in participants by 20%. This study provides, for the first time, precise estimates of sojourn time by age and sex, and it suggests that sojourn times are remarkably consistent across age groups and in both sexes.

colorectal neoplasms; diagnosis; natural history

Abbreviation: FOBT, fecal occult blood test.

Colorectal cancer is the third most common cancer and the fourth most common cancer cause of death globally (1). Incidence and mortality rates can be reduced by using a number of screening strategies, including fecal occult blood tests (FOBTs), sigmoidoscopy, and colonoscopy (2, 3), all of which appear to be cost-effective (4), if not cost-saving (5). For modeling effectiveness and cost-effectiveness of various screening strategies and for choosing the best strategy in a specific setting, reliable estimates of key parameters of transitions between various stages of cancer development, starting from development of adenomas to clinical diagnosis and outcome of colorectal cancer, are crucial. One such parameter is the transition rate from preclinical (undiagnosed) colorectal cancer to clinical (diagnosed) colorectal cancer, which is closely related to the mean sojourn time of cancers in the preclinical stage. For ethical reasons, transition rate and sojourn time cannot be directly observed, because preclinical cancer has to be removed once detected. Rather, these parameters must be estimated through indirect approaches, for example, from observed prevalence and incidence data from the prescreening era (6), newly introduced screening programs (7, 8), or screening trials (9). Previously, prevalences of preclinical cancers were estimated from autopsy studies (6) or from programs or trials that relied primarily on screening that used a FOBT (7–10), the limited sensitivity of which introduces an additional layer of complexity and uncertainty in sojourn time estimates. The aim of the present study was to estimate transition rates from preclinical (undiagnosed) to clinical (diagnosed) colorectal cancer by sex and age by combining data from the national screening colonoscopy database and national estimates of colorectal cancer incidence in Germany.

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MATERIALS AND METHODS

Data sources

Estimates of the incidence of colorectal cancer in Germany in 2003–2006 were provided by the German Association of Epidemiological Cancer Registries (11). Cancer registries have been built up in most of the federal states of Germany in the past 2 decades. This analysis is based on cancer incidence data from 10 of 16 states, the completeness of which is estimated to exceed 90%. Together, these registries cover 37.9 million people, or 46% of the German population. The relative contributions of populations from different regions, especially from Western and Eastern Germany and from urban and rural areas, are close to the national distribution; therefore, the registry populations can be assumed to be representative with respect to colorectal cancer incidence in the country as a whole.

Colonoscopy has been offered as a primary screening examination for colorectal cancer in Germany since October 2002. The program has been described in detail elsewhere (12–14). Briefly, women and men are entitled to have a first screening colonoscopy once they reach 55 years of age and a second screening colonoscopy after 10 or more years, provided the first screening colonoscopy was performed before the age of 65 years. 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 more than 96% reaching the cecum (15, 16).

In our analysis, national estimates of participation in screening colonoscopy and of the prevalence of colorectal cancer at screening colonoscopy were derived from the national screening colonoscopy registry. The national registry includes approximately 90% of German citizens who are covered by the statutory health insurance system. Among this population group, completeness of registration gradually approached 100% in the initial months of registry setup. Since then, registration has been close to complete, as 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 screening colonoscopy. In our analyses, we assumed participation in screening and prevalence of colorectal cancer at screening colonoscopy in the population covered by the statutory health insurance system to be representative of the total German population.

Statistical analysis

In the present study, transition rates from preclinical (undiagnosed) to clinical (diagnosed) colorectal cancer in Germany were estimated for the calendar period 2003–2006 from national estimates of colorectal cancer incidence, participation rates in screening colonoscopy, and estimates of prevalence of colorectal cancer at screening colonoscopy by age and sex. In the context of this article, the term ''clinical colorectal cancer'' refers to colorectal cancer that had been diagnosed by means other than screening colonoscopy (typically but not necessarily through work-up of symptoms). A key assumption is that colorectal cancer prevalence among those who have not undergone a screening colonoscopy (hereafter referred to as nonparticipants), which cannot be observed directly, is the same as the observed prevalence among those who have undergone a screening colonoscopy (hereafter referred to as participants). Under this assumption, the transition rate, denoted TRA, is given as

$$\mathrm{TRA} = \mathrm{INC}_n/\mathrm{PRE},$$

where INC_n denotes the incidence rate of colorectal cancer among nonparticipants (i.e., the incidence of colorectal cancers not detected by screening colonoscopy) and PRE denotes the (common) point prevalence of colorectal cancer among participants and nonparticipants.

INC_n can be derived as follows: Let INC be the observed incidence rate in the total population, let PAR be the annual rate of participation in screening colonoscopy, and let INC_p be the incidence rate of colorectal cancer among participants. INC_p in a given calendar year can be approximated by interpreting PRE, the prevalence of colorectal cancer (which is calculated as the number of colorectal cancers detected at screening colonoscopy divided by the number of participants during that year) as the 1-year cumulative incidence of colorectal cancer among participants. This approximation is based on the assumptions that, for any given calendar year, the observed incidence among participants is essentially due to colorectal cancers detected at screening and that other colorectal cancer diagnoses during the same year are very rare in this group (no such diagnoses would be expected before screening colonoscopy, and risk of colorectal cancer within 12 months after negative screening colonoscopy is very low (17)). Assuming that INC_p is constant over time (i.e., detection of cancers by screening is equally distributed over the year), we have

$$\mathrm{PRE} = 1 - \exp\big(-\mathrm{INC}_p\big),$$

which transforms to

$$\mathrm{INC}_p = -\ln(1 - \mathrm{PRE}).$$

Because the overall incidence of colorectal cancer in a population in a given year can be considered the weighted average of incidence in participants and nonparticipants in that year,

$$\begin{aligned}\mathrm{INC} &= \mathrm{INC}_n \times \big(1 - \mathrm{PAR}\big) + \mathrm{INC}_p \times \mathrm{PAR}\\ &= \mathrm{INC}_n \times \big(1 - \mathrm{PAR}\big) - \ln\big(1 - \mathrm{PRE}\big) \times \mathrm{PAR},\\ \mathrm{INC}_n &= (\mathrm{INC} + \ln(1 - \mathrm{PRE}) \times \mathrm{PAR})/(1 - \mathrm{PAR}),\end{aligned}$$

and

$$\begin{aligned}\mathrm{TRA} &= \mathrm{INC}_n/\mathrm{PRE}\\ &= (\mathrm{INC} + \ln(1 - \mathrm{PRE}) \times \mathrm{PAR})/(\mathrm{PRE} \times (1 - \mathrm{PAR})).\end{aligned}$$

Finally, assuming that the transition rate is constant over time, the mean sojourn time, denoted MST, can be derived by the equation

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$$\begin{aligned} MST &= 1/TRA \\ &= PRE \times (1 - PAR)/(INC + \ln(1 - PRE) \times PAR). \end{aligned}$$

Using this approach, we estimated the mean sojourn time from the incidence, prevalence, and participation rates separately for men and women and, within each sex, separately for the following age groups: 55–59, 60–64, 65–69, 70–74, 75–79, and ≥80 years.

We derived 95% confidence intervals for estimates of transition rates and mean sojourn times by using Monte Carlo simulation. In 100,000 runs, values for colorectal cancer incidence were randomly selected from Poisson distributions, and values for colonoscopy participation and colorectal cancer prevalence by age and sex were selected from binomial distributions, the parameters of which were derived from the empirical databases described above. Sample sizes for subgroups defined by sex and age ranged from 3,187 to 19,832 incident colorectal cancer cases in the cancer registry-covered population; from 21,043 to 372,730 participants among those eligible; and from 554 to 2,558 prevalent colorectal cancer cases among participants of screening colonoscopy. Transition rates and mean sojourn times were calculated as outlined above. We determined 95% confidence intervals as the range from the 2.5th percentile to the 97.5th percentile of simulated values of transition rates and mean sojourn times.

We conducted sensitivity analyses to evaluate the robustness of the analyses against violations of the underlying key assumptions. In particular, the prevalence of colorectal cancer among nonparticipants, which could not be observed directly but was assumed to equal to the prevalence in participants in the base case analyses, was varied, from 20% below to 20% above the prevalence observed in participants. Furthermore, analyses were repeated assuming a 10% higher incidence of colorectal cancer to account for potential underregistration of colorectal cancer by the cancer registries.

RESULTS

Table 1 shows the annual participation rates and prevalences of colorectal cancer according to sex and age among participants in screening colonoscopy in Germany in 2003–2006. The estimates are based on 1.875 million screening colonoscopies registered in the German national screening colonoscopy registry. The annual participation rates of those eligible ranged from 3% to 4% in persons 55–69 years of age to less than 1% in women and men older than 80 years of age. Prevalences of colorectal cancer were higher among men than among women and strongly increased with age in both sexes. Prevalence in male participants increased from 0.58% in those who were 55–59 years of age to 3.08% in those who were 80 years of age or older, and in female participants it increased from 0.31% in those who were 55–59 years of age to 2.36% in those who were 80 years of age or older. As Figure 1 shows, incidence likewise strongly increased with age and was substantially higher among men than among women of all ages.

Table 2 shows estimates of transition rates from preclinical (undiagnosed) colorectal cancer to clinically diagnosed colorectal cancer and of mean sojourn times according to sex and age in Germany in 2003–2006. Estimated transition rates were close to 20 per 100 preclinical cancers per year and were remarkably consistent among men and women and across age groups. Estimated mean sojourn times ranged from 4.5 years to 5.8 years for all age groups in both men and women. Because of the large size of the underlying databases, confidence intervals were rather small for all estimates (maximum width = 1 year). Estimated sojourn times were significantly higher for the oldest age groups in both women and men and for the youngest age groups in men than they were for those in the groups of men and women aged 65–69 years (which were chosen as sex-specific references because they included the largest numbers of prevalent cases; Table 1), even though differences between estimates of sojourn time were very small.

Table 1. Annual Rates of Participation in Screening Colonoscopy and Prevalences of Colorectal Cancer According to Sex and Age Among Participants in the German National Screening Colonoscopy Registry, 2003–2006

Age, years	Participation Rate, %	Recorded Colonoscopies	Prevalent Cases	Prevalence, %	95% Confidence Interval
		Men			
55–59	2.8	174,742	1,021	0.58	0.55, 0.62
60–64	3.4	225,985	1,963	0.87	0.83, 0.91
65–69	3.1	224,038	2,558	1.14	1.10, 1.19
70–74	2.3	116,040	1,936	1.67	1.59, 1.74
75–79	1.5	55,150	1,205	2.18	2.06, 2.31
≥80	0.6	17,963	554	3.08	2.84, 3.35
		Women			
55–59	3.8	269,941	830	0.31	0.29, 0.33
60–64	4.1	301,460	1,317	0.44	0.41, 0.46
65–69	3.2	269,344	1,673	0.62	0.59, 0.65
70–74	2.0	129,884	1,213	0.93	0.88, 0.99
75–79	1.1	65,749	944	1.44	1.34, 1.53
≥80	0.3	25,412	600	2.36	2.18, 2.56

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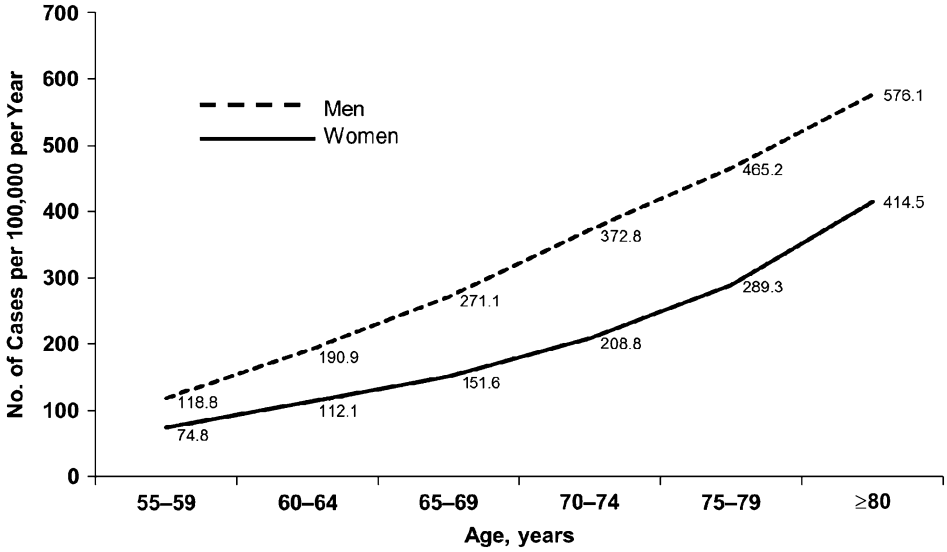

Figure 1. Incidence of colorectal cancer by sex and age in Germany, 2003–2006. Data are from the German Association of Epidemiological Cancer Registries estimates (11) based on data from population-based cancer registries from 10 German federal states (Bayern, Brandenburg, Bremen, Hamburg, Mecklenburg-Vorpommern, Niedersachsen, Nordrhein-Westfalen (Münster area only), Saarland, Sachsen, and Schleswig-Holstein).

Table 3 shows the results of the sensitivity analysis regarding the unknown prevalence of colorectal cancer in the unscreened population. If this prevalence is 10% below or 10% above the observed prevalence in the screened population, estimates of mean sojourn time are up to 0.8 years higher or up to 0.6 years lower, respectively, than in the base case analysis. If the prevalence is 20% below or 20% above the observed prevalence in the screened populations, estimates of mean sojourn time range from 5.9 to 7.3 years and from 3.6 to 4.8 years, respectively. Increasing incidence by 10% to account for possible underregistration of colorectal cancer increased estimates of mean sojourn time by 0.6–0.8 years (data not shown).

DISCUSSION

In the present study based on 1.875 million screening colonoscopies in Germany and population-based cancer registries

Table 2. Estimated Rate of Transition From Preclinical (Undiagnosed) to Clinically Diagnosed Colorectal Cancer and of Mean Colorectal Cancer Sojourn Time by Sex and Age, Germany, 2003–2006

Age, years	Transition Rate[a]	95% Confidence Interval	Mean Sojourn Time, years	95% Confidence Interval	*P* Value[b]
			Men		
55–59	18.1	16.7, 19.5	5.5	5.1, 6.0	<0.001
60–64	19.2	18.1, 20.3	5.2	4.9, 5.5	0.006
65–69	21.3	20.3, 22.4	4.7	4.5, 4.9	Referent
70–74	20.6	19.5, 21.7	4.9	4.6, 5.1	0.30
75–79	20.1	18.9, 21.4	5.0	4.7, 5.3	0.14
≥80	18.2	16.7, 19.9	5.5	5.0, 6.0	0.001
			Women		
55–59	21.3	19.5, 23.4	4.7	4.3, 5.1	0.62
60–64	22.5	20.9, 24.2	4.5	4.1, 4.8	0.61
65–69	21.9	20.6, 23.3	4.6	4.3, 4.8	Referent
70–74	20.8	19.4, 22.2	4.8	4.5, 5.1	0.24
75–79	19.2	17.9, 20.7	5.2	4.8, 5.6	0.006
≥80	17.3	16.0, 18.8	5.8	5.3, 6.3	<0.001

[a] The transition rate is the number of transitions per 100 prevalent colorectal cancer cases per year.
[b] *P* value for 2-sided test for difference from reference group; derived using Monte Carlo simulations.

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Table 3. Sensitivity of Estimated Mean Sojourn Times (in Years) to Prevalence of Colorectal Cancer in Nonparticipants in Screening Colonoscopy, Germany, 2003–2006[a]

Age, years	Ratio of Colorectal Cancer Prevalence in Nonparticipants to Prevalence in Participants				
	0.8	0.9	1.0 (Base Case Analysis)	1.1	1.2
Men					
55–59	7.2	6.3	5.5	5.0	4.5
60–64	6.8	5.9	5.2	4.7	4.2
65–69	6.1	5.3	4.7	4.2	3.8
70–74	6.3	5.5	4.9	4.4	4.0
75–79	6.3	5.6	5.0	4.5	4.1
≥80	6.9	6.1	5.5	5.0	4.6
Women					
55–59	6.2	5.3	4.7	4.2	3.8
60–64	5.9	5.1	4.5	4.0	3.6
65–69	5.9	5.2	4.6	4.1	3.7
70–74	6.2	5.4	4.8	4.3	4.0
75–79	6.6	5.8	5.2	4.7	4.3
≥80	7.3	6.4	5.8	5.2	4.8

[a] Results of the sensitivity analyses for the sojourn time where the prevalence for nonscreened subjects varied from 20% lower to 20% higher than the prevalence for screened subjects. The base case is when the prevalences of screened and nonscreened subjects are the same.

that included 37.9 million people, we derived estimates of colorectal cancer sojourn time by sex and 5-year age groups. Mean sojourn time was estimated to be between 4.5 and 5.8 years, with estimates being remarkably consistent across sexes and age groups. Because of the size of the underlying databases, the random errors in the estimates were very small. However, the validity of our analyses depends on the degree to which the prevalence of colorectal cancer among participants is representative of the prevalence in the entire population of the corresponding age and sex groups. Lower or higher prevalences in nonparticipants than in participants would imply somewhat longer or shorter mean sojourn times, respectively.

Our estimates of mean sojourn times between 4.5 and 5.8 years are similar to previous estimates derived from smaller databases. In an analysis based on the first round of the mass-screening program for colorectal cancer by using FOBTs in the department of Calvados, France, Launoy et al. (7), using the Bayesian technique of Gibbs sampling, estimated the mean sojourn time to be 4.7 (95% confidence interval: 3.1, 8.4) years. The mean sojourn time seemed to be higher for cancers in the distal colon than for those in the proximal colon, but site-specific confidence intervals were broad and overlapping to a large extent. On the basis of observations from first-detection rounds in FOBT-based screening trials, Loeve et al. (9) estimated the mean sojourn time to be 3.6 years. In a recent joint analysis of 3 randomized controlled trials of the use of FOBTs from the same group, in which sensitivity of FOBTs was assumed to be dependent upon the stage of colorectal cancer, the estimated average duration of preclinical colorectal cancer was 6.7 years (95% confidence interval: 5.8, 7.7) (10). To our knowledge, the present study is the first to estimate sojourn time based on a newly introduced population-wide screening colonoscopy program. It is furthermore unique in that it relied on the use of national databases.

Potential variation in sojourn time by age has previously been addressed based on data from a FOBT-based screening program by Prevost et al. (8), who estimated mean sojourn time to be approximately 3 years in those 55–64 years of age and 6 years in those 65–74 years of age. However, confidence intervals of those estimates were very broad and overlapping to a very large extent. In our study, the estimated mean sojourn time was remarkably consistent for both sexes and over a broad age range. These results differ from previous findings for transition rates from advanced adenomas to preclinical colorectal cancer, which were likewise similar among men and among women, but which were found to increase with age (18). Whereas transition rates from advanced adenomas to preclinical colorectal cancer may primarily reflect biologic processes that may accelerate at older age, clinical diagnosis of colorectal cancer may reflect a combination of biologic and behavioral and health systems factors. Growth of colorectal cancer appears to be faster at older ages (19), but greater delays in cancer diagnosis at older ages could compensate for the potential shortening of sojourn time by faster growth.

As demonstrated in our sensitivity analyses, the most critical issue in the interpretation of our data is the question of to what extent the prevalence of colorectal cancer in the unscreened population equals the observed prevalence in those undergoing screening colonoscopy. There are factors that could potentially lead to both lower and higher prevalences among participants. On one hand, prevalence could be lower because participants, who tend to be better educated (20–22), might be more health conscious. Apparent prevalence could also be lower because of missed colorectal cancers at screening colonoscopies (23), although the very low incidence of colorectal cancer after a negative screening colonoscopy suggests that miss rates of colorectal cancer are very small (24). On the other hand, the prevalence could be higher if people at high risk of colorectal cancer, such as those with a positive family history of colorectal cancer (21, 25) or people who have not had a previous colonoscopy for any reason and who tend to have higher prevalences of colorectal neoplasms (15), are more likely to undergo screening colonoscopy. Because the impacts of potential differences in these factors between participants and nonparticipants are expected to partly cancel each other out, overall differences in colorectal cancer prevalence might be smaller than those addressed in our sensitivity analyses. This suggestion seems to be supported by recently published findings from a large sigmoidoscopy trial in the United Kingdom, in which colorectal cancer incidence and mortality rates were very similar in those who did not attend the offered screening and the control group (26). However, in that trial, participants were preselected by their interest in having flexible sigmoidoscopy, which could limit comparability of study settings.

Another issue that deserves discussion is that some colorectal cancer cases in Germany are diagnosed incidentally or

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by screening methods other than screening colonoscopy. As an alternative to screening colonoscopy, administration of FOBTs every 2 years is offered to adults aged 55 years or older in Germany. Recent data from an ongoing population-based case-control study (17, 27) suggest that overall, more than 20% of colorectal cancers are detected by screening or incidentally, whereas only about 5% are detected by screening colonoscopy. Nonparticipants in screening colonoscopy therefore include a nonnegligible minority of people in whom colorectal cancer is detected by FOBT or incidentally, which could lead to some artificial truncation of preclinical phases and hence underestimation of mean sojourn times. If we assume that 15% of cancers among nonparticipants were detected by FOBT screening and that the apparent sojourn time of those cancers was approximately halved by FOBT screening, we would expect sojourn times in the absence of FOBT screening to be approximately 8% (0.4 years) longer than those estimated in our analyses.

Furthermore, our estimates of sojourn time refer to a setting in which some proportion of the eligible population has had a previous colonoscopy for reasons other than screening (15, 16). Sojourn time in such a population might differ to some extent from the sojourn time in an entirely unscreened population (e.g., because of selection effects). For example, slower-growing neoplasms (with a potentially longer sojourn time) might have had a higher chance of being detected and removed at a precancerous stage at previous colonoscopy. Notwithstanding potential differences in sojourn time in a setting with no previous colonoscopies, our estimates could be of high practical relevance for modeling early detection and prevention strategies in a real-life setting in which a substantial proportion of older adults has had a colonoscopy for diagnostic purposes.

Although our analysis provides detailed estimates of sojourn time according to sex and age, no distinction according to stage at diagnosis or cancer subsite could be made because of incompleteness of stage and subsite information in the national screening colonoscopy registry and the cancer registries. In microsimulation models, sojourn time has been estimated by stages (10). Furthermore, assumptions on stage-specific sojourn times in different cancer stages are often made in cost-effectiveness analyses (5, 9, 28–31). For example, Vijan et al. (30) assumed that it took 2 years from onset of localized cancer to transition to regional cancer, an additional year from onset of regional cancer to transition to disseminated cancer, and less than 1 year to diagnosis of disseminated cancer. In a recent study on cost-effectiveness of computed tomographic colonography, Lansdorp-Vogelaar et al. (32) assumed the mean duration for preclinical cancer to be 2 years in stage I, 1 year in stage II, 1.5 years in stage III, and 0.8 years in stage IV, which corresponded to mean ''cumulative duration'' of 2, 3, 4.5, and 5.3 years for stages I, II, III, and IV, respectively, and a mean sojourn time across studies of 3.6 years. Our overall estimates might be considered as weighted averages of stage-specific ''cumulative sojourn times,'' with weights equal to the stage distribution in cancer patients not detected by screening colonoscopy.

Despite its limitations, our study expands the scarce empirical evidence on colorectal cancer sojourn time. Sojourn time is a critical parameter for developing strategies of early detection and in modeling effectiveness and cost-effectiveness of colorectal cancer screening (5, 9, 10, 28–32). We hope that our detailed and precise results of sojourn time by age and sex will be useful to inform such analyses. Notwithstanding the lack of sojourn time estimates by stage, our overall estimates might be useful to calibrate assumptions on stage-specific sojourn times commonly made in cost-effectiveness analyses. The finding of very limited variation of sojourn times by age and sex suggests that differentiation of sojourn time by these key sociodemographic variables may not be warranted.

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