COLON

Open

Head-to-Head Comparison of the Performance of 17 Risk Models for Predicting Presence of Advanced Neoplasms in Colorectal Cancer Screening

Le Peng, MM, PhD[1,2], Yesilda Balavarca, PhD[3], Korbinian Weigl, MPH, PhD[1,2,4], Michael Hoffmeister, PhD[1] and Hermann Brenner, MD, MPH[1,3,4]

OBJECTIVES: **Many risk scores have been proposed to predict presence of advanced colorectal neoplasms, but a comprehensive comparison conducted in the same population is sparse. The aim of this study was to evaluate and directly compare the diagnostic performance of published risk prediction models for advanced colorectal neoplasms.**

METHODS: **Data were drawn from 2 cohorts of subjects undergoing screening colonoscopy in Germany, i.e., KolosSal (n = 16,195) and BliTz (n = 7,444). Absolute risks and relative risks were generated for the presence of at least 1 advanced neoplasm, taking the lowest risk group as the reference group. Performance of risk models was assessed by the area under the receiver operating characteristic curve (AUC) and compared by the net reclassification improvement.**

RESULTS: **The 2 cohorts included 1,917 (11.8%) and 848 (11.4%) participants with advanced neoplasm, respectively. Absolute risks were mostly between 5% and 10% among participants in the lowest risk group and between 15% and 20% among participants in the highest risk group, and relative risks mostly ranged from 2.0 to 4.0 across the risk models in both cohorts. The AUCs ranged from 0.58 to 0.65 in KolosSal and from 0.57 to 0.61 in BliTz for all risk scores. Compared to models with lower AUC, classification was significantly improved in most models with higher AUC.**

DISCUSSION: **Risk models for advanced colorectal neoplasms generally yielded modest discriminatory power, despite some variation in performance between models. Future studies should evaluate the performance of these risk models in racially diverse populations and investigate possible extensions, such as combination with polygenic risk scores.**

SUPPLEMENTARY MATERIAL accompanies this paper at http://links.lww.com/AJG/B264

Am J Gastroenterol 2019;114:1520–1530. https://doi.org/10.14309/ajg.0000000000000370

INTRODUCTION

Colorectal cancer (CRC) is the third most commonly diagnosed cancer and the second leading cause of cancer death worldwide. More than 1.8 million people were newly diagnosed with CRC, and approximately 881,000 deaths were due to CRC in 2018 (1). The natural history of CRC usually involves slow progression from precancerous polyps to cancer, which offers opportunities for screening and early detection (2). Colonoscopy is the reference standard for detecting advanced adenomas and CRC and is recommended for CRC screening by various expert committees (3,4). Although it is highly effective (5), application of this invasive screening procedure may be limited by lower adherence rates (6) and higher complication rates (7) compared with other noninvasive screening methods such as fecal immunochemical tests (FITs).

Risk scores based on easy-to-collect factors such as age, sex, and family history (FH) might be an effective tool for risk stratification. Depending on specific settings, they could be used for various purposes, such as (1) to differentiate between people who should or should not undergo screening (e.g., in low-resource settings where screening is not generally affordable, (2) to derive different starting ages of screening according to individual risk), or (3) to differentiate people with increased risk who should undergo colonoscopy as the initial CRC screening tool and people

[1]Division of Clinical Epidemiology and Aging Research, German Cancer Research Center (DKFZ), Heidelberg, Germany; [2]Medical Faculty Heidelberg, Heidelberg University, Heidelberg, Germany; [3]Division of Preventive Oncology, German Cancer Research Center (DKFZ) and National Center for Tumor Diseases (NCT), Heidelberg, Germany; [4]German Cancer Consortium (DKTK), German Cancer Research Center (DKFZ), Heidelberg, Germany. **Correspondence:** Hermann Brenner, MD, MPH. E-mail: h.brenner@dkfz.de.
Received October 26, 2018; accepted June 26, 2019; published online August 20, 2019

with average or low risk who could be screened appropriately with other noninvasive methods such as FITs, thereby reducing unnecessary colonoscopies and improving the overall screening efficiency.

In a recent systematic review (8), we have identified 17 original risk scores for risk stratification. However, given that they were developed and validated in different and rather diverse study populations, comparability of diagnostic performance between scores has remained very limited. We therefore aimed for a head-to-head validation and comparison of the previously published risk scores for predicting advanced colorectal neoplasms in 2 large-scale screening cohorts.

METHODS

Study population

Participants for this analysis were drawn from 2 cohorts of participants of screening colonoscopy from Germany, i.e., the KolosSal (Effektivität der Früherkennungs-Koloskopie:Eine Saarland-weite Studie) and the BliTz (Begleitende Evaluierung innovativer Testverfahren zur Darmkrebsfrüherkennung) study. In Germany, screening colonoscopy is offered free of charge as a primary screening examination from the age 55 years on. Most screening colonoscopies are conducted in private gastroenterology practices. Details on both studies have been reported elsewhere (9–11). Briefly, the KolosSal study was set up to monitor long-term reduction of CRC incidence and mortality among participants of screening colonoscopy. This study is conducted by German Cancer Research Center in collaboration with 33 gastroenterology practices in Saarland, a small state (~1 million inhabitants) located in Southwest Germany (11), and 19,177 participants was recruited from 2005 to August 2014. The BliTz study was set up to validate new blood and stool tests for noninvasive CRC screening. This study is conducted by German Cancer Research Center in collaboration with 20 gastroenterology practices in Southern Germany, and 9,245 participants were recruited from 2005 to June 2016. Participants in this study were asked to donate blood and stool samples before colonoscopy (9,10). Most participants from both studies underwent screening colonoscopy for the first time, and there was no overlap between the studies. Both studies were approved by the ethics committee of Heidelberg University and the ethics committees of the responsible state medical boards (KolosSal: Saarland; BliTz: Baden-Württemberg, Rhineland-Palatinate, and Hesse). All participants gave written informed consent.

Data collection

In both studies, participants were asked to complete a standardized questionnaire delivered before screening colonoscopy, including questions about sociodemographic factors such as age and sex, FH of CRC, and lifestyle factors such as cigarette smoking, alcohol consumption, dietary habits, and physical activity. Questionnaires were almost identical in both studies. Data from colonoscopy and pathology reports were independently extracted by 2 trained research assistants who were blinded to the questionnaire information and the results of any laboratory analyses. Data entries were controlled for inconsistencies and checked for plausibility. Any discrepancies were resolved by rechecking the original records and by contacting physicians. Participants were classified into 4 subgroups according to the most advanced finding at screening colonoscopy: CRC, advanced adenoma, nonadvanced adenoma, and hyperplastic polyps or no findings. Participants with nonadvanced adenoma, hyperplastic polyps, or no findings were combined in a common subgroup "no advanced neoplasm." The main outcome for the present analyses was advanced neoplasm, which was defined as either CRC or advanced adenoma as most models calculated in the original analyses chose advanced neoplasm (advanced adenomas and CRC) for the predicted endpoint. Advanced adenomas were defined as adenomas with at least one of the following features: ≥1 cm, tubulovillous or villous components, or high-grade dysplasia (9).

We first identified 20 risk prediction models in the literature (9,12–30). For each risk score, the exact definition of the variables and the score prediction algorithm were extracted. In case one of the variables was not defined identical to the variable available in our data sets, we substituted the original ones with an appropriate proxy wherever possible. If the variables were not available in our data sets and could not be replaced (i.e., laboratory markers), we built the risk scores without them if the score still had a meaningful numbers of variables. Algorithms applied to obtain the risk scores are summarized in Supplementary Table 1 (see Supplementary Digital Content 1, http://links.lww.com/AJG/B264). Ultimately, we evaluated a total of 17 risk prediction tools (9,12–26) including 14 risk scores identified from our systematic review (8) and 3 risk models extracted from 2 additional articles (17,22). Three prediction tools identified in our systematic review were not included in our evaluation because they had been established in a population with different age structure, i.e., participants younger than 50 years only (27) or included laboratory values or other key variables that were not available in our studies (28,29) and without which 1 model only included age and sex and the other model only included age, sex, and coronary heart disease. The 17 risk prediction tools contained 6 tools from the United States, 3 tools from Korea, 2 tools from Hong Kong, 1 each from Germany, Spain, Poland, China, and Japan, and a cluster of 11 Asian cities.

Statistical analyses

For the current analyses, we excluded participants younger than 50 years or 75 years and older. Main characteristics of the 2 study populations were described using frequencies for categorical variables and mean values and standard deviations (SDs) for continuous variables. A risk score for each participant was obtained by summing up the score values from the prediction algorithm of a risk model. The participants were subsequently stratified into 5 risk categories according to the quintiles of the score. Absolute risks and relative risks were generated for the presence of at least 1 advanced neoplasm, taking the lowest risk group as the reference group. The discriminatory power was measured for all risk models using the area under the receiver operating characteristic curve (AUC) (9). AUCs were calculated both using quintiles of score values and using original exact score values. The net reclassification improvement (NRI) was calculated between any 2 risk scores (except Cao's models for female participants and male participants). An NRI > 0 suggests more accurate prediction of presence or absence of advanced neoplasia by the assessed model compared to the reference model, while an NRI < 0 suggests less accurate prediction (31). SAS 9.4 (SAS Institute, Cary, NC) and R (version 3.5.3) were used for analyses. Two-sided P values <0.05 were considered statistically significant.

RESULTS

There were 19,177 and 9,245 participants initially recruited in KolosSal and BliTz. After excluding subjects younger than

Table 1. Main characteristics of the populations of KolosSal and BliTz study

Characteristics	KolosSal			BliTz		
	No advanced neoplasm, n = 14,278 (%)	Advanced neoplasm, n = 1,917 (%)	Total, n = 16,195 (%)	No advanced neoplasm, n = 6,596 (%)	Advanced neoplasm, n = 848 (%)	Total, n = 7,444 (%)
Age (years)						
Mean (SD)	62.1 (5.7)	63.4 (5.8)	62.3 (5.8)	61.5 (5.9)	62.5 (6.0)	61.6 (5.9)
50–59	5,990 (42.0)	636 (33.2)	6,626 (40.9)	3,035 (46.0)	336 (39.6)	3,371 (45.3)
60–64	3,217 (22.5)	427 (22.3)	3,644 (22.5)	1,447 (21.9)	195 (23.0)	1,642 (22.1)
65–69	3,062 (21.5)	488 (25.5)	3,550 (21.9)	1,267 (19.2)	172 (20.3)	1,439 (19.3)
70–74	2,009 (14.1)	366 (19.1)	2,375 (14.7)	847 (12.8)	145 (17.1)	992 (13.3)
Sex						
Female	7,560 (53.0)	689 (35.9)	8,249 (50.9)	3,440 (52.2)	325 (38.3)	3,765 (50.6)
Male	6,718 (47.1)	1,228 (64.1)	7,946 (49.1)	3,156 (47.9)	523 (61.7)	3,679 (49.4)
BMI (kg/m^2)						
<25	4,526 (32.7)	493 (26.6)	5,019 (32.0)	2,211 (34.0)	249 (29.7)	2,460 (33.5)
25 to <30	6,262 (45.2)	846 (45.7)	7,108 (45.3)	2,802 (43.1)	374 (44.6)	3,176 (43.3)
30 to <35	2,357 (17.0)	402 (21.7)	2,759 (17.6)	1,125 (17.3)	173 (20.6)	1,298 (17.7)
≥35	710 (5.1)	110 (5.9)	820 (5.2)	364 (5.6)	43 (5.1)	407 (5.5)
FH of CRC in FDR						
No	12,008 (86.4)	1,559 (84.4)	13,567 (86.2)	5,655 (86.8)	702 (84.6)	6,357 (86.6)
Yes	1,889 (13.6)	288 (15.6)	2,177 (13.8)	860 (13.2)	128 (15.4)	988 (13.5)
Smoking (pack-years)						
0	6,939 (51.1)	764 (42.5)	7,703 (50.1)	3,293 (51.4)	342 (41.7)	3,635 (50.3)
<10	1,990 (14.7)	215 (12.0)	2,205 (14.3)	1,167 (18.2)	131 (16.0)	1,298 (18.0)
10 to <20	1,690 (12.5)	224 (12.5)	1,914 (12.5)	795 (12.4)	122 (14.9)	917 (12.7)
20 to <30	1,108 (8.2)	214 (11.9)	1,322 (8.6)	500 (7.8)	75 (9.2)	575 (8.0)
≥30	1,852 (13.6)	379 (21.1)	2,231 (14.5)	648 (10.1)	150 (18.3)	798 (11.1)
Alcohol intake (g/d)						
0	3,546 (26.8)	413 (23.4)	3,959 (26.4)	1,623 (25.6)	178 (21.7)	1801 (25.1)
<5	2,168 (16.4)	216 (12.2)	2,384 (15.9)	1,298 (20.4)	127 (15.5)	1,425 (19.9)
5 to <30	6,320 (47.8)	892 (50.5)	7,212 (48.1)	3,010 (47.4)	420 (51.2)	3,430 (47.8)
≥30	1,198 (9.1)	244 (13.8)	1,442 (9.6)	422 (6.6)	96 (11.7)	518 (7.2)
Regular use of aspirin						
No	11,882 (84.6)	1,577 (83.8)	13,459 (84.5)	5,688 (86.6)	721 (85.2)	6,409 (86.4)
Yes	2,167 (15.4)	306 (16.3)	2,473 (15.5)	880 (13.4)	125 (14.8)	1,005 (13.6)

Table 1. (*continued*)

Characteristics	KolosSal			BliTz		
	No advanced neoplasm, n = 14,278 (%)	Advanced neoplasm, n = 1,917 (%)	Total, n = 16,195 (%)	No advanced neoplasm, n = 6,596 (%)	Advanced neoplasm, n = 848 (%)	Total, n = 7,444 (%)
Regular use of NSAIDs other than aspirin						
No	13,535 (96.3)	1,830 (97.2)	15,365 (96.4)	6,360 (96.8)	828 (97.9)	7,188 (97.0)
Yes	514 (3.7)	53 (2.8)	567 (3.6)	208 (3.2)	18 (2.1)	226 (3.1)
Red meat intake (times/d)						
≤1	12,670 (90.3)	1,625 (86.6)	14,295 (89.9)	5,951 (90.7)	770 (91.1)	6,721 (90.8)
>1	1,359 (9.7)	252 (13.4)	1,611 (10.1)	609 (9.3)	75 (8.9)	684 (9.2)
Diabetes						
No	12,389 (88.7)	1,574 (84.7)	13,963 (88.3)	5,873 (89.9)	747 (88.3)	6,620 (89.7)
Yes	1,575 (11.3)	284 (15.3)	1859 (11.8)	658 (10.1)	99 (11.7)	757 (10.3)

Missing values in KolosSal (total column): BMI, n = 489; family history of CRC in FDR, n = 451; smoking, n = 820; alcohol intake, n = 1,198; regular use of aspirin, n = 263; regular use of NSAIDs other than aspirin, n = 263; red meat intake, n = 289; diabetes, n = 373.Missing values in BliTz (total column): BMI, n = 103; family history of CRC in FDR, n = 99; smoking, n = 221; alcohol intake, n = 270; regular use of aspirin, n = 30; regular use of NSAIDs other than aspirin, n = 30; red meat intake, n = 39; diabetes, n = 67.

BMI, body mass index; BliTz, Begleitende Evaluierung innovativer Testverfahren zur Darmkrebsfrüherkennung; CRC, colorectal cancer; FDR, first-degree relative; FH, family history; KolosSal, Effektivität der Früherkennungs-Koloskopie:Eine Saarland-weite Studie; NSAIDs, nonsteroidal anti-inflammatory drugs.

50 years or 75 years and older, those who had incomplete colonoscopy or inadequate bowel preparation and those whose colonoscopy findings were undefined polyps or missing, 16,195 and 7,444 participants were entered into analyses. Detailed information on the participant selection is presented in Supplementary Figure 1a, b (see Supplementary Digital Content 1, http://links.lww.com/AJG/B264).

Table 1 summarizes the characteristics of the participants in KolosSal and BliTz. Advanced neoplasms were detected in 1,917 (11.8%) and 848 (11.4%) subjects in both studies, respectively. Overall, the distributions of participant characteristics were similar in KolosSal and BliTz. Mean ages of participants were 62.3 years (SD ± 5.8 years) and 61.6 years (SD ± 5.9 years), respectively. The participants in our cohorts were slightly older than those used for the development of the original models. Slightly more than half of total participants in each cohort were female (50.9% and 50.6%), and the sex proportions of participants in most original models were similar to those in our cohorts. Approximately two-thirds of all participants had a body mass index ≥25 kg/m^2, and approximately half of the participants were either current or former smokers; approximately 14% of participants reported an FH of CRC in a first-degree relative in both cohorts.

Table 2 provides an overview of the risk factors that were included in the risk scores. The most commonly included factors were age, sex, history of CRC in first-degree relative, body mass index, smoking, alcohol intake, and the use of nonsteroidal anti-inflammatory drugs and aspirin. Less commonly used risk factors included factors such as red meat consumption, physical activities, or height. The commonly used risk factors could mostly be included exactly as specified in the original scores in our analyses (indicated by symbol "×" in Table 2). The less often used risk factors had to be entered in modified version or excluded from our comparative analyses (indicated by symbols "●" and "○", respectively).

Summaries of identified risk scores values for both participants without and with advanced neoplasms in KolosSal and BliTz are presented in Table 3. The median score value in the group of participants with advanced neoplasm was consistently larger than or equal to that in the group of participants without advanced neoplasm in both cohorts. Median scores and interquartile ranges for both groups were very similar in KolosSal and BliTz.

The absolute risks of presence of at least 1 advanced neoplasm by score quintiles of each risk model are shown in Supplementary Table 2 (see Supplementary Digital Content 1, http://links.lww.com/AJG/B264 ([KoloSal] see Supplementary Digital Content 1, http://links.lww.com/AJG/B264) and Supplementary Table 3 ([BliTz] see Supplementary Digital Content 1, http://links.lww.com/AJG/B264). An increasing trend of absolute risk from the lowest (Q1) to the highest quintile/quartile (Q5/Q4) was observed within almost all risk scores in both cohorts (Supplementary Figures 2 and 3, see Supplementary Digital Content 1, http://links.lww.com/AJG/B264), indicating that the risk of advanced neoplasms was higher for people who had a higher risk score compared with those who had a lower risk score. With few exceptions, absolute risks were mostly between 5% and 10% among participants in Q1 and between 15% and 20% among participants in Q5.

The relative risks of presence of at least 1 advanced neoplasm by score quintiles and the areas under the curve and NRI for the

Table 2. Overview of risk factors used for generation of risk scores[a]

	More commonly included risk factors								Less commonly included risk factors		
Publication	Age	Sex	FH in FDR	BMI	Smoking	Alcohol	NSAIDs	Aspirin	×	●	○
Sekiguchi 2018 (12)	×	×	×	×	×						
Hong 2017 (13)	×	×			×	●		×			
Murchie 2017 (14)	×	×		×	×						Race
Sung 2017 (15)	×	×	×	×	×						
Yang 2017 (16)	×	×	×	×	×						
Cao (female) 2015 (17)	×	×	×	×	×	×	×	×		Red meat	Calcium, oral contraceptive use
Cao (male) 2015 (17)	×	×	×	×	×		×	×		Physical activities	Sitting watching TV/VCR, a joint term of multivitamin and alcohol
Imperiale 2015 (18)	×	×	×		×					Waist circumference	
Kim 2015 (19)	×	×	×	×	×						
Schroy III 2015 (20)	×	●			×	×			Height		Race
Kaminski 2014 (21)	×	×	×	×	×						
Tao 2014 (9)	×	×	×		×	×	×	×	Previous colonoscopy and previous polyps	Red meat	
Wong 2014 (22)	×	×	×	×	×	×			Hypertension		
Cai 2012 (23)	×	×			×				Diabetes	Vegetables and white meat	Pickled food and fried food
Yeoh 2011 (24)	×	×	×		×						
Lin 2006 (25)	×	×	×								FH in SDR
Betés 2003 (26)	×	×		×							

× = identical variable as in the original study was used, ● = adequate replacement variable of the original study was used, ○ = variable could not be replaced and was removed from the models.
BMI, body mass index; FDR, first-degree relative; FH, family history; FIT, fecal immunochemical test; NSAIDs, nonsteroidal anti-inflammatory drugs excluding aspirin; SDR, second-degree relative.
[a]Details on these factors and algorithms applied to obtain risk scores are available in Supplementary Table 1 (see Supplementary Digital Content 1, http://links.lww.com/AJG/B264).

different scores are presented in Table 4 (KolosSal) and Table 5 (BliTz). Similar increasing trends regarding the relative risks from Q2 to Q5/Q4 were seen in both studies (Figure 1 and Figure 2). With very few exceptions, relative risks for Q5 compared with Q1 were generally between 2.0 and 4.0. In KolosSal, the AUCs generated by using quintiles/quartiles of the score (Figure 3) and by using the continuous score both ranged between 0.58 and 0.65. In BliTz, the AUCs generated by using quintiles/quartiles of score ranged from 0.57 to 0.61 (Figure 4), and almost the same AUCs were obtained using continuous score (0.57–0.62). Comparing diagnostic performance of the same risk scores in both screening cohorts yielded almost identical results.

The NRI values between any 2 risk scores in KolosSal and BliTz are demonstrated in Supplementary Tables 4 and 5 (see Supplementary Digital Content 1, http://links.lww.com/AJG/B264). For easier reading, the models were ordered according to the AUC in KolosSal in both tables, and all reported NRIs refer to comparison of scores with higher AUC with scores with lower AUC in KolosSal. With very few exceptions, NRIs were positive, indicating better classification by scores with higher AUC. Although most NRIs were below 0.2, even modest improvements in classification were often statistically significant.

DISCUSSION

This study evaluated and compared the predictive performance of 17 previously published risk scores with respect to detection of advanced neoplasms at screening colonoscopy in 2 large screening studies. The AUCs of all risk scores ranged from 0.57 to 0.65 in both studies, indicating variable, but overall modest performance in predicting presence of at least 1 advanced neoplasm. Analyses of the NRI might be helpful in choosing between different scores.

Our estimates of predictive performance for detecting advanced neoplasms of the different models, ranging from 0.57 to 0.65, are somewhat lower than the estimates reported in the original studies. For example, AUCs of studies included in our

Table 3. Summary of identified risk scores values in the KolosSal and BliTz study

	KolosSal							BliTz						
		No advanced neoplasm			Advanced neoplasm				No advanced neoplasm			Advanced neoplasm		
Risk score	N (total)	N	Median	IQR	N	Median	IQR	N (total)	N	Median	IQR	N	Median	IQR
Sekiguchi 2018 (12)	14,924	13,193	3.5	3.5–4.5	1,731	4.5	3.5–5.0	7,034	6,240	3.5	3.0–4.5	794	4.5	3.5–4.5
Hong 2017 (13)	13,663	12,047	5.1	4.7–5.5	1,616	5.3	4.9–5.8	6,797	6,017	5.1	4.7–5.5	780	5.3	4.9–5.7
Murchie 2017 (14)	15,578	13,755	4.1	3.8–4.4	1,823	4.3	4.0–4.6	7,295	6,458	4.1	3.8–4.4	837	4.3	3.9–4.5
Sung 2017 (15)	15,363	13,576	3.0	3.0–4.0	1,787	4.0	3.0–4.0	7,210	6,391	3.0	3.0–4.0	819	4.0	3.0–4.0
Yang 2017 (16)	15,578	13,755	9.0	7.0–11.0	1,823	10.0	8.0–11.0	7,160	6,347	9.0	7.0–11.0	813	10.0	8.0–11.0
Cao (female) 2015 (17) [a]	7,044	6,475	0.2	0.0–0.5	569	0.3	0.1–0.6	3,359	3,078	0.2	0.0–0.4	281	0.2	0.1–0.4
Cao (male) 2015 (17) [a]	7,153	6,070	1.7	1.3–2.0	1,083	1.8	1.5–2.1	3,449	2,963	1.6	1.2–1.9	486	1.7	1.4–2.0
Imperiale 2015 (18)	14,924	13,193	4.0	3.0–6.0	1,731	5.0	4.0–7.0	7,034	6,240	4.0	3.0–6.0	794	5.0	4.0–6.0
Kim 2015 (19)	15,363	13,576	4.0	3.0–5.0	1,787	5.0	4.0–5.0	7,210	6,391	4.0	3.0–5.0	819	4.0	4.0–5.0
Schroy III 2015 (20)	13,962	12,326	3.0	2.0–4.0	1,636	4.0	2.0–5.0	6,705	5,944	3.0	2.0–4.0	761	4.0	2.0–5.0
Kaminski 2014 (21)	14,900	13,173	4.0	3.0–5.0	1,727	5.0	4.0–6.0	7,028	6,234	4.0	3.0–5.0	794	5.0	4.0–5.0
Tao 2014 (9) [b]	4,171	3,615	433.8	366.0–492.1	556	485.3	414.1–533.6	6,510	5,770	408.1	350.0–482.6	740	461.4	387.2–513.1
Wong 2014 (22)	13,949	12,316	0.9	0.7–1.4	1,633	1.3	0.8–1.5	6,606	5,850	0.9	0.4–1.4	756	1.3	0.8–1.5
Cai 2012 (23)	14,802	13,092	5.0	4.0–6.0	1,710	5.0	5.0–7.0	7,027	6,225	5.0	4.0–6.0	802	5.0	4.0–6.0
Yeoh 2011 (24)	15,615	13,797	3.0	3.0–4.0	1,818	4.0	3.0–4.0	7,309	6,482	3.0	3.0–4.0	827	4.0	3.0–4.0
Lin 2006 (25)	15,744	13,897	3.0	2.0–4.0	1,847	3.0	2.0–4.0	7,345	6,515	2.0	2.0–3.0	830	3.0	2.0–4.0
Betés 2003 (26)	15,706	13,855	3.0	2.0–4.0	1,851	4.0	3.0–5.0	7,341	6,502	3.0	2.0–4.0	839	4.0	3.0–5.0

IQR, interquartile range.

[a]The outcome of the original model was high-risk colorectal adenoma (advanced adenoma or ≥3 adenomas). To be comparable with other models, the outcome was changed to advanced neoplasm (advanced adenoma or CRC) in our analyses.

[b]The score by Tao et al. was originally developed in participants of KolosSal recruited up to June 2009, therefore, only participants recruited from June 2009 on were included in the validation for this score in KolosSal.

Table 4. Relative risk of presence of at least 1 advanced neoplasm by quintiles and area under the curve of risk scores in KolosSal

	Relative risk (%, 95% CI), Q1 as the reference					AUC (95% CI)	
Risk score	Q1	Q2	Q3	Q4	Q5	Quintiles/Quartiles of score	Continuous score
Sekiguchi 2018 (12)	1	1.55 (1.32–1.82)	1.83 (1.48–2.27)	2.36 (2.02–2.76)	2.96 (2.53–3.47)	0.61 (0.60–0.63)	0.62 (0.60–0.63)
Hong 2017 (13)	1	1.43 (1.18–1.72)	1.75 (1.46–2.09)	2.35 (1.98–2.79)	2.97 (2.52–3.51)	0.62 (0.60–0.63)	0.62 (0.61–0.64)
Murchie 2017 (14)	1	1.18 (0.99–1.41)	1.75 (1.49–2.05)	1.99 (1.70–2.32)	2.56 (2.21–2.98)	0.61 (0.59–0.62)	0.61 (0.60–0.63)
Sung 2017 (15) [a]	1	1.75 (1.49–2.04)	2.22 (1.91–2.59)	3.06 (2.61–3.60)	—	0.60 (0.59–0.62)	0.60 (0.59–0.62)
Yang 2017 (16)	1	1.75 (1.49–2.06)	1.63 (1.36–1.96)	2.47 (2.11–2.88)	2.73 (2.31–3.23)	0.60 (0.58–0.61)	0.60 (0.59–0.61)
Cao (female) 2015 (17) [b]	1	1.53 (1.13–2.06)	1.70 (1.27–2.28)	1.97 (1.49–2.62)	2.25 (1.71–2.97)	0.58 (0.55–0.60)	0.58 (0.56–0.61)
Cao (male) 2015 (17) [b]	1	1.22 (1.00–1.49)	1.25 (1.02–1.52)	1.62 (1.34–1.95)	1.92 (1.60–2.30)	0.58 (0.56–0.59)	0.58 (0.56–0.60)
Imperiale 2015 (18)	1	1.81 (1.49–2.20)	2.35 (1.92–2.87)	2.50 (2.03–3.09)	3.26 (2.69–3.96)	0.60 (0.59–0.61)	0.61 (0.59–0.62)
Kim 2015 (19)	1	1.20 (0.95–1.52)	1.85 (1.47–2.31)	2.33 (1.86–2.91)	2.82 (2.23–3.56)	0.60 (0.58–0.61)	0.60 (0.58–0.61)
Schroy III 2015 (20)	1	1.29 (1.07–1.56)	1.72 (1.43–2.06)	2.24 (1.89–2.66)	2.71 (2.29–3.20)	0.61 (0.60–0.62)	0.62 (0.60–0.63)
Kaminski 2014 (21)	1	1.55 (1.22–1.96)	1.97 (1.56–2.48)	2.76 (2.21–3.44)	3.47 (2.77–4.33)	0.61 (0.60–0.63)	0.61 (0.60–0.63)
Tao 2014 (9) [c]	1	1.47 (1.05–2.05)	1.74 (1.26–2.41)	2.58 (1.91–3.49)	3.75 (2.82–5.00)	0.65 (0.62–0.67)	0.65 (0.63–0.67)
Wong 2014 (22)	1	1.21 (1.01–1.44)	1.24 (1.06–1.45)	1.88 (1.62–2.18)	1.86 (1.60–2.15)	0.58 (0.56–0.59)	0.58 (0.57–0.60)
Cai 2012 (23)	1	1.57 (1.26–1.95)	2.19 (1.78–2.70)	2.62 (2.12–3.23)	3.37 (2.74–4.13)	0.61 (0.60–0.62)	0.61 (0.60–0.63)
Yeoh 2011 (24)	1	1.69 (1.45–1.96)	2.20 (1.90–2.55)	2.33 (1.95–2.78)	2.86 (2.34–3.50)	0.59 (0.58–0.60)	0.59 (0.58–0.60)
Lin 2006 (25)	1	1.72 (1.46–2.03)	1.78 (1.51–2.09)	2.56 (2.19–3.00)	2.56 (2.11–3.11)	0.59 (0.58–0.60)	0.59 (0.57–0.60)
Betés 2003 (26)	1	1.08 (0.87–1.34)	1.43 (1.17–1.76)	1.98 (1.63–2.40)	2.55 (2.10–3.09)	0.61 (0.59–0.62)	0.61 (0.59–0.62)

AUC, area under the curve, CI, confidence interval, Q1–Q5, quintiles/quartiles of risk scores.
[a]Quintiles could not be generated due to skewed distribution and integer-based nature of this risk score, so the full participants were classified into 4 risk groups.
[b]The outcome of the original model was high-risk colorectal adenoma (advanced adenoma or ≥ 3 adenomas). To be comparable with other models, the outcome was changed to advanced neoplasm (advanced adenoma or CRC) in our analyses.
[c]The score by Tao et al. was originally developed in participants of KolosSal recruited up to June 2009; therefore, only participants recruited from June 2009 on were included in the validation for this score in KolosSal.

previous review (8) ranged from 0.62 to 0.74. Several factors may contribute to this "performance gap." First, none of the original studies had conducted an external validation in a different study population, and differences in prevalence and extent of factors predisposing to advanced neoplasms may account for some of the observed drop of performance in external validation. Second, some of the risk factors in some models were either not available, or ascertained in a slightly different manner, and could thus not be considered exactly as suggested in our validation. Third, age may have made a larger contribution to AUCs in some original studies due to inclusion of a broader age range (and inclusion of younger age groups in particular). Our study was only conducted among the target population for CRC screening (age range: 50–74 years), which limits the contribution of age to risk stratification.

Although the AUCs for advanced neoplasms observed in this study may appear modest on first view, they are comparable or even higher than the AUCs for CRC in either "environmental" (risk factor) or polygenic risk scores (32) in a recent study. Polygenic risk scores, alone or in combination with environmental scores, are increasingly propagated for risk stratification in cancer screening. Recently, it has been shown that a polygenic risk score for CRC also predicts presence of advanced neoplasms among participants of screening colonoscopy similarly well (33), and that polygenic risk scores provide risk prediction far beyond risk prediction by FH of CRC (34). It is to be expected that risk prediction by polygenic risk scores will further improve as more genetic risk variants are discovered. These findings suggest that the combination of risk scores based on risk factor information with polygenic risk scores may have a large potential for enhanced risk stratification in the future.

FITs are recommended for CRC screening by national and international expert panels, and FIT-based CRC screening is offered in a rapidly increasing number of countries (3,35–38). Given the superiority of FIT in predicting presence of advanced neoplasia, the questions arises which role if any risk scores could have even in settings where FIT-based screening is an established option. Risk prediction models may be used to tailor screening based on the risk of carrying advanced neoplasia. Possible uses to be considered might be the application of risk scores for initial risk stratification and definition of starting ages of screening or for referring to either FIT or colonoscopy as primary screening test or no screening at all in settings where capacities for those tests are limited. For example, participants with a higher risk score might preferably directly undergo colonoscopy, whereas those with a lower risk score might use FIT in the first place and undergo colonoscopy only in case of a positive FIT. Risk-adapted screening strategies might improve effectiveness and acceptance of currently used screening modalities compared with untargeted "one fits all" approaches, as they reduce the burden of invasive procedures for those at lower risk while focusing on those with higher risk (8).

Table 5. Relative risk of presence of at least 1 advanced neoplasm by quintiles and area under the curve of risk scores in BliTz

	Relative risk (%, 95% CI), Q1 as the reference					AUC (95% CI)	
Risk score	Q1	Q2	Q3	Q4	Q5	Quintiles/Quartiles of score	Continuous score
Sekiguchi 2018 (12)	1	1.28 (0.82–2.00)	1.68 (1.33–2.12)	2.11 (1.68–2.66)	2.76 (2.16–3.54)	0.59 (0.57–0.61)	0.60 (0.58–0.62)
Hong 2017 (13)	1	1.54 (1.19–2.00)	1.65 (1.27–2.13)	2.25 (1.76–2.87)	2.74 (2.16–3.47)	0.60 (0.58–0.62)	0.61 (0.59–0.63)
Murchie 2017 (14)	1	1.41 (1.09–1.81)	1.75 (1.38–2.22)	2.13 (1.69–2.68)	2.44 (1.94–3.06)	0.59 (0.57–0.61)	0.60 (0.58–0.62)
Sung 2017 (15) [a]	1	1.39 (1.13–1.72)	1.95 (1.59–2.38)	2.45 (1.96–3.06)	—	0.59 (0.57–0.61)	0.59 (0.57–0.61)
Yang 2017 (16)	1	1.53 (1.21–1.94)	1.78 (1.39–2.28)	1.95 (1.55–2.46)	2.44 (1.92–3.10)	0.58 (0.56–0.60)	0.58 (0.56–0.60)
Cao (female) 2015 (17) [b]	1	1.07 (0.71–1.62)	1.32 (0.89–1.94)	1.77 (1.23–2.55)	1.84 (1.28–2.64)	0.57 (0.54–0.61)	0.58 (0.54–0.61)
Cao (male) 2015 (17) [b]	1	1.08 (0.79–1.46)	1.56 (1.18–2.06)	1.37 (1.02–1.83)	1.89 (1.44–2.47)	0.57 (0.54–0.60)	0.58 (0.55–0.60)
Imperiale 2015 (18)	1	1.83 (1.37–2.45)	1.53 (1.14–2.05)	2.38 (1.84–3.09)	3.14 (2.40–4.10)	0.60 (0.58–0.62)	0.61 (0.58–0.63)
Kim 2015 (19)	1	1.56 (1.09–2.25)	2.14 (1.51–3.04)	2.50 (1.76–3.56)	3.41 (2.37–4.92)	0.59 (0.57–0.61)	0.59 (0.57–0.61)
Schroy III 2015 (20)	1	1.16 (0.90–1.51)	1.61 (1.26–2.05)	1.80 (1.43–2.28)	2.29 (1.82–2.89)	0.59 (0.57–0.61)	0.59 (0.57–0.61)
Kaminski 2014 (21)	1	1.83 (1.31–2.55)	2.25 (1.62–3.11)	2.87 (2.09–3.94)	3.49 (2.53–4.83)	0.60 (0.58–0.62)	0.60 (0.58–0.62)
Tao 2014 (9)	1	1.75 (1.31–2.34)	2.28 (1.73–3.00)	2.66 (2.03–3.48)	3.36 (2.58–4.36)	0.61 (0.59–0.64)	0.62 (0.60–0.64)
Wong 2014 (22)	1	1.11 (0.86–1.44)	1.28 (1.02–1.59)	1.79 (1.44–2.21)	1.95 (1.59–2.40)	0.58 (0.56–0.60)	0.59 (0.57–0.61)
Cai 2012 (23)	1	1.07 (0.81–1.40)	1.45 (1.23–1.88)	2.04 (1.57–2.63)	2.24 (1.73–2.89)	0.60 (0.58–0.62)	0.60 (0.58–0.62)
Yeoh 2011 (24)	1	1.51 (1.21–1.88)	2.09 (1.69–2.59)	2.30 (1.77–2.98)	2.66 (1.97–3.60)	0.59 (0.57–0.61)	0.59 (0.57–0.61)
Lin 2006 (25) [a]	1	1.50 (1.22–1.86)	1.50 (1.21–1.86)	2.03 (1.65–2.49)	—	0.57 (0.55–0.59)	0.57 (0.55–0.59)
Betés 2003 (26)	1	1.12 (0.84–1.48)	1.25 (0.95–1.64)	1.67 (1.29–2.16)	2.11 (1.64–2.72)	0.58 (0.56–0.60)	0.59 (0.57–0.61)

AUC, area under the receiver-operating characteristic curve; CI, confidence interval; FIT, fecal immunochemical test; Q1–Q5, quintiles/quartiles of risk scores.
[a]Quintiles could not be generated due to skewed distribution and integer-based nature of this risk score, so the full participants were classified into 4 risk groups.
[b]The outcome of the original model was high-risk colorectal adenoma (advanced adenoma or ≥3 adenomas). To be comparable with other models, the outcome was changed to advanced neoplasm (advanced adenoma or CRC) in our analyses.

To the best of our knowledge, this is the first study that compared the performance of various risk models in predicting the risk of advanced neoplasms in 2 independent populations simultaneously. Both samples were taken from large-scale studies with a total of 23,639 participants. Colonoscopy was conducted for all subjects in these 2 studies and served as the gold standard, allowing for reliable detection of advanced adenomas, which is (next to detection of CRC) a key target for CRC screening.

However, there are some limitations that need to be addressed. First, both cohorts were potentially subject to inaccuracies of self-reported risk factors such as under-reporting or imprecise reporting of lifestyle factors (e.g., smoking and alcohol intake) or missing reporting of risk factors (e.g., the information "alcohol intake" was missing among 1,198 [7.4%] participants in KolosSal). With more accurate and more complete reporting of risk factors, better prediction performance might have been achieved for the validations of the models. Second, as some variables in the original models were not available or defined differently from variables in our cohorts, we made slight adaptions where appropriate, i.e., replaced these variables with adequate surrogates wherever possible or removed them if necessary. Although these modifications might have rendered the revised models not entirely comparable with the original models, the modifications most likely had limited influence on the overall performance of

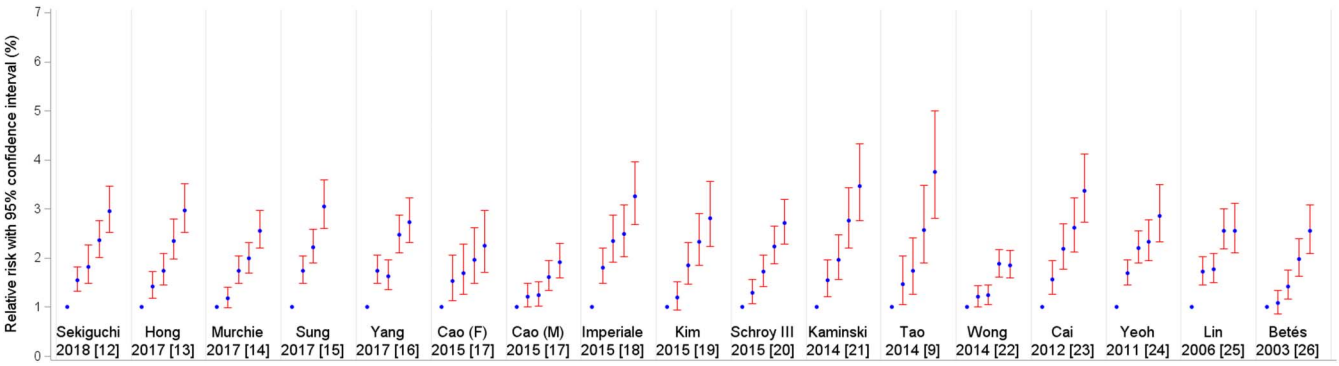

Figure 1. Relative risk of presence at least 1 advanced neoplasm by quintiles/quartiles of risk scores in KolosSal. F = female, M = male.

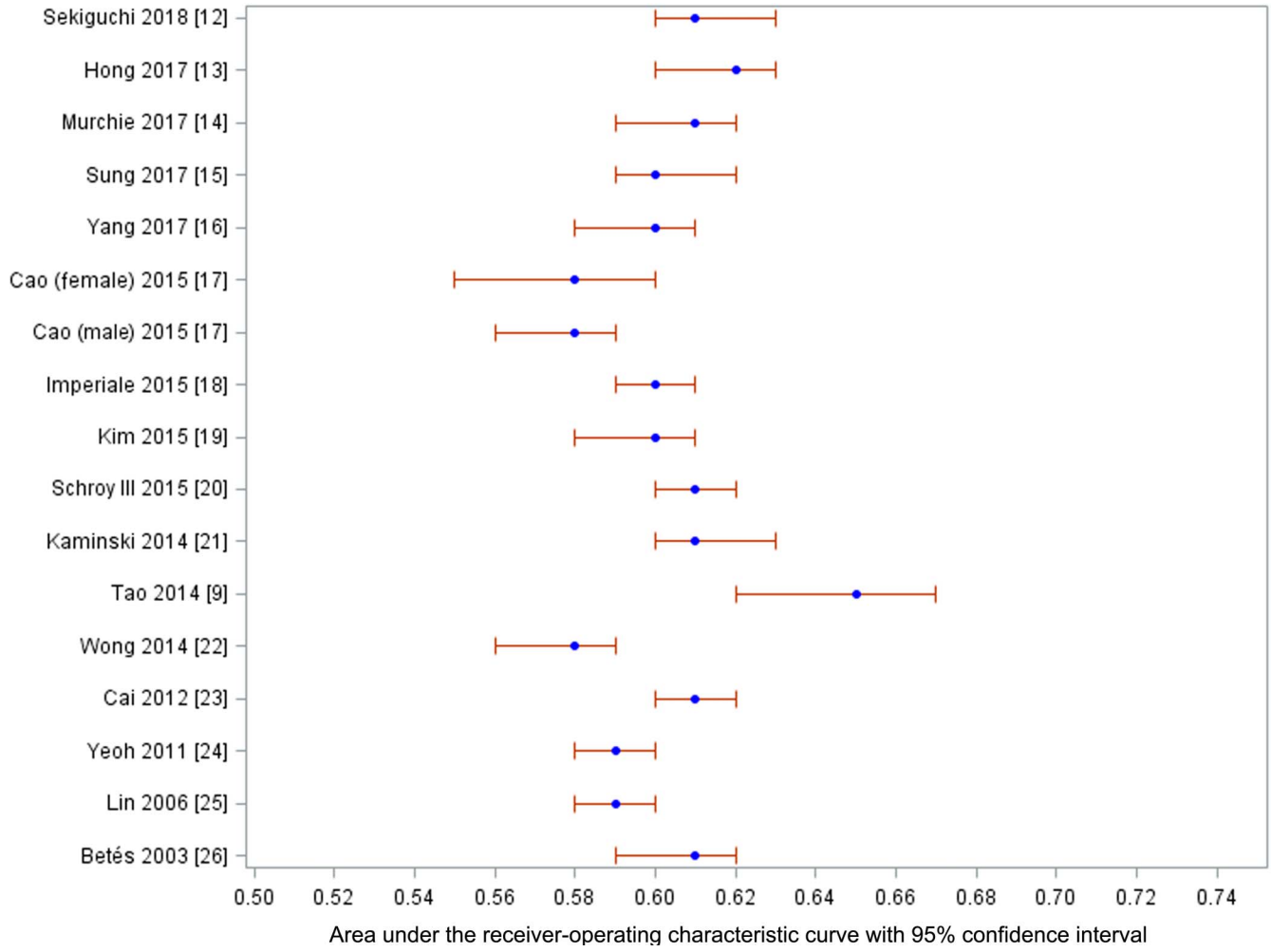

Figure 2. Area under the receiver-operating characteristic curve for detection of at least 1 advanced neoplasm of risk scores in KolosSal.

these models. Third, we were unable to validate 2 risk scores by Park et al. (28) and Chen et al. (29) because the laboratory results (serology of *Helicobacter pylori*, high triglyceride level, and low high-density lipoprotein level) used in the score by Park et al. (28), and the variables "egg intake" and "defecation frequency" used in the score by Chen et al. (29) were not collected in our cohorts. Both scores have shown good performance (AUC > 0.70) in the original populations. Fourth, most AUCs were lower compared with the original AUCs, indicating that models may lose discriminatory power in validation studies when applied in other populations. Different age ranges of the populations, variations in risk factors, various methods of data collection, different measurements of laboratory indicators, and changing prevalences of CRC and advanced adenomas might contribute to the variations of the performance of the risk scores. Fifth, although AUCs and NRIs are widely used metrics for evaluating risk discrimination,

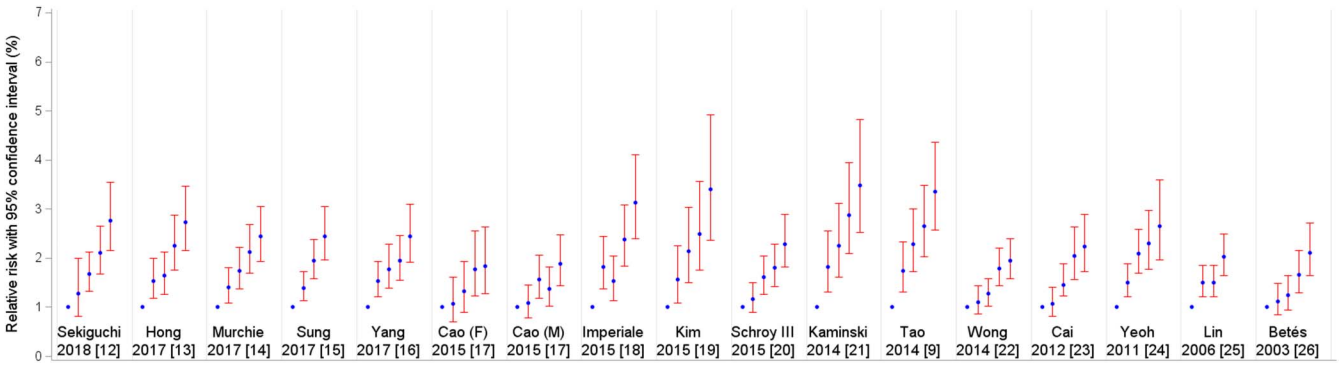

Figure 3. Relative risk of presence at least 1 advanced neoplasm by quintiles/quartiles of risk scores in BliTz. F = female, M = male.

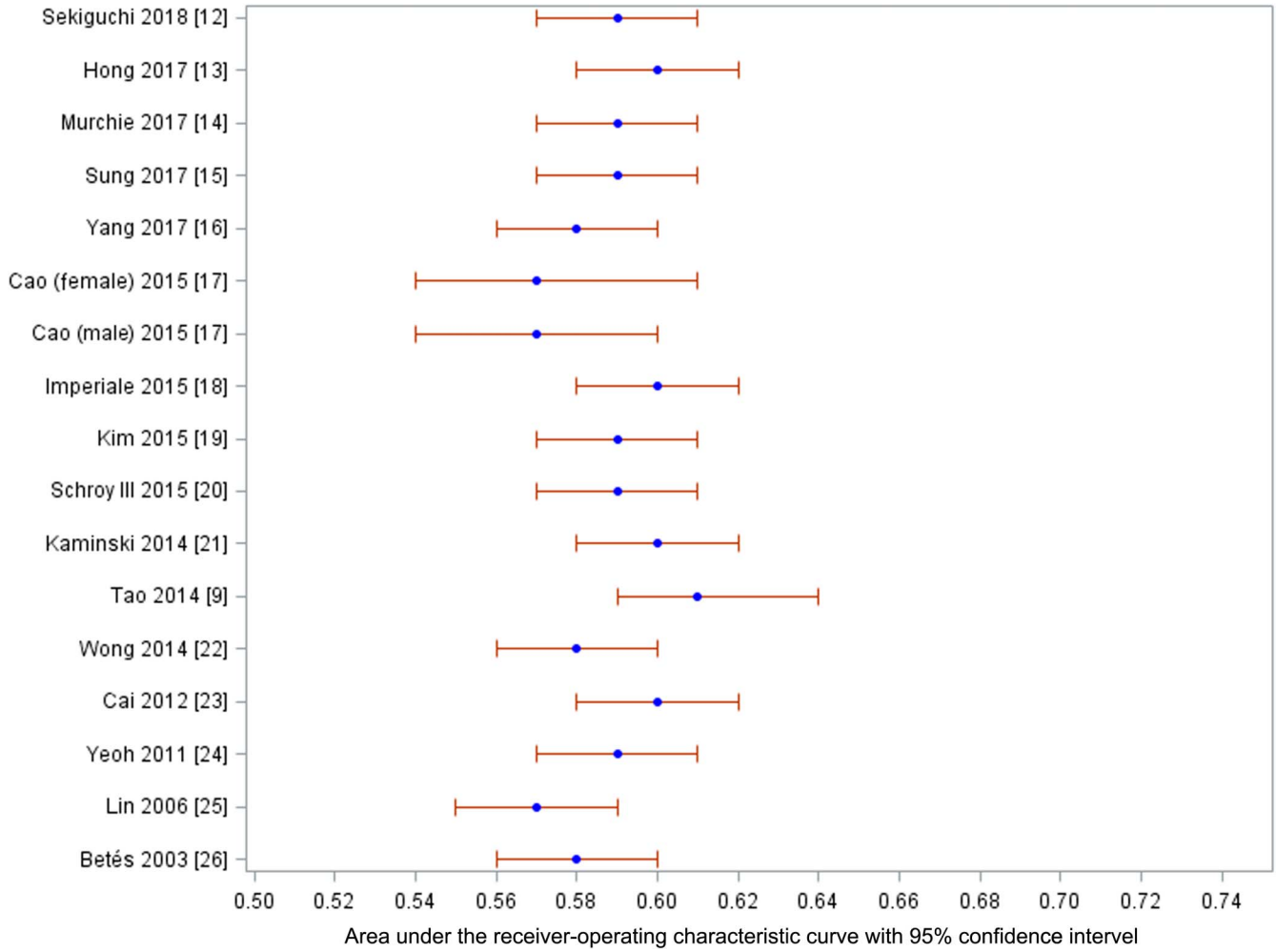

Figure 4. Area under the curve for detection of at least 1 advanced neoplasm of risk scores in BliTz.

they are affected by additional factors, such as the variation of specific risk factors in the specific populations in which they are used, and such variation, along with other availability, and ease of collection of risk factor information need to be taken into account in the choice of risk scores in practice. In addition, as our study populations consist of white participants from Germany, the results presented in this article might not be applicable and generalizable to countries with differing ethnic groups.

In conclusion, our study demonstrates modest predictive performance of a large number of risk factor based scores for presence of advanced neoplasms in 2 large studies of participants of screening colonoscopy, with some variation in performance between models. Although overall predictive performance of the models was found to be modest and generally somewhat lower than that reported in original publications, it is comparable or even slightly higher than that reported in a recent large scale genome-wide association study which investigated both environmental and polygenic risk scores for predicting presence of CRC. In countries with limited resources, risk scores may serve as the first step for risk stratification in CRC screening. Combination of risk factors with emerging and gradually improving polygenic risk scores might be a particular promising tool for risk stratification in the future. Given the similarity in predictive performance of most environmental scores, additional features, such as brevity and ease of implementation in routine practice, or relevance of the included items might drive the selection of best suited environmental score for the specific setting or population under consideration.

ACKNOWLEDGEMENTS

The authors thank Xuechen Chen for her assistance in data analysis.

CONFLICTS OF INTEREST

Guarantor of the article: Hermann Brenner, MD, MPH.

Specific author contributions: Study concept and design: H.B.; analysis of data: L.P., Y.B., and K.W.; interpretation of data: L.P., Y.B., K.W., M.H., and H.B.; and drafting the manuscript: L.P., Y.B., K.W., and H.B. All authors provided comments, revised the draft, and approved the final version of the manuscript.

Financial support: L.P. was partly supported by the China Scholarship Council (CSC). Parts of this work were funded by grants from the German Cancer Aid (Deutsche Krebshilfe, Reference Number: 111365), from the German Research Council (DFG, Grant Number: BR1704/16-1), and from the German Federal Ministry of Education and Research (BMBF, Grant Number: 01GL1712). The sponsors had no role in the study design and in the collection, analysis, and interpretation of data.

Potential competing interests: None.

Study Highlights

WHAT IS KNOWN

- ✓ Risk scores based on easy-to-collect factors such as age, sex, and family history might be an effective tool for risk stratification in colorectal cancer screening.
- ✓ The predictive performance of previously published risk scores derived in different populations varies considerably.

WHAT IS NEW HERE

- ✓ For the first time, multiple risk scores were evaluated in parallel in the same study populations.
- ✓ The performance of the evaluated risk models for predicting presence of advanced colorectal neoplasms was found to be modest and generally somewhat lower than that reported in the original publications.
- ✓ Differences in performance between scores, along with additional factors, such as availability of risk factor information, length, and ease of application of scores, may help in choosing the best suited score in specific settings.

REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68:394–424.
2. Brenner H, Altenhofen L, Stock C, et al. Natural history of colorectal adenomas: Birth cohort analysis among 3.6 million participants of screening colonoscopy. Cancer Epidemiol Biomarkers Prev 2013;22:1043–51.
3. Rex DK, Boland CR, Dominitz JA, et al. Colorectal cancer screening: Recommendations for physicians and patients from the U.S. Multi-society Task Force on colorectal cancer. Am J Gastroenterol 2017;112:1016–30.
4. Bibbins-Domingo K, Grossman DC, Curry SJ, et al. Screening for colorectal cancer: US Preventive Services Task Force Recommendation Statement. JAMA 2016;315:2564–75.
5. Brenner H, Stock C, Hoffmeister M. Effect of screening sigmoidoscopy and screening colonoscopy on colorectal cancer incidence and mortality: Systematic review and meta-analysis of randomised controlled trials and observational studies. BMJ 2014;348:g2467.
6. Inadomi JM, Vijan S, Janz NK, et al. Adherence to colorectal cancer screening: A randomized clinical trial of competing strategies. Arch Intern Med 2012;172:575–82.
7. Geiger TM, Ricciardi R. Screening options and recommendations for colorectal cancer. Clin Colon Rectal Surg 2009;22:209–17.
8. Peng L, Weigl K, Boakye D, et al. Risk scores for predicting advanced colorectal neoplasia in the average-risk population: A systematic review and meta-analysis. Am J Gastroenterol 2018;113:1788–800.
9. Tao S, Hoffmeister M, Brenner H. Development and validation of a scoring system to identify individuals at high risk for advanced colorectal neoplasms who should undergo colonoscopy screening. Clin Gastroenterol Hepatol 2014;12:478–85.
10. Brenner H, Tao S, Haug U. Low-dose Aspirin use and performance of immunochemical fecal occult blood tests. JAMA 2010;304:2513–20.
11. Brenner H, Haug U, Arndt V, et al. Low risk of colorectal cancer and advanced adenomas more than 10 years after negative colonoscopy. Gastroenterology 2010;138:870–6.
12. Sekiguchi M, Kakugawa Y, Matsumoto M, et al. A scoring model for predicting advanced colorectal neoplasia in a screened population of asymptomatic Japanese individuals. J Gastroenterol 2018;138:870–6.
13. Hong SN, Son HJ, Choi SK, et al. A prediction model for advanced colorectal neoplasia in an asymptomatic screening population. PLoS One 2017;12:e0181040.
14. Murchie B, Tandon K, Hakim S, et al. A new scoring system to predict the risk for high-risk adenoma and comparison of existing risk calculators. J Clin Gastroenterol 2017;51:345–51.
15. Sung JJY, Wong M, Lam TYT, et al. A modified colorectal screening score for prediction of advanced neoplasia: A prospective study of 5,744 subjects. J Gastroenterol Hepatol 2018;33:187–94.
16. Yang HJ, Choi S, Park SK, et al. Derivation and validation of a risk scoring model to predict advanced colorectal neoplasm in adults of all ages. J Gastroenterol Hepatol 2017;32:1328–35.
17. Cao Y, Rosner BA, Ma J, et al. Assessing individual risk for high-risk colorectal adenoma at first-time screening colonoscopy. Int J Cancer 2015;137:1719–28.
18. Imperiale TF, Monahan PO, Stump TE, et al. Derivation and validation of a scoring system to stratify risk for advanced colorectal neoplasia in asymptomatic adults a cross-sectional study. Ann Intern Med 2015;163:339–46.
19. Kim DH, Cha JM, Shin HP, et al. Development and validation of a risk stratification-based screening model for predicting colorectal advanced neoplasia in Korea. J Clin Gastroenterol 2015;49:41–9.
20. Schroy PC, Wong JB, O'Brien MJ, et al. A risk prediction index for advanced colorectal neoplasia at screening colonoscopy. Am J Gastroenterol 2015;110:1062–71.
21. Kaminski MF, Polkowski M, Kraszewska E, et al. A score to estimate the likelihood of detecting advanced colorectal neoplasia at colonoscopy. Gut 2014;63:1112–9.
22. Wong MC, Lam TY, Tsoi KK, et al. Predictors of advanced colorectal neoplasia for colorectal cancer screening. Am J Prev Med 2014;46:433–9.
23. Cai QC, Yu ED, Xiao Y, et al. Derivation and validation of a prediction rule for estimating advanced colorectal neoplasm risk in average-risk Chinese. Am J Epidemiol 2012;175:584–93.
24. Yeoh KG, Ho KY, Chiu HM, et al. The Asia-Pacific colorectal screening score: A validated tool that stratifies risk for colorectal advanced neoplasia in asymptomatic Asian subjects. Gut 2011;60:1236–41.
25. Lin OS, Kozarek RA, Schembre DB, et al. Risk stratification for colon neoplasia: Screening strategies using colonoscopy and computerized tomographic colonography. Gastroenterology 2006;131:1011–9.
26. Betes M, Munoz-Navas MA, Duque JM, et al. Use of colonoscopy as a primary screening test for colorectal cancer in average risk people. Am J Gastroenterol 2003;98:2648–54.
27. Jung YS, Park CH, Kim NH, et al. Impact of age on the risk of advanced colorectal neoplasia in a Young population: An analysis using the predicted probability model. Dig Dis Sci 2017;62:2518–25.
28. Park YM, Kim HS, Park JJ, et al. A simple scoring model for advanced colorectal neoplasm in asymptomatic subjects aged 40–49 years. BMC Gastroenterol 2017;17:7.
29. Chen G, Mao B, Pan Q, et al. Prediction rule for estimating advanced colorectal neoplasm risk in average-risk populations in southern Jiangsu Province. Chin J Cancer Res 2014;26:4–11.
30. Aniwan S, Rerknimitr R, Kongkam P, et al. A combination of clinical risk stratification and fecal immunochemical test results to prioritize colonoscopy screening in asymptomatic participants. Gastrointest Endosc 2015;81:719–27.
31. Wong MC, Ching JY, Ng S, et al. The discriminatory capability of existing scores to predict advanced colorectal neoplasia: A prospective colonoscopy study of 5,899 screening participants. Sci Rep 2016;6:20080.
32. Jeon J, Du M, Schoen RE, et al. Determining risk of colorectal cancer and starting age of screening based on lifestyle, environmental, and genetic factors. Gastroenterology 2018;154:2152–64.e19.
33. Weigl K, Thomsen H, Balavarca Y, et al. Genetic risk score is associated with prevalence of advanced neoplasms in a colorectal cancer screening population. Gastroenterology 2018;155:88–98.e10.
34. Weigl K, Chang-Claude J, Knebel P, et al. Strongly enhanced colorectal cancer risk stratification by combining family history and genetic risk score. Clin Epidemiol 2018;10:143–52.
35. Halloran SP, Launoy G, Zappa M. European guidelines for quality assurance in colorectal cancer screening and diagnosis: First Edition—Faecal occult blood testing. Endoscopy 2012;44(Suppl 3):SE65–87.
36. USPST Force, Bibbins-Domingo K, Grossman DC, et al. Screening for colorectal cancer: US preventive Services Task Force Recommendation Statement. JAMA 2016;315:2564–75.
37. Wolf AMD, Fontham ETH, Church TR, et al. Colorectal cancer screening for average-risk adults: 2018 guideline update from the American Cancer Society. CA Cancer J Clin 2018;68:250–81.
38. Schreuders EH, Ruco A, Rabeneck L, et al. Colorectal cancer screening: A global overview of existing programmes. Gut 2015;64:1637–49.