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International variation in the prevalence of preclinical colorectal cancer: Implications for predictive values of noninvasive screening tests and potential target populations for screening

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Cancer Epidemiology

Screening for colorectal cancer (CRC) is implemented in an increasing number of countries. We aimed to assess international variation in the prevalence of preclinical CRC and the resulting variation in positive and negative predictive values (PPVs, NPVs) of existing and potential CRC screening tests in various countries. Using age- and sex-specific CRC incidence data and transition rates from preclinical to clinical CRC we estimated overall and age- and sex-specific prevalence of preclinical CRC in the target population aged 50–74 years in different parts of the world. These prevalence estimates were used to derive PPVs and NPVs for existing and potential noninvasive screening tests with varying levels of sensitivity and specificity. Within all regions and countries, prevalence strongly increases with age and is higher in men than in women. In addition, major variation was seen between regions and countries, with overall prevalence varying between 1 and 0.1%. As a result, PPVs are expected to strongly vary between ~10% for men in high incidence countries, such as Australia and Germany, and 1% for women in low incidence countries, whereas NPVs are expected to be consistently well above 99%. Variation in CRC prevalence profoundly affects expected PPVs of screening tests, and PPVs should be carefully considered when decisions on screening tests and strategies are made for specific populations and health care systems. Here, we provide estimates of preclinical CRC and expected PPVs and NPVs of noninvasive screening tests, which may enhance the empirical basis for planning of population-based CRC screening strategies.

Colorectal cancer (CRC) is the third most common cancer and the fourth most common cancer cause of death globally, accounting for ~700,000 deaths per year.[1] Prognosis is strongly stage-dependent, with 5-year survival ranging from close to 90% for stage I cancers to little over 10% for stage IV cancers even in the most developed countries.[2,3] As a result, and given the relatively slow development of CRC from early preclinical to advanced clinical stages, which typically takes several years,[4] perspectives for reducing the burden of the disease by screening and early detection are much better than for most other forms of cancer.

CRC screening programs are now being implemented in an increasing numbers of countries.[5] In most cases, a two-step approach is employed, with initial screening by a noninvasive test, such as a fecal immunochemical test (FIT) for hemoglobin, to be followed by colonoscopy in case of a positive test result. This strategy is associated with better screening uptake, and through lowering the number of colonoscopies, it saves resources and reduces discomfort and potential harms related to invasive screening.[6] From an economic perspective it is desired to minimize the number of false positive results of prescreening tests. It is widely appreciated that the diagnostic yield, on the one hand and the burden of follow-up colonoscopy, on the other hand, strongly depend on the sensitivity and the specificity of the primary screening test, which are regularly being evaluated in diagnostic studies. However, they also depend on the prevalence of preclinical CRC in the target

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What's new?

Colorectal cancer (CRC) screening is implemented in an increasing number of countries, usually in a two-step approach consisting in a noninvasive test followed by colonoscopy in case of a positive result. Prevalence of preclinical colorectal cancer strongly affects screening efficiency, but such data is scarce. Here, the authors provide detailed age- and sex-specific preclinical CRC prevalence estimates for various countries and geographical regions and show their implications on expected positive and negative predictive values of existing and potential noninvasive screening tests. Knowledge of these predictive values should enhance the empirical basis for decisions on CRC screening tests and target populations.

population of screening,[7] which may strongly vary between countries and should be taken into account when implementing CRC screening in a specific population. However, data on the prevalence of such preclinical CRC in the target population for CRC screening are sparse.

In this article, we aimed to assess the international and interregional variation in preclinical CRC and its impact on predictive values for noninvasive screening tests in different populations. To do so, we estimated the age- and sex-specific prevalence as well as the overall prevalence of preclinical CRC in the target population of CRC screening for a large variety of regions of the world. We then used these estimates to derive positive and negative predictive values (PPVs, NPVs), that is, the probabilities of positive and negative screening results correctly indicating presence or absence of CRC, respectively, that are to be expected with various realistic levels of sensitivities and specificities of CRC screening tests. Thereby, we aimed to enhance the evidence base for decision-making in the planning of population-based CRC screening.

Material and Methods

Prevalence of preclinical CRC

Age- and sex-specific CRC incidence, denoted $I_{age,sex}$, and age- and sex-specific transition rates of preclinical to clinical cancer, denoted $T_{age,\ sex}$, were used to calculate the age- and sex-specific prevalence of preclinical CRC in 5-year age groups (50–54, 55–59, 60–64, 65–69 and 70–74), denoted $P_{age,\ sex}$, as follows:

$$P_{age,\,sex} = I_{age,\,sex} / T_{age,\,sex}.$$

CRC incidence data for major geographic regions (Europe: Central-East, North, South and West; America: Central, North and South; Asia: East, South-Central, South-East and West; Africa and Australia) and individual countries within geographical regions (except for Africa, where CRC incidence is very low and reliable CRC incidence data are still lacking for many countries) were taken from the GLOBOCAN 2012 database.[8] The list of countries in each geographical region is given in Supporting Information Table S1.

Transition rates, that is, the annual probability of transition from already existing but not clinically manifest (preclinical) to clinically manifest CRC, were based on previous analyses of data from the German screening colonoscopy registry and German population-based cancer registries.[4] Age-specific estimates of annual transition rates ranged from 18.1% [95% confidence interval (CI) 16.7–19.5] to 22.5% (95% CI, 20.9–24.2), which correspond to "mean sojourn times" from preclinical to clinical cancers of 5.5 and 4.5 years, respectively (see Supporting Information Table S2). Transition rates for the 50–54 year old population were not available; therefore, the same transition rates as for the age group 55–59 were applied. Transition rates in the same order of magnitude, but without stratification by age and/or sex have been estimated for a few other countries.[9–11] Given the lack of detailed transition rates by age and sex from other countries and assuming regional variation of such transition rates to be small, the age- and sex-specific transition rates derived from the German screening colonoscopy registry were applied for all calculations.

To quantify variation in prevalence between the youngest and oldest age group, between men and women, and Australia (highest prevalence region) and other regions, ratios in prevalence were calculated using the estimates derived by the above described approaches.

Positive and negative predictive values

Using the derived prevalence of preclinical CRC, age- and sex-specific positive and negative predictive values, denoted $PPV_{age,\ sex}$ and $NPV_{age,\ sex}$, respectively, were calculated as:

$$NPV_{age,sex} = \frac{Sp * (1 - P_{age,\,sex})}{(1 - Sp) * P_{age,\,sex} + Sp * (1 - P_{age,\,sex})}$$

and

$$PPV_{age,\,sex} = \frac{Sc * P_{age,\,sex}}{Sc * P_{age,\,sex} + (1 - Sp) * (1 - P_{age,\,sex})},$$

where *Se* and *Sp* denote the sensitivity and specificity of the screening test.

We derived hypothetical PPVs and NPVs potentially achievable with combinations of test sensitivity of 0.7, 0.8 or 0.9 with test specificity of 0.7, 0.8 or 0.9, as well as with exceptionally high sensitivity and specificity of 0.95. Moreover, PPVs and NPVs were calculated for FITs, assuming pooled estimates of diagnostic performance from a recent meta-analysis (sensitivity: 0.79, specificity: 0.94[12]), and for a recently approved stool-DNA test (Cologuard, sensitivity: 0.923, specificity: 0.866[13]) and a blood-based test (Epi proColon, sensitivity: 0.482, specificity: 0.915[14]).

Table 1. Age-specific and overall prevalence of preclinical colorectal cancer, by geographical region, sex and age

	Prevalence (%)						Ratios in prevalence		
Region	50–54	55–59	60–64	65–69	70–74	Overall[1]	70–74 *vs.* 50–54	Men *vs.* women	Australia *vs.* other regions
Men									
N. Europe	0.26	0.49	0.77	1.07	1.51	0.74	5.8	1.6	1.2
W. Europe	0.32	0.58	0.87	1.17	1.60	0.82	5.1	1.8	1.1
S. Europe	0.35	0.62	0.92	1.16	1.53	0.84	4.4	1.9	1.1
C.-E. Europe	0.27	0.53	0.83	1.12	1.42	0.69	5.4	1.7	1.3
N. America	0.31	0.47	0.62	0.76	1.00	0.56	3.2	1.5	1.6
C. America	0.10	0.14	0.18	0.21	0.29	0.16	3.0	1.4	5.7
S. America	0.15	0.23	0.34	0.46	0.67	0.31	4.6	1.3	2.9
W. Asia	0.17	0.27	0.39	0.48	0.62	0.31	3.7	1.6	2.9
S.-C. Asia	0.08	0.12	0.15	0.17	0.22	0.13	2.8	1.6	7.2
S.-E. Asia	0.14	0.24	0.34	0.41	0.52	0.27	4.3	1.7	2.2
E. Asia	0.19	0.31	0.45	0.59	0.82	0.40	4.3	1.7	2.2
Africa	0.08	0.12	0.14	0.17	0.20	0.13	2.4	1.4	7.1
Australia	0.36	0.66	0.99	1.30	1.77	0.90	4.9	1.6	n/a
Women									
N. Europe	0.18	0.30	0.43	0.66	0.94	0.46	5.1	n/a	1.2
W. Europe	0.20	0.31	0.42	0.61	0.85	0.44	4.2	n/a	1.2
S. Europe	0.22	0.33	0.44	0.60	0.79	0.44	3.6	n/a	1.2
C.-E. Europe	0.19	0.31	0.43	0.60	0.7	0.42	4.1	n/a	1.3
N. America	0.20	0.28	0.36	0.51	0.71	0.36	3.5	n/a	1.5
C. America	0.07	0.09	0.11	0.16	0.23	0.11	3.4	n/a	4.9
S. America	0.11	0.16	0.23	0.35	0.54	0.23	4.9	n/a	2.4
W. Asia	0.12	0.16	0.22	0.29	0.37	0.20	3.2	n/a	2.8
S.-C. Asia	0.05	0.07	0.09	0.11	0.14	0.08	2.5	n/a	6.9
S.-E. Asia	0.10	0.14	0.18	0.24	0.32	0.17	4.5	n/a	2.4
E. Asia	0.11	0.17	0.24	0.34	0.49	0.23	4.5	n/a	2.4
Africa	0.06	0.08	0.10	0.12	0.14	0.09	2.3	n/a	6.0
Australia	0.23	0.38	0.54	0.82	1.16	0.55	5.0	n/a	n/a

C, Central; E, East; N, North; S, South; W, West.
[1]Weighted sum of age-specific prevalence estimates using region-specific underlying population age structure as shown in Supporting Information Table S3.

Geographic variation in screening test performance

Age-specific and overall PPVs and NPVs were estimated for 6 exemplary countries for each geographical region worldwide: Australia, Germany (Europe), the U.S. (North America), Brazil (South America), Morocco (Africa) and India (Asia).

Overall sex- and country-specific prevalences, PPVs and NPVs for the 50–74 year old populations were calculated by weighting age-specific estimates of prevalences, PPVs and NPVs, respectively, by the population weights, that is, proportions of people in these groups in each of the analyzed populations. Age-specific population weights, which were derived from data in the GLOBOCAN 2012 database[8] are provided in Supporting Information Table S3.

PPVs and NPVs for different prevalence levels and test performances

To show the impact of the disease prevalence in a target population, PPVs and NPVs were calculated for individual screening tests for each CRC prevalence level between 0.2 and 3.0% by 0.2 units. These data, in combination with estimated country-specific prevalences (Table 2 and Supporting Information Table S4), provide an easy to use tool for the estimation of expected PPVs and NPVs for various actual and potential screening tests in the populations of interest. Overall predictive values of a given screening test in a given country can be calculated as:

$$PPV_{Overall} = \sum PPV_i * W_i$$

and

$$NPV_{Overall} = \sum NPV_i * W_i,$$

where PPV_i corresponds to the PPV of the given test (Table 4) at the prevalence level in age group i of the given country (Table 2 and Supporting Information Table S4), and W_i corresponds to the weight of corresponding age group i in the given country (Supporting Information Table S3).

Additionally, to demonstrate the impact of the prevalence and the screening tests' sensitivity and specificity on PPVs, we provide surface plots for PPVs corresponding to sensitivities and specificities between 0.7 and 0.95 on a continuous scale for selected prevalences (0.2, 0.5, 1.0 and 1.5%).

Results

Prevalence of preclinical CRC

Age-specific prevalences of preclinical CRC in major regions of the world are presented in Table 1. Very low rates are found for the 50–54 year old populations in all parts of the world (0.08–0.36% for men and 0.05–0.23% for women), while increasing variation is seen in older age groups, for example, prevalences of around 0.13% in 70–74 year old men in South-Central Asia and Africa compared with 1.4–1.8% in Europe and Australia. The prevalence of preclinical CRC in men is higher than in women, with an overall male-to-female prevalence ratio of 1.9 in Southern Europe (0.84 vs. 0.44%, respectively) compared with a male-to-female prevalence ratio of 1.3 in South America (0.31 *vs.* 0.23%, respectively). The highest prevalence of preclinical CRC is expected in Australia in all age groups and for both sexes.

Age-specific and overall prevalences of preclinical CRC for each European country are presented in Table 2. High variation between prevalence estimates is seen even within the same geographical regions. For example, estimated overall prevalence in 50–74 year old men in Southern Europe varied from 0.19% in Albania to 1.01% in Slovenia. The highest overall prevalences in men were found for Hungary (1.27%), Slovakia (1.19%) and Czech Republic (1.13%), and in women for Denmark (0.68%), The Netherlands and Norway (0.64%, both). The lowest prevalence estimates for men (0.19%) and women (0.14%) were seen in Albania.

Geographic variation in PPVs and NPVs

Table 3 provides the expected overall CRC prevalences, PPVs and NPVs in the age range 50–74 years for screening tests with various levels of sensitivities and specificities in the populations of Australia, Germany, the U.S., Brazil, Morocco and India. In general, PPVs remain below 15% for any screening test, even in case of exceptionally high sensitivity and specificity of 0.95 and in countries with relatively high CRC prevalence, such as Australia and Germany. In both of the countries, a screening test with a sensitivity and specificity of 0.9 would result in PPVs of 7% in men and 4–5% in women. Applying the summary estimates of sensitivity (0.79) and specificity (0.94) from a recent meta-analysis,[12] a positive FIT test confers 10% probability for a true diagnosis for men, and >5% for women in these countries. PPVs for the Cologuard test (with 0.923 sensitivity and 0.866 specificity[13]) and Epi proColon test (with 0.482 sensitivity and 0.915 specificity[14]) are expected to be consistently lower. In populations with disease prevalence below 0.2% (Morocco and India) all screening tests with the studied characteristics would perform poorly: even with a test that has 0.95 sensitivity and specificity only a PPV of 2.4% could be achieved. Age-specific PPVs and NPVs for each of the countries are shown in Supporting Information Tables S5–S10.

The strong dependence of the PPV especially on screening test's specificity can be seen in Table 3. An increase in specificity from 0.7 to 0.9 (at the same sensitivity level) resulted into 3-fold higher PPVs (*e.g.*, Germany, men, 50–74, sensitivity = 0.7: PPV increased from 1.95 to 5.58%). At the same time, an increase in the test's sensitivity level from 0.7 to 0.9 (at the same specificity level) only resulted in a very modest increase in PPVs (*e.g.,* Germany, men, 50–74, specificity = 0.7: PPV increased from 1.95 to 2.49%). Adding an extra 5% points to a test's sensitivity and specificity (from 0.9 to 0.95), a very strong improvement in test's performance could be achieved with a doubling of the expected PPVs.

PPVs and NPVs for different prevalence levels and test performances

Table 4 presents calculated PPVs and NPVs for prevalences between 0.2 and 3.0%. In general, PPVs exceed 5% in populations with the prevalence as low as 0.6, 0.8 and 0.8% for the tests with 0.9 specificity and 0.9, 0.8 and 0.7 sensitivities, respectively. Having a prevalence of 3% in the target population, a test with a sensitivity and specificity of both 0.9 would reach PPV of 22%. Among the currently available screening tests, PPVs of 10% or higher would also expected with FIT, Cologuard and Epi proColon in populations with at least 0.8, 1.6 and 2.0% CRC prevalence, respectively. FIT would be expected to outperform both the Cologuard test and Epi ProColon test with respect to PPV regardless of CRC prevalence.

Except for unusually high CRC prevalences, NPVs would be expected to be between 99 and 100% (mostly between 99.5 and 100%) for all tests.

Surface plots for PPVs for prevalence levels of 0.2, 0.5, 1.0 and 1.5% are shown in Figure 1. For a disease prevalence of 0.5% and below, PPV varies only very little at any combination of sensitivity and specificity levels, even up to 95%. At high levels of sensitivity and specificity, and with a disease prevalence of 1.5%, PPV levels exceed 20%.

Table 2. Age-specific and overall prevalence (in %) of preclinical colorectal cancer in European countries

	Men							Women						
Country	**50–54**	**55–59**	**60–64**	**65–69**	**70–74**	**Overall[1]**	**Rank[2]**	**50–54**	**55–59**	**60–64**	**65–69**	**70–74**	**Overall[1]**	**Rank[2]**
N. Europe	**0.26**	**0.49**	**0.77**	**1.07**	**1.51**	**0.74**		**0.18**	**0.30**	**0.43**	**0.66**	**0.94**	**0.46**	
Denmark	0.34	0.64	0.98	1.38	1.94	0.97	6	0.27	0.44	0.63	0.95	1.33	0.68	1
Estonia	0.22	0.48	0.78	1.14	1.58	0.72	26	0.18	0.29	0.40	0.60	0.89	0.45	17
Finland[3]	0.20	0.39	0.61	0.83	1.15	0.58	34	0.16	0.25	0.34	0.49	0.68	0.36	34
Iceland	0.15	0.39	0.74	0.90	1.23	0.57	36	0.26	0.39	0.49	0.64	0.93	0.48	14
Ireland[3]	0.32	0.59	0.90	1.27	1.81	0.85	14	0.20	0.32	0.47	0.72	1.07	0.49	13
Latvia[3]	0.18	0.40	0.66	0.94	1.34	0.60	32	0.14	0.26	0.39	0.60	0.82	0.42	24
Lithuania[3]	0.20	0.40	0.68	0.99	1.43	0.61	30	0.14	0.25	0.37	0.54	0.74	0.38	32
Norway[3]	0.28	0.55	0.88	1.27	1.83	0.84	17	0.24	0.42	0.62	0.95	1.36	0.64	2
Sweden[3]	0.21	0.42	0.67	0.98	1.41	0.69	28	0.19	0.32	0.47	0.73	1.04	0.52	8
United Kingdom[3]	0.26	0.50	0.76	1.05	1.49	0.74	24	0.17	0.28	0.40	0.62	0.89	0.44	18
W. Europe	**0.32**	**0.58**	**0.87**	**1.17**	**1.60**	**0.82**		**0.20**	**0.31**	**0.42**	**0.61**	**0.85**	**0.44**	
Austria[3]	0.26	0.49	0.75	1.01	1.39	0.70	27	0.16	0.25	0.34	0.48	0.67	0.36	35
Belgium[3]	0.38	0.67	1.02	1.30	1.72	0.91	10	0.23	0.36	0.52	0.74	1.01	0.52	7
France[3]	0.31	0.52	0.77	1.07	1.48	0.74	25	0.20	0.29	0.40	0.62	0.88	0.43	21
Germany[3]	0.32	0.60	0.90	1.18	1.61	0.85	15	0.19	0.29	0.39	0.55	0.78	0.42	25
Luxembourg[3]	0.29	0.48	1.16	1.10	2.05	0.84	16	0.18	0.24	0.34	0.47	0.67	0.34	37
The Netherlands	0.34	0.68	1.06	1.46	2.03	0.98	5	0.26	0.43	0.62	0.93	1.29	0.64	3
Switzerland[3]	0.29	0.55	0.83	1.07	1.44	0.75	20	0.20	0.31	0.42	0.59	0.80	0.43	22
S. Europe	**0.35**	**0.62**	**0.92**	**1.16**	**1.53**	**0.84**		**0.22**	**0.33**	**0.44**	**0.60**	**0.79**	**0.44**	
Albania	0.10	0.15	0.22	0.27	0.31	0.19	40	0.09	0.11	0.14	0.18	0.23	0.14	40
Bosnia and Herzegovina	0.20	0.34	0.52	0.58	0.63	0.41	38	0.15	0.19	0.22	0.35	0.43	0.24	38
Croatia[3]	0.31	0.62	0.98	1.36	1.89	0.90	11	0.19	0.31	0.44	0.65	0.91	0.46	15
Cyprus	0.23	0.39	0.60	0.77	1.10	0.54	37	0.20	0.29	0.36	0.52	0.75	0.38	31
Greece	0.12	0.21	0.31	0.42	0.62	0.31	39	0.08	0.13	0.17	0.24	0.35	0.18	39
Italy[3]	0.36	0.67	1.00	1.25	1.62	0.92	7	0.26	0.40	0.53	0.69	0.88	0.53	6
Macedonia	0.30	0.51	0.69	0.81	0.98	0.59	33	0.16	0.27	0.38	0.59	0.81	0.39	30
Malta[3]	0.35	0.62	0.85	1.12	1.49	0.79	18	0.24	0.40	0.45	0.74	0.87	0.49	12
Montenegro	0.55	0.71	0.65	0.93	1.21	0.74	22	0.28	0.29	0.33	0.52	0.60	0.37	33
Portugal[3]	0.38	0.68	0.97	1.22	1.59	0.89	12	0.22	0.32	0.42	0.57	0.76	0.43	19
Serbia	0.46	0.77	1.05	1.24	1.48	0.91	8	0.23	0.35	0.45	0.59	0.73	0.43	20
Slovenia[3]	0.35	0.70	1.10	1.57	2.17	1.01	4	0.21	0.36	0.51	0.74	1.02	0.52	9
Spain[3]	0.39	0.68	0.99	1.27	1.75	0.91	9	0.21	0.31	0.40	0.58	0.81	0.43	23
C.-E. Europe	**0.27**	**0.53**	**0.83**	**1.12**	**1.42**	**0.69**		**0.19**	**0.31**	**0.43**	**0.60**	**0.76**	**0.42**	
Belarus	0.25	0.50	0.76	0.99	1.28	0.61	31	0.17	0.29	0.42	0.62	0.79	0.40	27
Bulgaria	0.35	0.66	0.97	1.23	1.58	0.88	13	0.22	0.37	0.50	0.68	0.86	0.50	11
Czech Republic[3]	0.39	0.80	1.25	1.67	2.27	1.13	3	0.19	0.33	0.49	0.73	1.01	0.50	10
Hungary[3]	0.57	1.02	1.45	1.73	2.17	1.27	1	0.27	0.42	0.57	0.78	1.03	0.58	4
Moldova	0.27	0.55	0.98	1.30	1.56	0.75	19	0.21	0.36	0.50	0.67	0.82	0.45	16
Poland[3]	0.29	0.58	0.88	1.16	1.55	0.74	23	0.16	0.25	0.35	0.51	0.72	0.35	36
Romania	0.33	0.60	0.85	1.05	1.32	0.75	21	0.18	0.28	0.38	0.54	0.70	0.39	29
Russian Federation	0.22	0.43	0.70	0.97	1.30	0.57	35	0.18	0.32	0.44	0.61	0.77	0.41	26
Slovakia	0.45	0.86	1.40	1.94	2.71	1.19	2	0.23	0.36	0.52	0.79	1.14	0.53	5
Ukraine	0.25	0.49	0.78	0.99	1.20	0.64	29	0.19	0.32	0.42	0.54	0.65	0.40	28

C, Central; E, East; N, North; S, South; W, West.

[1]Weighted sum of age-specific prevalence estimates using country-specific underlying population age structure as shown in Supporting Information Table S3.

[2]The rank refers to the country ranking after sorting by the overall prevalence among men and women.

[3]Countries with a screening program in place (partial or population-based) in 2012 as described by Schreuders *et al.*[5] or Ponti *et al.*[15]

Table 3. Overall age-adjusted positive and negative predictive values of screening tests with defined levels of sensitivity and specificity for colorectal cancer detection in selected countries

	Positive predictive value (%)[1]/negative predictive value (%)[1]					
Sensitivity/specificity	**Australia**	**Germany**	**The U.S.**	**Brazil**	**Morocco**	**India**
Men						
Prevalence (%)[1]	0.90	0.85	0.53	0.30	0.19	0.13
0.7/0.7	2.07/99.61	1.95/99.63	1.23/99.77	0.71/99.87	0.45/99.92	0.30/99.94
0.7/0.8	3.07/99.66	2.89/99.68	1.83/99.80	1.05/99.89	0.67/99.93	0.45/99.95
0.7/0.9	5.92/99.70	5.58/99.72	3.58/99.82	2.08/99.90	1.34/99.94	0.90/99.96
0.8/0.7	2.36/99.74	2.22/99.76	1.40/99.85	0.81/99.91	0.51/99.94	0.34/99.96
0.8/0.8	3.49/99.77	3.29/99.79	2.08/99.87	1.20/99.92	0.77/99.95	0.51/99.97
0.8/0.9	6.69/99.80	6.31/99.81	4.07/99.88	2.37/99.93	1.53/99.96	1.02/99.97
0.9/0.7	2.65/99.87	2.49/99.88	1.57/99.92	0.90/99.96	0.58/99.97	0.39/99.98
0.9/0.8	3.91/99.89	3.68/99.89	2.34/99.93	1.35/99.96	0.86/99.98	0.58/99.98
0.9/0.9	7.45/99.90	7.03/99.90	4.56/99.94	2.66/99.97	1.71/99.98	1.15/99.99
0.95/0.95	14.30/99.95	13.54/99.95	9.11/99.97	5.41/99.98	3.54/99.99	2.39/99.99
FIT[2]	10.46/99.80	9.89/99.81	6.51/99.88	3.83/99.93	2.48/99.96	1.67/99.97
Cologuard[3]	5.83/99.92	5.50/99.92	3.53/99.95	2.05/99.97	1.32/99.98	0.88/99.99
Epi proColon[4]	4.86/99.49	4.58/99.52	2.93/99.70	1.69/99.83	1.09/99.89	0.73/99.93
Women						
Prevalence (%)[1]	0.55	0.42	0.35	0.23	0.13	0.08
0.7/0.7	1.28/99.76	0.97/99.82	0.81/99.85	0.54/99.90	0.30/99.95	0.18/99.97
0.7/0.8	1.90/99.79	1.45/99.84	1.21/99.87	0.80/99.91	0.44/99.95	0.28/99.97
0.7/0.9	3.71/99.81	2.84/99.86	2.39/99.88	1.59/99.92	0.89/99.96	0.55/99.97
0.8/0.7	1.46/99.84	1.11/99.88	0.93/99.90	0.61/99.93	0.34/99.96	0.21/99.98
0.8/0.8	2.16/99.86	1.65/99.89	1.38/99.91	0.92/99.94	0.51/99.97	0.31/99.98
0.8/0.9	4.21/99.88	3.23/99.91	2.73/99.92	1.81/99.95	1.01/99.97	0.63/99.98
0.9/0.7	1.63/99.92	1.24/99.94	1.04/99.95	0.69/99.97	0.38/99.98	0.24/99.99
0.9/0.8	2.43/99.93	1.85/99.95	1.55/99.96	1.03/99.97	0.57/99.98	0.35/99.99
0.9/0.9	4.70/99.94	3.62/99.95	3.05/99.96	2.03/99.97	1.14/99.99	0.71/99.99
0.95/0.95	9.32/99.97	7.28/99.98	6.20/99.98	4.17/99.99	2.37/99.99	1.48/100
FIT[2]	6.70/99.88	5.19/99.91	4.39/99.92	2.94/99.95	1.65/99.97	1.03/99.98
Cologuard[3]	3.65/99.95	2.80/99.96	2.36/99.97	1.57/99.98	0.87/99.99	0.54/99.99
Epi proColon[4]	3.03/99.69	2.32/99.76	1.95/99.80	1.29/99.87	0.72/99.93	0.45/99.96

[1]Weighted sum of age-specific estimates using country-specific underlying population age structure as shown in Supporting Information Table S3.
[2]FIT, sensitivity 0.79 and specificity 0.94.[12]
[3]Cologuard, sensitivity 0.923 and specificity 0.866.[13]
[4]Epi proColon, sensitivity 0.482 and specificity 0.915.[14]

Discussion

To our knowledge, this study provides the first evaluation of preclinical CRC in different regions of the world, and presents expected PPVs and NPVs when applying screening tests with various levels of sensitivities and specificities for CRC detection. We found substantial variation in the presence of preclinical CRC between geographical regions and countries, and consistent variation between men and women and different age groups. As a consequence, PPVs for screening tests were found to vary substantially between countries, while NPVs were generally high (mostly >99%) in all populations.

Worldwide, CRC screening is meanwhile implemented in >60 countries.[5] Most commonly, a two-step approach is employed, with screening by a noninvasive test, such as FIT, as the first step, and referral to colonoscopy in case of a positive result.[5] Compared with using colonoscopy as primary screening test, preselection by noninvasive testing may improve screening uptake and reduce the burden of colonoscopy, including the need for bowel preparation and the risk of discomfort and potential complications.

Extensive research is going on regarding development and evaluation of novel noninvasive screening tests, using a

Table 4. Detailed predictive values for screening tests with defined levels of sensitivity and specificity for populations with different disease prevalence

Sensitivity/ specificity	Prevalence (%)														
	0.2	0.4	0.6	0.8	1.0	1.2	1.4	1.6	1.8	2.0	2.2	2.4	2.6	2.8	3.0
	Positive predictive value (%)														
0.7/0.7	0.5	0.9	1.4	1.8	2.3	2.8	3.2	3.7	4.1	4.5	**5.0**	**5.4**	**5.9**	**6.3**	**6.7**
0.7/0.8	0.7	1.4	2.1	2.7	3.4	4.1	4.7	**5.4**	**6.0**	**6.7**	**7.3**	**7.9**	**8.5**	**9.2**	**9.8**
0.7/0.9	1.4	2.7	4.1	**5.3**	**6.6**	**7.8**	**9.0**	**10.2**	**11.4**	**12.5**	**13.6**	**14.7**	**15.7**	**16.8**	**17.8**
0.8/0.7	0.5	1.1	1.6	2.1	2.6	3.1	3.6	4.2	4.7	**5.2**	**5.7**	**6.2**	**6.6**	**7.1**	**7.6**
0.8/0.8	0.8	1.6	2.4	3.1	3.9	4.6	**5.4**	**6.1**	**6.8**	**7.5**	**8.3**	**9.0**	**9.6**	**10.3**	**11.0**
0.8/0.9	1.6	3.1	4.6	**6.1**	**7.5**	**8.9**	**10.2**	**11.5**	**12.8**	**14.0**	**15.3**	**16.4**	**17.6**	**18.7**	**19.8**
0.9/0.7	0.6	1.2	1.8	2.4	2.9	3.5	4.1	4.7	**5.2**	**5.8**	**6.3**	**6.9**	**7.4**	**8.0**	**8.5**
0.9/0.8	0.9	1.8	2.6	3.5	4.3	**5.2**	**6.0**	**6.8**	**7.6**	**8.4**	**9.2**	**10.0**	**10.7**	**11.5**	**12.2**
0.9/0.9	1.8	3.5	**5.2**	**6.8**	**8.3**	**9.9**	**11.3**	**12.8**	**14.2**	**15.5**	**16.8**	**18.1**	**19.4**	**20.6**	**21.8**
0.95/0.95	3.7	**7.1**	**10.3**	**13.3**	**16.1**	**18.8**	**21.2**	**23.6**	**25.8**	**27.9**	**29.9**	**31.8**	**33.7**	**35.4**	**37.0**
FIT[1]	2.6	**5.0**	**7.4**	**9.6**	**11.7**	**13.8**	**15.8**	**17.6**	**19.4**	**21.2**	**22.9**	**24.5**	**26.0**	**27.5**	**28.9**
Cologuard[2]	1.4	2.7	4.0	**5.3**	**6.5**	**7.7**	**8.9**	**10.1**	**11.2**	**12.3**	**13.4**	**14.5**	**15.5**	**16.6**	**17.6**
Epi proColon[3]	1.1	2.2	3.3	4.4	**5.4**	**6.4**	**7.5**	**8.4**	**9.4**	**10.4**	**11.3**	**12.2**	**13.1**	**14.0**	**14.9**
	Negative predictive value (%)														
0.7/0.7	**99.9**	**99.8**	**99.7**	**99.7**	**99.6**	**99.5**	99.4	99.3	99.2	99.1	99.0	99.0	98.9	98.8	98.7
0.7/0.8	**99.9**	**99.8**	**99.8**	**99.7**	**99.6**	**99.5**	**99.5**	99.4	99.3	99.2	99.2	99.1	99.0	98.9	98.9
0.7/0.9	**99.9**	**99.9**	**99.8**	**99.7**	**99.7**	**99.6**	**99.5**	**99**.5	99.4	99.3	99.3	99.2	99.1	99.0	99.0
0.8/0.7	**99.9**	**99.9**	**99.8**	**99.8**	**99.7**	**99.7**	**99.6**	**99.5**	**99.5**	99.4	99.4	99.3	99.2	99.2	99.1
0.8/0.8	**99.9**	**99.9**	**99.8**	**99.8**	**99.7**	**99.7**	**99.6**	**99.6**	**99.5**	**99.5**	99.4	99.4	99.3	99.3	99.2
0.8/0.9	**100**	**99.9**	**99.9**	**99.8**	**99.8**	**99.7**	**99.7**	**99.6**	**99.6**	**99.5**	**99.5**	**99.5**	99.4	99.4	99.3
0.9/0.7	**100**	**99.9**	**99.9**	**99.9**	**99.9**	**99.8**	**99.8**	**99.8**	**99.7**	**99.7**	**99.7**	**99.6**	**99.6**	**99.6**	**99.6**
0.9/0.8	**100**	**99.9**	**99.9**	**99.9**	**99.9**	**99.8**	**99.8**	**99.8**	**99.8**	**99.7**	**99.7**	**99.7**	**99.7**	**99.6**	**99.6**
0.9/0.9	**100**	**100**	**99.9**	**99.9**	**99.9**	**99.9**	**99.8**	**99.8**	**99.8**	**99.8**	**99.8**	**99.7**	**99.7**	**99.7**	**99.7**
0.95/0.95	**100**	**100**	**100**	**100**	**99.9**	**99.9**	**99.9**	**99.9**	**99.9**	**99.9**	**99.9**	**99.9**	**99.9**	**99.8**	**99.8**
FIT[1]	**100**	**99.9**	**99.9**	**99.8**	**99.8**	**99.7**	**99.7**	**99.6**	**99.6**	**99.5**	**99.5**	**99.5**	99.4	99.4	99.3
Cologuard[2]	**100**	**100**	**99.9**	**99.9**	**99.9**	**99.9**	**99.9**	**99.9**	**99.8**	**99.8**	**99.8**	**99.8**	**99.8**	**99.7**	**99.7**
Epi proColon[3]	**99.9**	**99.8**	**99.7**	**99.5**	99.4	99.3	99.2	99.1	99.0	98.9	98.7	98.6	98.5	98.4	98.3

[1]FIT, sensitivity 0.79 and specificity 0.94.[12]
[2]Cologuard, sensitivity 0.923 and specificity 0.866.[13]
[3]Epi proColon, sensitivity 0.482 and specificity 0.915.[14]
PPVs **in bold** mark estimates exceeding 5%.
NPVs **in bold** mark estimates exceeding 99.5%.

variety of different approaches, such as stool, blood, urine and breath sample-based testing, while addressing different molecular targets, such as genetic, epigenetic or proteomic markers.[15–18] With the results provided in our manuscript, expected PPVs and NPVs in different populations for any new test with known sensitivity and specificity can be easily estimated. For example, a blood test based on a 29-gene expression panel, with reported sensitivity of 79.5% and specificity of 90%,[19] would have PPVs of around 4.1% in men and 2.7% in women and NPVs of 99.9% in both genders in the average-risk population of the U.S.

As is well known, caution is required when diagnostic performance is derived from the published literature. Performance parameters of new screening tests, such as sensitivity and specificity, are often estimated in case-control studies, conducted in clinical settings and comparing clinically manifest cases with healthy controls. Such studies may often overestimate sensitivity to be expected in a screening setting.[20] While a case-control setting facilitates evaluation of test performance for rare conditions, such as specific cancers, clinically detected cancers often differ from screening-detected cancers in many respects. In particular, there is often a shift

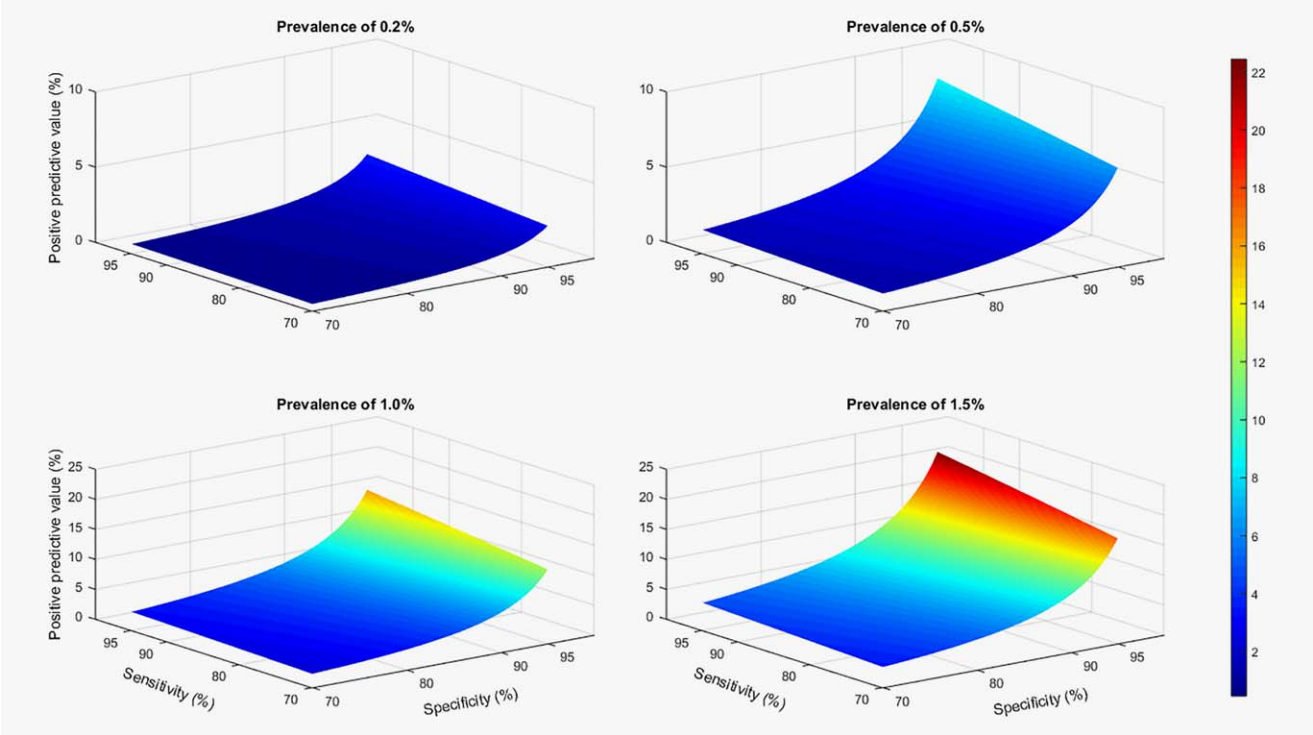

Figure 1. Surface plot for positive predictive values corresponding to sensitivities and specificities between 0.7 and 0.95.

of the stage distribution towards more advanced cases that may result in overestimation of sensitivity compared to a true screening setting. For example, reported sensitivity of Epi proColon ranged from 67[21] to 96%[22] in case-control studies compared with only 48% (the estimate used in our analyses) when the test was validated in an average-risk population.[14]

Particular caution is warranted regarding the interpretation of PPVs reported from case-control studies. Such PPVs, if not adjusted for the actual prevalence in a given population, are often very high, sometimes even reaching 99–100%.[23,24] These seemingly high PPV levels are due to the high "prevalence" of the disease in the study population which results from the ratio of cases and controls determined by study design. As demonstrated in our study, even a screening test with sensitivity and specificity of 95% would result in PPVs below 10% even in most populations with relatively high CRC prevalence. Caution is also required when PPVs are reported from studies oversampling older adults within the target population from the studies conducted in a screening setting, such as in a study on the Cologuard test,[13] which may lead to overestimation of the PPV due to the higher prevalence of CRC at older ages. Our study may therefore help to provide more realistic estimates of PPVs to be expected in population-wide screening than those reported in many diagnostic studies. We obtained fairly high NPVs for all of screening tests (mostly >99%), which is largely a consequence of the low prevalence of (preclinical) CRC in all populations. These findings are consistent with the results of studies on asymptomatic average-risk populations.[13,25,26]

Several limitations have to be kept in mind when interpreting the results of our study. Firstly, only limited data on transition rates from preclinical to clinical CRC were available in the literature, and we applied transition rates derived at very high levels of precision from the nationwide screening colonoscopy registry in Germany, the largest of its kind in the world, and German cancer registry data. Nevertheless, available estimates of annual transition rates of preclinical CRC from the U.S. and some European countries are very close to the ones we used here,[9–11,27,28] suggesting that transition rates may not differ much between populations. Still, we cannot completely rule out the possibility of transition rates being somewhat different in more distinct populations. Furthermore, our estimates of preclinical CRC are for 2012 in this study, and mid- and long-term changes in cancer incidence over the time may affect the correctness of derived predictive values. Implementation of new screening programs in countries shortly before the year 2012 could theoretically have artificially increased numbers of "incident" CRC cases (*e.g.*, in 2012 screening programs were implemented in Ireland, Norway and Malta[5]), resulting in apparently larger numbers of preclinical CRC and higher PPVs. However, for this to have a substantial impact, presumably a powerful screening tool (*e.g.*, sigmoidoscopy or colonoscopy) and high uptake of screening would be required. After an initial hypothetical increase in CRC detection, a decline and stabilization

would be expected a few years after the start of the screening. In contrary, countries with long standing screening programs may have lower CRC incidence than that before the screening was implemented due to prevented CRC through the removal of precancerous adenomas, which would have developed to CRC.[29]

Our analysis was based on cancer incidence data from the GLOBOCAN 2012 database[8] where "Colorectum" cancer was defined by the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) codes C18-C21, that is, including cancer of the anus (ICD-10: C21). While it was not possible to distinguish between these cancer sites in the database, the frequency of anal cancer compared with cancers of the colon and rectum (ICD-10: C18-C20) is relatively low (up to 4%[30]), although some sex-, age- and race-specific variation between countries exists. However, variation between the proportions of colon and rectum cancers between men and women, as well as between different age groups have been described,[31,32] which may be an additional source variation in predictive values for tests whose diagnostic performance varies between colon and rectum cancers.

In our analysis, we exclusively focused on the prevalence of preclinical CRC, which is the key target for detecting CRC in an earlier stage. However, beyond early detection of cancer, CRC screening allows the removal of precursor lesions during colonoscopy and thus is also able to prevent the development of the disease.[33–35] For this reason, CRC screening generally targets not only cancers but all advanced neoplasms (cancers and advanced adenomas). Even though currently available noninvasive tests such as FITs detect a minority of advanced adenomas, PPVs for a combined endpoint of advanced neoplasms (*i.e.*, either CRC or advanced adenoma) are much higher than PPVs for CRC only, given a much higher prevalence of advanced adenomas in screening populations.[36,37]

Finally, more comprehensive modeling is required to estimate the overall effectiveness of a certain screening strategy in a particular population. Such analyses, which can best be performed by microsimulation models need to take multiple additional factors into account, such as time trends in cancer incidence, the composition of and changes in the underlying population's age structure, and effects of the screening program modalities on the detection of CRC precursors. While such modeling is beyond the scope of the work presented here, the detailed estimates of prevalence of preclinical CRC and PPVs by sex and age should be helpful to inform such models.

In summary, we estimated prevalences of preclinical CRC cases in the target population for CRC screening in various regions of the world and found substantial geographic-, age- and gender-specific variation. We show that these variations profoundly affect the expected PPVs of CRC screening tests at realistic test performance levels. Noninvasive CRC testing is an attractive approach to help defining a subpopulation who should undergo follow-up colonoscopy both from the screenee's and health provider's perspective, yet careful planning is advised when using these tests to avoid too many false positive results and to optimize the use of resources. Our detailed estimates of prevalences of preclinical CRC and PPVs by country, age and sex should help to enhance the evidence-base for such planning.

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