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Research Article

Natural History of Colorectal Adenomas: Birth Cohort Analysis Among 3.6 Million Participants of Screening Colonoscopy

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Abstract

Background: Most colorectal cancers (CRC) develop from adenomas. Knowledge of the natural history of colorectal adenomas, which is not directly observable for ethical reasons, is crucial for designing cost-effective CRC screening strategies.

Methods: We derived transition rates from carriage of nonadvanced adenoma to carriage of advanced adenoma to carriage of CRC by sex and age in birth cohort analyses among 3,593,420 participants in the German screening colonoscopy program in 2003–2010.

Results: Transition rates from advanced adenoma to CRC carriage were similar in men and women, but monotonically and significantly increased with age. Estimated annual transition percentages [(95% confidence interval (CI)] in age groups 55–59, 60–64, 65–69, 70–74, and 75–79 years were 2.6 (2.4–2.9), 3.1 (2.8–3.3), 3.8 (3.5–4.1), 5.1 (4.8–5.5), and 5.2 (4.6–5.8) among men, and 2.5 (2.2–2.7), 2.7 (2.4–3.0), 3.8 (3.5–4.1), 5.0 (4.5–5.4), and 5.6 (4.9–6.3) among women. Estimated annual transitions from carriage of nonadvanced to carriage of advanced adenoma were in a narrow range from 3.6% to 4.7% for all age and sex groups.

Conclusions: Despite low annual transition rates, cumulative transition rates from advanced adenoma to CRC carriage are expected to exceed by 60%, 50%, and 40% for age intervals 55–80, 65–80, and 70–80 years, respectively, in both sexes. Cumulative transition rates from nonadvanced adenoma to CRC carriage are expected to be close to 30% for age interval 55–80 years, but less than 2% for age interval 75–80 years.

Impact: Our results enhance the empirical basis for modeling CRC screening strategies. *Cancer Epidemiol Biomarkers Prev; 22(6); 1043–51. ©2013 AACR.*

Introduction

Colorectal cancer (CRC) is the third most common cancer and the fourth most common cancer cause of death globally (1). Because of the slow development of most CRCs through the adenoma–carcinoma sequence, perspectives for early detection are better than for other cancers, and various screening examinations, including fecal occult blood tests (FOBT), sigmoidoscopy, and colonoscopy, were found to be effective in reducing CRC incidence and mortality in randomized and observational studies (2–13). Various screening strategies have been shown to be cost-effective, if not cost-saving, in a number of studies, but results have varied widely, partly due to uncertainties regarding crucial parameters of the natural history of the disease (14–15). Very influential parameters in this context are the transition rates from advanced adenoma to CRC and from nonadvanced to advanced adenoma (16, 17). In the era of widespread availability of colorectal endoscopy, these parameters can no longer be estimated by direct observation, because adenomas have to be removed once detected. Therefore, estimates mostly relied on very small studies from the preendoscopy era, such as longitudinal radiographic examinations of the large bowel, without any stratification by sex and age (18–24). Previously, we derived estimates of transition rates from advanced adenoma to CRC using a cross-sectional approach by combining early data from the German screening colonoscopy program with cancer registry data (25). Using data from the meanwhile strongly expanded database of the German screening colonoscopy registry, we now applied a longitudinal (birth cohort) approach to derive detailed and precise sex- and age-specific transition rates from both advanced adenoma to CRC and nonadvanced to advanced adenoma.

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Materials and Methods

Screening colonoscopy program

In Germany, screening colonoscopy is offered as a primary screening examination for early detection and

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Age (y)	Calendar year							
	2003	2004	2005	2006	2007	2008	2009	2010
55	1,948	1,949	1,950	1,951	1,952	1,953	1,954	1,955
56	1,947	1,948	1,949	1,950	1,951	1,952	1,953	1,954
57	1,946	1,947	1,948	1,949	1,950	1,951	1,952	1,953
58	1,945	1,946	1,947	1,948	1,949	1,950	1,951	1,952
59	1,944	1,945	1,946	1,947	1,948	1,949	1,950	1,951
60	1,943	1,944	1,945	1,946	1,947	1,948	1,949	1,950

Figure 1. Illustration of the principle of birth cohort analyses: data for the age group of 55–59 years in 2003–2009 (dashed frame) and age group of 56–60 years in 2004–2010 (solid frame) refer to the same birth cohort as indicated by the years of birth which are given in the cells.

prevention of CRC since October 2002. Women and men ages 55 years or more are eligible for a first screening colonoscopy. If this first screening colonoscopy is conducted before 65 years of age, a second screening colonoscopy is offered 10 years later. Certification to conduct screening colonoscopy is tightly regulated on the basis of extensive previous training and experience, and its maintenance is subject to rigorous quality control. Histopathologic examination is conducted decentrally by certified pathology labs.

Screening colonoscopy registry

Results of all screening colonoscopies are reported anonymously on a standardized form to a national registry by the physicians (26). Reporting is virtually complete, as it is a prerequisite for physicians' reimbursement of screening colonoscopies by the health insurance funds. The registry includes only colonoscopies conducted as primary screening examinations (i.e., colonoscopies conducted for surveillance, work-up of symptoms, or other screening tests are not included). Items reported include basic sociodemographic variables as well as information on findings at colonoscopy, including number, size, and histologic characteristics of polyps. In case of multiple neoplasms, only the most advanced one is to be recorded. The reporting forms are scanned, processed, and checked for completeness and plausibility using standardized algorithms at regional data centers before anonymized transfer to the national data center. Approximately 2.5% to 3% of eligible people participate in screening colonoscopy each year. For this analysis, we used data from 3,593,420 first time screening colonoscopies in 2003–2010 among participants 55 to 80 years of age.

Statistical analysis

A birth cohort analysis was conducted in which the increase in prevalence of colorectal neoplasms within one year within the same birth cohorts was assessed, as illustrated for the increase in prevalence from the age of 55–59 to 56 –60 years in birth cohort 1944–1954 in Fig. 1. Using the notation shown in Table 1, and assuming members of each birth cohort having their first screening colonoscopy one year apart to have comparable age-specific prevalences of colorectal neoplasms, estimates of the transition rate from carriage of advanced adenoma

Table 1. Parameters used for estimating transition rates

Notation	Parameter
$T_{CRC\_MAN,a}$	Annual transition rate from carriage of preclinical CRC to clinically manifest CRC, at age *a*
$T_{ADV\_CRC,a}$	Annual transition rate from carriage of at least one advanced adenoma (but no CRC) to carriage of preclinical CRC, at age *a*
$T_{NON\_ADV,a}$	Annual transition rate from carriage of at least one nonadvanced adenoma (but no advanced adenoma) to carriage of at least one advanced adenoma, at age *a*
$PART_a$ and $PART_{a+1}$	Total number of screening colonoscopy participants at age *a* in 2003–2009 and age *a*+1 in 2004–2010, respectively
ADV_a and ADV_{a+1}	Numbers of participants at age *a* in 2003–2009 and age *a+1* in 2004–2010, respectively, with at least one advanced adenoma (>1 cm in diameter, tubulovillous or villous components, or high-grade dysplasia), but no CRC
NON_a	Numbers of participants at age *a* in 2003–2009 with at least one nonadvanced adenoma, but no advanced adenoma or CRC
CRC_a and CRC_{a+1}	Numbers of participants at age *a* in 2003–2009 and age *a+1* in 2004–2010, respectively, with CRC
S	Mean sojourn time of CRC, i.e., the mean time a CRC exists before it becomes clinically manifest
P	Proportion of CRC developing from advanced adenomas according to the adenoma–carcinoma sequence

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(defined as 3+ adenomas, at least 1 adenoma $\geq$ 1 cm or at least 1 adenoma with villous components or high-grade dysplasia) to carriage of preclinical CRC were derived (separately for each sex) for each 5-year age group, with ages a = 55–59 to 75–79 years and ages $a+1$ = 56–60 to 76–80 years, as

$$T_{ADV\_CRC,a} = P \times (CRC_{a+1}/PART_{a+1} - (1 - T_{CRC\_MAN,a}) \times CRC_a/PART_a)/(ADV_a/PART_a) \quad \text{(Eq. 1)}.$$

Equation 1 quantifies the proportion of people with at least one advanced adenoma who develop preclinical CRC within 1 year: the core term of the numerator,

$$\begin{aligned}&(CRC_{a+1}/PART_{a+1} - (1 - T_{CRC\_MAN,a}) \times CRC_a/PART_a)\\ &= (CRC_{a+1}/PART_{a+1} - (1 - (1 - \exp(-1/S))) \times CRC_a/PART_a)\\ &= (CRC_{a+1}/PART_{a+1} - \exp(-1/S) \times CRC_a/PART_a),\end{aligned}$$

quantifies the increase in prevalence of preclinical CRC between ages a and $a+1$, taking into account that a certain proportion [given by $T_{CRC\_MAN,a} = (1 - \exp(-1/S)$, a function of mean sojourn time] of preclinical cancers prevalent at age a will have become clinically manifest by age $a+1$ (see Table 1 for definition of all parameters). The age-specific increase in prevalence is multiplied by the factor P, the proportion of CRC assumed to develop from advanced adenomas. The thus adjusted increase in prevalence of preclinical CRC is related to the prevalence of advanced adenomas at age a, i.e., $(ADV_a/PART_a)$, the denominator of Eq. 1.

The mean sojourn time S has been estimated from FOBT-based screening trials or programs to be 3.6 years (17), 4.7 years (27), or 6.7 years (28). We assumed a value of 4.7 years in our main analysis and of 3.6 and 6.7 years in sensitivity analyses. Likewise, P was set to 0.85 in the main analysis and varied between 0.7 and 1.0 in sensitivity analyses. This range corresponds to the range of values assumed in previous cost-effectiveness analyses of CRC screening (16, 29–32). Cancers not developing from advanced adenomas may include cancers developing from serrated polyps in particular (33).

In an analogous subsequent step, the proportion of people with at least one nonadvanced adenoma who develop an advanced adenoma within 1 year was estimated as follows:

$$T_{NON\_ADV,a} = (ADV_{a+1}/PART_{a+1} - (1 - T_{ADV\_CRC,a}) \times ADV_a/PART_a)/(NON_a/PART_a) \quad \text{(Eq. 2)},$$

where $T_{ADV\_CRC,a}$ represents the transition rate from carriage of advanced adenoma to carriage of preclinical CRC [calculated according to (Eq. 1)]. In this step, it is assumed that the proportion of advanced adenomas that do not develop from nonadvanced adenomas and the proportion of nonadvanced adenomas that develop into cancer within one year can be neglected.

Finally, we estimated the cumulative transition rates from various ages (55, 60, 65, 70, and 75 years) up to the age of 80 years from carriage of advanced adenoma to carriage of CRC and from carriage of nonadvanced adenoma to carriage of CRC expected in the absence of competing causes of death and in the absence of detection and removal of the adenomas. These estimates were derived by applying the annual age-specific transition rates to cohorts of men or women with nonadvanced adenoma (but no advanced neoplasm) or advanced adenoma in Markov models with one-year age intervals. In sensitivity analyses, the cumulative estimates were derived from Markov models additionally taking age- and sex-specific overall mortality (obtained from national life tables for the 2009/2011 period) into account.

Bootstrap analysis with resampling within sex–age subgroups was used to derive 95% confidence intervals (CI) of sex- and age-specific transition rates and for statistical testing of differences in transition rates by age groups. Ninety-five percent CIs were determined as the 2.5th and 97.5th percentile of transition rate estimates obtained in 1,000 runs. Statistical tests were 2-sided with $\alpha = 0.05$. The analyses were done with the SAS statistical software system, version 9.2 (SAS Institute Inc.).

Results

Table 2 provides the total number of screening colonoscopy participants, as well as the numbers of those with neoplasms by 5-year age groups and calendar years for men and women, respectively. Overall, 3,593,420 participants of screening colonoscopy (1,615,723 male and 1,977,697 female) were included in the analyses. Among male participants in 2003–2009, overall prevalence of nonadvanced adenomas, advanced adenomas, and CRC increased from 16.0%, 6.6%, and 0.6% in age group 55–59 years to 18.2%, 10.4%, and 2.5% in age group 75–79 years. Age-specific prevalences were substantially lower in female participants. They increased from 9.6%, 3.5%, and 0.3% in age group 55–59 years to 12.8%, 6.8%, and 1.6% in age group 75–79 years, respectively. Slightly higher prevalences of advanced adenomas and CRC were consistently seen among male and female participants of the same birth cohorts in 2004 to 2010 who were then representing the age groups of 56–60, 61–65, 66–70, 71–75, and 76–80 years.

Estimated annual transition rates from carriage of advanced adenoma to carriage of CRC and from carriage of nonadvanced adenoma to carriage of advanced adenoma and their 95% CIs are shown in Table 3 for the main analyses, assuming that the CRC sojourn time equals 4.7 years and that 85% of CRC develop from advanced adenomas. Estimated annual transition rates from carriage of advanced adenoma to carriage of CRC are similar for men and women, but strongly increase with age in both sexes, from 2.6% in age group of 55–59 years to 5.2% in age group of 75–79 years among men and from 2.5% in age group 55–59 years to 5.6% in age group of 75–79 years among

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Table 2. Participants in screening colonoscopy in Germany by sex, age, calendar year, and most advanced finding

			Men	Women
Age *a*, *a*+1	**Calendar years**	**Group**	***N* (%)**	***N* (%)**
55–59	2003–2009	$PART_a$	371,715 (100)	527,569 (100)
		NON_a	59,329 (16.0)	50,514 (9.6)
		ADV_a	24,442 (6.6)	18,654 (3.5)
		CRC_a	2,238 (0.6)	1,649 (0.3)
56–60	2004–2010	$PART_{a+1}$	380,875 (100)	503,674 (100)
		NON_{a+1}	65,461 (17.2)	52,784 (10.5)
		ADV_{a+1}	26,922 (7.1)	19,322 (3.8)
		CRC_{a+1}	2,634 (0.7)	1,787 (0.4)
60–64	2003–2009	$PART_a$	358,323 (100)	449,365 (100)
		NON_a	61,765 (17.2)	48,617 (10.8)
		ADV_a	29,337 (8.2)	20,428 (4.5)
		CRC_a	3,424 (1.0)	2,173 (0.5)
61–65	2004–2010	$PART_{a+1}$	367,281 (100)	435,383 (100)
		NON_{a+1}	67,506 (18.4)	50,963 (11.7)
		ADV_{a+1}	31,708 (8.6)	20,967 (4.8)
		CRC_{a+1}	3,923 (1.1)	2,336 (0.5)
65–69	2003–2009	$PART_a$	377,034 (100)	433,323 (100)
		NON_a	70,029 (18.6)	52,444 (12.1)
		ADV_a	34,608 (9.2)	22,805 (5.3)
		CRC_a	4,827 (1.3)	3,075 (0.7)
66–70	2004–2010	$PART_{a+1}$	356,527 (100)	397,154 (100)
		NON_{a+1}	69,641 (19.5)	51,707 (13.0)
		ADV_{a+1}	34,124 (9.6)	21,880 (5.5)
		CRC_{a+1}	5,155 (1.4)	3,206 (0.8)
70–74	2003–2009	$PART_a$	217,394 (100)	236,482 (100)
		NON_a	41,401 (19.0)	30,830 (13.0)
		ADV_a	21,593 (9.9)	14,427 (6.1)
		CRC_a	4,110 (1.9)	2,497 (1.1)
71–75	2004–2010	$PART_{a+1}$	200,458 (100)	216,105 (100)
		NON_{a+1}	39,784 (19.8)	29,588 (13.7)
		ADV_{a+1}	20,482 (10.2)	13,879 (6.4)
		CRC_{a+1}	4,268 (2.1)	2,613 (1.2)
75–79	2003–2009	$PART_a$	100,616 (100)	114,451 (100)
		NON_a	18,268 (18.2)	14,593 (12.8)
		ADV_a	10,463 (10.4)	7,818 (6.8)
		CRC_a	2,470 (2.5)	1,785 (1.6)
76–80	2004–2010	$PART_{a+1}$	87,512 (100)	99,440 (100)
		NON_{a+1}	16,381 (18.7)	13,258 (13.3)
		ADV_{a+1}	9,232 (10.5)	6,900 (6.9)
		CRC_{a+1}	2,295 (2.6)	1,700 (1.7)

NOTE: Summary data from the German national registry, 2003–2010.

$PART_a$ ($PART_{a+1}$) = total participants at age *a* (*a*+1) in 2003–9 (2004–10).

NON_a (NON_{a+1}) = participants with nonadvanced adenoma at age *a* (*a*+1) in 2003–2009 (2004–10).

ADV_a (ADV_{a+1}) = participants with advanced adenoma at age *a* (*a*+1) in 2003–9 (2004–10).

CRC_a (CRC_{a+1}) = participants with colorectal cancer at age *a* (*a*+1) in 2003–9 (2004–10).

women. For age groups of 65–69, 70–74, and 75–79 years, estimated transition rates are statistically significantly higher than those for age group of 55–59 years among both men and women. Estimated transition rates from carriage of nonadvanced to carriage of advanced adenoma were in a narrow range from 3.6% and 4.7% for all age groups in both sexes, with no consistent variation by age and sex.

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Table 3. Estimated average annual transition rate in % from carriage of advanced adenoma to carriage of CRC and from carriage of nonadvanced adenoma to carriage of advanced adenoma

		Men			Women		
Transition	**Age, y**	**PE**	**95% CI**	***P*[b]**	**PE**	**95% CI**	***P*[b]**
Advanced adenoma to colorectal cancer[a]	55–59	2.6	2.4–2.9	Ref.	2.5	2.2–2.7	Ref.
	60–64	3.1	2.8–3.3	0.02	2.7	2.4–3.0	0.20
	65–69	3.8	3.5–4.1	<0.0001	3.8	3.5–4.1	<0.0001
	70–74	5.1	4.8–5.5	<0.0001	5.0	4.5–5.4	<0.0001
	75–79	5.2	4.6–5.8	<0.0001	5.6	4.9–6.3	<0.0001
Nonadvanced to advanced adenoma	55–59	4.2	3.8–4.6	Ref.	4.0	3.6–4.5	Ref.
	60–64	4.0	3.6–4.4	0.60	3.6	3.2–4.1	0.19
	65–69	4.0	3.6–4.3	0.45	3.7	3.2–4.1	0.22
	70–74	4.1	3.6–4.6	0.85	4.7	4.1–5.3	0.06
	75–79	3.7	2.9–4.6	0.38	3.7	2.8–4.7	0.57

NOTE: Base case analyses based on data from the German national screening colonoscopy registry, 2003–2010.

Abbreviation: PE, point estimate.

[a]sample calculation for men of the age of 55 to 59 years, based on the equation 1 given in the statistical methods section and data shown in Table 2, assuming a mean sojourn time of 4.7 years and that 85% of CRCs develop from advanced adenomas:
Estimated transition rate $= 0.85 \times (2{,}634/380{,}875 – \exp(-1/4.7) \times 2{,}238/371{,}715)/(24{,}442/371{,}715)$.

[b]*P* for difference from reference group 55 to 59 years.

Sensitivity analyses assuming mean CRC sojourn times of 3.6 or 6.7 (rather than 4.7) years yielded approximately 10% to 20% higher or 10% to 20% lower estimates of annual transition rates from carriage of advanced adenoma to carriage of CRC, respectively (Table 4). Similarly, sensitivity analyses assuming 70% or 100% (rather than 85%) of CRC to develop from advanced adenomas yielded approximately 15% to 20% lower or 15% to 20% higher estimates of annual transition rates from carriage of advanced adenoma to carriage of CRC, respectively. With variations mostly in the range of 5% to 10%, estimates of transition rates from carriage of nonadvanced adenoma to carriage of advanced adenoma were even substantially less sensitive to assumptions on mean sojourn time and the proportion of CRC developing from advanced adenomas.

Table 5 shows the estimated cumulative transition rates from various ages up to 80 years of age from carriage of advanced adenoma to carriage of CRC and from carriage of nonadvanced adenoma to carriage of CRC. According to our base case analyses, almost two-third of people with an advanced adenoma at the age of 55 years would be expected to develop CRC before the age of 80 years in the absence of detection and removal of the neoplasm. Probabilities to develop CRC before the age of 80 years would still be above 50%, above 40%, and close to 25% for men and women with an advanced adenoma at the age of 65, 70, and 75 years, respectively. For those with nonadvanced adenoma (but no advanced neoplasm) at the age of 55 years, close to 30% would be expected to develop CRC before the age of 80 years in the absence of detection and removal of the adenoma. In contrast, this probability would be less than 10% or even less than 2% for those with nonadvanced adenoma (but no advanced neoplasm) at the age of 70 or 75 years, respectively. In sensitivity analyses accounting for age- and sex-specific overall mortality, the cumulative transition rates were approximately 20% and 10% lower for men and women, respectively.

Discussion

In this birth cohort analysis based on data from more than 3.5 million participants of screening colonoscopy in Germany, annual transition rates from carriage of advanced adenoma to carriage of CRC were estimated to increase from approximately 2.5% to 3% in the age groups of 55–64 years to approximately 5%–5.5% in age groups of 70–79 years. Age-specific estimates were very similar for men and women. Estimated annual transitions from carriage of nonadvanced to carriage of advanced adenoma were close to 4% for all age groups in both men and women. Cumulative transition rates from carriage of advanced adenoma to carriage of CRC are estimated to be more than 60%, 50%, and 40% for age intervals 55–80, 65–80, and 70–80 years, respectively. Close to 30% of those with nonadvanced adenoma (but no advanced neoplasm) at the age of 55 years, but less than 2% of those with nonadvanced adenoma at the age of 75 years would be expected to develop CRC in the absence of adenoma detection and removal.

The increase of transition rates from carriage of advanced adenoma to carriage of CRC with age which is consistent with the well-known strong increase of CRC incidence with age seems highly plausible given the increasing vulnerability to cancer at old age, for example, by reduced tumor defense mechanisms.

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Table 4. Sensitivity analyses: estimates of annual transition rates (%) by sex and age under various assumptions for the mean CRC sojourn time and the proportion of cancers developing from adenomas

			Mean sojourn time, (y)			Proportion of cancers developing from adenomas		
Transition	**Sex**	**Age, y**	**3.6**	**4.7**	**6.7**	**0.7**	**0.85**	**1.0**
Advanced adenoma to CRC	Men	55–59	3.0	2.6	2.2	2.2	2.6	3.1
		60–64	3.6	3.1	2.5	2.5	3.1	3.6
		65–69	4.4	3.8	3.2	3.1	3.8	4.5
		70–74	6.0	5.1	4.3	4.2	5.1	6.1
		75–79	6.2	5.2	4.2	4.3	5.2	6.1
	Women	55–59	2.8	2.5	2.1	2.0	2.5	2.9
		60–64	3.2	2.7	2.2	2.2	2.7	3.2
		65–69	4.4	3.8	3.2	3.1	3.8	4.4
		70–74	5.7	5.0	4.2	4.1	5.0	5.8
		75–79	6.6	5.6	4.6	4.6	5.6	6.6
Nonadvanced to advanced adenoma	Men	55–59	4.3	4.2	4.0	4.0	4.2	4.4
		60–64	4.3	4.0	3.8	3.8	4.0	4.3
		65–69	4.2	4.0	3.7	3.6	4.0	4.3
		70–74	4.5	4.1	3.7	3.7	4.1	4.6
		75–79	4.3	3.7	3.2	3.2	3.7	4.2
	Women	55–59	4.2	4.0	3.9	3.9	4.0	4.2
		60–64	3.8	3.6	3.4	3.4	3.6	3.8
		65–69	3.9	3.7	3.4	3.4	3.7	3.9
		70–74	5.1	4.7	4.4	4.3	4.7	5.1
		75–79	4.3	3.7	3.2	3.3	3.7	4.3

German national screening colonoscopy registry, 2003–2010.

Table 5. Estimated cumulative transition rates from various ages to age 80 in % from carriage of advanced adenoma to carriage of CRC and from carriage of nonadvanced adenoma to carriage of CRC

Transition	**Age interval (y)**	**Men (y)**	**Women (y)**
Advanced adenoma to colorectal cancer	55–80	63.6	63.3
	60–80	58.5	58.3
	65–80	51.4	52.3
	70–80	41.1	42.0
	75–80	23.4	25.0
Nonadvanced adenoma to colorectal cancer	55–80	29.3	28.8
	60–80	21.8	21.6
	65–80	14.4	15.0
	70–80	7.3	8.4
	75–80	1.8	1.9

NOTE: Base case analyses based on data from the German national screening colonoscopy registry, 2003–2010.

Our estimates of annual transition rates refer to people with at least one advanced adenoma or at least one nonadvanced adenoma rather than to single advanced adenomas or nonadvanced adenomas, respectively. The dataset used for our analysis did not include detailed information on the numbers of advanced adenomas and nonadvanced adenomas in the same person. In another study conducted among screening colonoscopy participants in Germany, approximately one-third of carriers of adenomas had more than one adenoma (34). Transition rates per advanced adenoma or per nonadvanced adenoma would therefore be expected to be somewhat lower than the transition rates per adenoma carrier. However, transition rates per adenoma carrier rather than transition rates per adenoma are the crucial parameters for screening strategies which we wish to inform by our study.

Our estimates of annual transition rates between 2.5% and 5.6% among women and between 2.6% and 5.2% among men would translate to a mean advanced adenoma dwell time, that is, the time it takes for carriers of advanced adenomas to develop cancer, of 18–40 and 19–38 years, respectively (the mean dwell times are obtained as 1 divided by the annual transition rates). Likewise, our estimates of annual transition rates from 3.6% to 4.7% would translate to a mean nonadvanced adenoma dwell time of 21–28 years. Assumptions regarding transition

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rates and average adenoma dwell times have varied widely in cost-effectiveness analyses of CRC screening. For example, Vijan and colleagues assumed a dwell time of 10 years for those adenomas eventually converting to cancer (32). Frazier and colleagues assumed an annual transition rate from high-risk polyps to localized cancer of 5% (16), which was derived from a study of patients who refused resection of a high-risk polyp (24), and which was varied from 2% to 10% in sensitivity analyses. This variation had a very large impact on estimated cost effectiveness. Song and colleagues likewise assumed an annual transition rate from large polyps to cancer of 5% (31). Khandker and colleagues varied 10-year transition rates from polyps to cancer between 25% and 100% in sensitivity analyses and found this variation to have a strong impact on indicators of cost effectiveness (29). These patterns underline the necessity of accurate and precise estimates of transition rates.

Our estimates of transition rates from carriage of advanced adenoma to carriage of CRC agree well with those from our previous study, in which we had combined data of the German national screening colonoscopy registry with cancer registry-based data on CRC incidence in Germany (25). The previous study had likewise estimated transition rates to be similar for men and women, and to increase with age, from 2.6% to 4.5% among men and from 2.6% to 5.8% among women across the age groups from 55–59 to 75–79 years. Although this consistency is reassuring, the current study offers a number of major advantages. First, all estimates are based on the same database of screening colonoscopy participants. Thus, they should be unaffected by potential differences between participants and nonparticipants of screening colonoscopy. Second, our estimates pertain to participants belonging to the same birth cohorts, which should help to prevent potential bias by previously identified major birth cohort effects (35). Third, our current estimates are based on a much larger database of the German national screening colonoscopy registry (2003–2010, >3.5 million records) than the previous estimates (2003–2004, <0.9 million records), which allowed estimating transition rates at high levels of precision. Finally, we are now able to provide previously unreported transition rates from carriage of nonadvanced to carriage of advanced adenoma, as well as cumulative transition rates from both carriage of advanced adenoma and carriage of nonadvanced adenoma to carriage of CRC.

Our study also has limitations. Although our results reflect transition rates among participants of screening colonoscopy, they may not necessarily be representative for such transition rates in nonparticipants. Data available suggest that approximately 25% to 30% of the German population in the eligible age range will have a screening colonoscopy within the 10-year time interval foreseen for this screening offer. Although use of lower gastrointestinal endoscopy was found to be higher among better educated than among less educated people in a recent survey from European countries including Germany, no association with gastrointestinal endoscopy use was seen for CRC risk factors potentially related to education such as smoking or obesity (36). Potential bias from this source should therefore be limited.

Although the German national screening colonoscopy registry is unique regarding its size and comprehensive population coverage, it relies on findings at colonoscopy reported from a large number of endoscopists. Heterogeneity in quality of performance of colonoscopy and reporting of its results is necessarily larger than in studies restricted to specialized centers, despite strict measures of quality assurance. However, detection rates of adenomas and CRC by sex and age observed in our study are highly consistent with observations from screening colonoscopy programs in other European countries, such as Poland (37) and Austria (38). Although colonoscopy is considered to be the gold standard for detection of colorectal neoplasms and miss rates of large neoplasms are very small, a nonnegligible proportion of small adenomas are missed (39), which may have led to some underestimation of their prevalences and to some overestimation of transition rates which would though be mostly confined to the transition rates from carriage of nonadvanced adenoma to carriage of advanced adenoma.

For example, Van Rijn and colleagues estimated miss rates of 2.1% for polyps 1 cm or more and of 22% for polyps of any size in a meta-analysis of tandem colonoscopy studies (39). Reanalyses of our data correcting the observed prevalences by presumed miss rates of 1%, 2.5%, and 25% for CRC, advanced adenomas, and nonadvanced adenomas, respectively, would not affect the estimates of transition rates from carriage of advanced adenoma to carriage of CRC to any relevant extent (<2% in all cases). However, estimates of transition rates from carriage of nonadvanced adenoma to advanced adenoma would be approximately 20% lower. Somewhat lower transition rates would result in case of even higher miss rates. For example, assuming a 12% rather than 2.5% miss rate of advanced adenomas would result in 11% lower transition rates from advanced adenoma to CRC carriage. Despite potential overestimation of "true" ("biologic") transition rates due to missed adenomas, our estimates would still be valid for transition rates regarding neoplasms observable in routine screening colonoscopies. The latter might even be more relevant for modeling the impact of different types of screening strategies.

In addition, some misclassification of adenomas has to be assumed, given the decentral histopathologic examination by a large number of certified pathology labs. Also, the screening colonoscopy registry did not include sufficiently detailed data to calculate specific transition rates for proximal and distal neoplasms, which would be of particular interest in the light of differences in their biology, epidemiology, and potential for prevention. In particular, the proportion of cancers arising in serrated lesions rather than advanced adenomas is assumed to be higher in the proximal colon than in the distal colon and rectum (33).

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CRC sojourn time, whose estimates from FOBT-based screening trials or programs have varied almost 2-fold (17, 27, 28), accounts for an additional source of uncertainty. FOBT-based estimates of mean sojourn time might be somewhat too short given that bleeding adenomas are expected to be "older" than nonbleeding adenomas detected at colonoscopy. However, in our analyses, sojourn time only affects persistence of preclinical CRC from one year to the subsequent year, and sensitivity analyses showed our estimates of transition rates to be rather robust over the range of sojourn times estimates. Recently, detailed age- and sex-specific estimates of sojourn time by sex and age were derived from the combination of data from the national screening colonoscopy registry and data on CRC incidence in Germany (40). All of these estimates were very close to the base case value (4.7 years) used in our current analysis.

In summary, despite its limitations, our study enhances the empirical evidence for the magnitude of transition rates from carriage of advanced adenoma to carriage of CRC and from carriage of nonadvanced to carriage of advanced adenoma, the increase of the former transition rates with age, and the consistency of both transition rates across both sexes. Our results thereby substantially strengthen the empirical basis for investigating effectiveness and cost-effectiveness of various screening strategies.

The relatively low annual transition rates suggested by our analyses, which translate into long average dwell times of several decades, may have a number of important clinical implications. First, most adenomas may never develop into cancer during lifetime. In particular, as indicated by our analyses of cumulative transition rates, the vast majority of people with nonadvanced adenoma (but no advanced neoplasm) at older ages would never develop CRC even without detection and removal of the adenoma. Second, even if missed at a first colonoscopy, there is a very good chance for adenomas to be detected and removed at a second colonoscopy before progression, even with long screening intervals, such as 10 years. Third, repeat annual screening examinations with noninvasive tests, such as FOBTs may detect a substantial proportion of advanced adenomas before they turn into cancer, despite the relatively low per-test sensitivity for detecting advanced adenomas (41). This proportion may be further increased by tests with enhanced sensitivity in the future (42).

On the other hand, the high cumulative transition rates for people with advanced adenoma and even for people with nonadvanced adenoma present already at younger ages underline the need and the merits of most careful detection and complete removal of all such neoplasms at screening colonoscopy.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Disclaimer

The sponsors did not have any role in this study.

Authors' Contributions

Conception and design: H. Brenner
Development of methodology: H. Brenner
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): L. Altenhofen
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): H. Brenner, L. Altenhofen, C. Stock
Writing, review, and/or revision of the manuscript: H. Brenner, L. Altenhofen, C. Stock, M. Hoffmeister
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): L. Altenhofen

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