Received: 2 December 2022 | Revised: 14 April 2023 | Accepted: 25 May 2023

DOI: 10.1002/cac2.12448

CANCER COMMUNICATIONS Open Access

LETTER TO THE EDITOR

A single measurement of fecal hemoglobin concentration outperforms polygenic risk score in colorectal cancer risk assessment

Dear Editors,

Large-scale genome-wide association studies have identified an increasing number of single nucleotide polymorphisms (SNPs) that are associated with colorectal cancer (CRC) risk [1]. Polygenic risk scores (PRS) based on all established SNPs enable clinically relevant risk assessment that may help to develop novel risk-adapted prevention and screening strategies.

Most CRCs develop slowly from advanced adenomas (AAs). Biomarkers indicating the presence of such precursors may be promising candidates for CRC risk assessment. We compared a fecal immunochemical test (FIT) with PRS for predicting the presence of preclinical CRC or AA in participants undergoing screening colonoscopy in Germany.

The analyses were based on the BliTz study, an ongoing study on novel approaches to CRC screening conducted among screening colonoscopy participants [2]. We included participants recruited between November 2008 and January 2019. Stool samples were analyzed at a central laboratory with a commercial FIT (see Supplementary Methods for details) [3].

Genotyping was performed in all participants with advanced neoplasms (advanced neoplasms [ANs], CRC or AA) and a random sample of age- and sex-matched participants without AN (Supplementary Methods). For PRS, we considered 140 common risk variants that were associated with higher CRC risk in the world's largest CRC genome-wide association studying populations of European descent [1]. A weighted PRS was constructed, accounting for the numbers of risk alleles and beta-coefficients with CRC risk (Supplementary Table S1).

Colonoscopy and histology reports were used to extract information on the colonoscopy findings. Most advanced colonoscopic findings were classified into CRC, AA, non-advanced adenoma (NAA), and other/no findings. We assessed the ability of FIT and PRS to predict the presence of AN using receiver operating characteristics (ROC) curves. Areas under the curves (AUCs) were compared by DeLong's test [4] (Supplementary Methods).

Of 5,368 participants with FIT and genotyping results, 2,343 were excluded because of age (< 50 or ≥ 80 years, $n = 190$), history of CRC or inflammatory bowel disease ($n = 43$), colonoscopy in the previous 5 years ($n = 359$), inadequate bowel preparation ($n = 535$), incomplete colonoscopy ($n = 39$), only NAA ($n = 1{,}010$) or undefined polyp(s) found ($n = 167$) (Supplementary Figure S1). In sensitivity analyses, participants with NAAs only, whose relevance with respect to CRC risk is less certain, were kept in the group of participants not carrying AAs. Among participants with AN ($n = 523$), the mean age was 63 years, 61% were men, 13% had a family history of CRC, and 22% had a previous colonoscopy. Of the 2,502 participants without neoplasm, the mean age was 61 years, 44% were males, 12% had a family history, and 34% had a previous colonoscopy.

FIT distinguished between participants with CRC and healthy participants with high accuracy (AUC = 0.982, $P < 0.001$) (Figure 1A). Despite a lower AUC for AA (0.703, Figure 1B), FIT outperformed PRS (AUCs for CRC and AA = 0.615 and 0.589, respectively, $P < 0.001$). Both FIT and PRS hardly discriminated between participants with NAA and those with no findings (AUCs 0.555 each, $P = 0.960$, Figure 1C). ROC curves for any AN vs. no neoplasms indicated the superiority of FIT over PRS (Figure 1D, AUC 0.721 vs. 0.591, $P < 0.001$). Combining both tests did not significantly improve AUCs for AN compared to FIT alone (0.742 vs. 0.721, $P = 0.258$). FIT was superior to PRS in younger (50-59 years) and older (60-79 years) participants (Figure 1E-F, difference in AUCs [ΔAUC] = 0.110 and 0.141, $P = 0.001$ and < 0.001, respectively), men and women

Abbreviations: AN, advanced neoplasia; AUC, area under the curve; FIT, fecal immunochemical test; PRS, polygenic risk score; ROC, receiver operating characteristics; CRC, colorectal cancer; SNP, single nucleotide polymorphism.

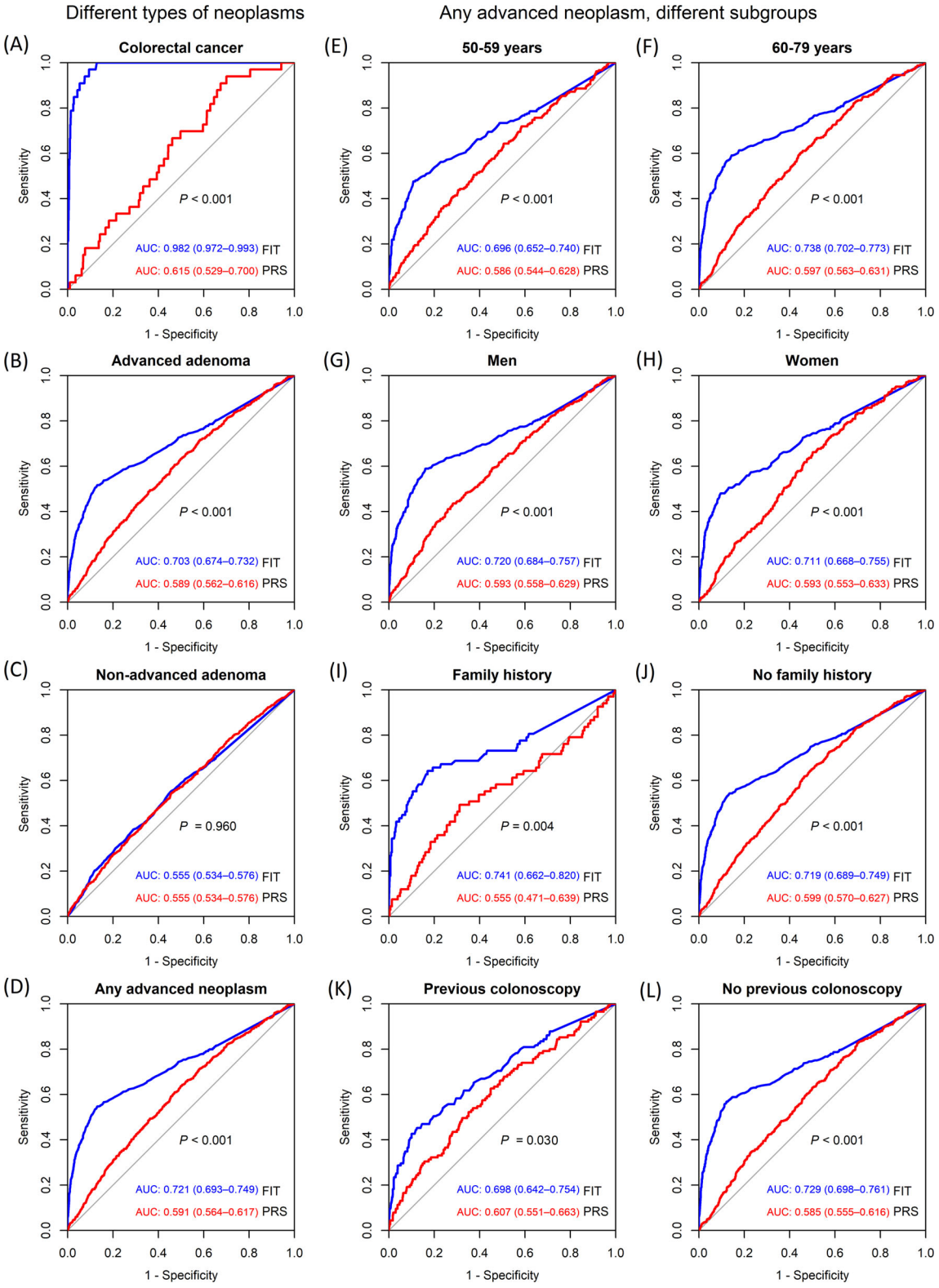

FIGURE 1 ROC curves, AUCs and *p* values for the difference in AUCs between fecal immunochemical test (FOB Gold) and weighted polygenic risk score for prediction of colorectal neoplasia, for colorectal cancer **(A)**, advanced adenoma **(B)**, non-advanced adenoma **(C)**, any advanced neoplasm **(D)**, and for any advanced neoplasia in subgroups stratified by age 50 - 59 years **(E)** and 60 - 79 years **(F)**, male **(G)**, female **(H)**, presence **(I)** or absence **(J)** of family history of CRC, and with **(K)** or without **(L)** a history of colonoscopy.
Abbreviations: AUC, area under the curve; FIT, fecal immunochemical test; PRS, polygenic risk score; ROC, receiver operating characteristics. *P* values for comparison of AUCs for detection of any advanced neoplasm were 0.258 (FIT+PRS vs. FIT), <0.001 (FIT vs. PRS), and <0.001 (FIT+PRS combined vs. PRS).

(Figure 1G-H, ΔAUC = 0.127 and 0.118, $P < 0.001$ and $P < 0.001$, respectively). Furthermore, FIT outperformed PRS in participants with and without a family history of CRC (Figure 1I-J, ΔAUC = 0.186 and 0.120, $P = 0.004$ and $P < 0.001$, respectively), and those with and without previous colonoscopy (Figure 1K-L, ΔAUC = 0.091 and 0.144, $P = 0.030$ and $P < 0.001$, respectively). Including participants with only NAAs in the group without AN did not change the results materially (AUC FIT: 0.710, AUC PRS: 0.574, $P < 0.001$) (data not shown).

In this study, FIT, a well-established strong indicator for estimating CRC risk, consistently outperformed PRS in predicting the presence of AN across both sexes, older and younger participants, those with and without a family history and those with and without previous colonoscopy.

FIT is widely employed as a dichotomous test for annual or biennial CRC screening. Clearly, positive FIT results need to be timely followed up by colonoscopy. However, as we demonstrated, in agreement with results for quantitative FITs with a similarly wide analytical range [2], FIT values below the cutoff (i.e., the vast majority) provide important risk information that is essentially discarded when using FIT as a dichotomous test. Such information could be useful (even more so than risk information from PRS) for deciding on future screening by either colonoscopy or FIT or for defining personalized screening intervals such as one year for "high-negative FIT results" (e.g., 10-15 μg/g) and ≥2 years for "low-negative FIT results" (e.g., 0-10 μg/g) [5]. For example, a quantitative "risk assessment FIT" could be offered every five years, with transition to annual or biennial FIT once a certain hemoglobin concentration, such as 10 μg/g, is exceeded. More refined approaches could be based on longitudinal FIT measurements from repeat screening rounds [6]. The shape of the ROC curves could help identify suitable cutoffs for defining "high-negative" and "low-negative" FIT in subgroups specified, e.g., by age or sex, using the Youden index as an indicator.

FIT possesses further advantages over PRS in risk assessment. It can be done in most standard laboratories and is substantially cheaper than PRS. In the US, FIT costs ~$24-40 [7, 8], whereas PRS was offered at ~$200 in 2019 [9]. Genetic data are more sensitive than FIT data and require consulting of screenees by qualified personnel for test interpretation. However, unlike FIT, array-based genotyping could enable simultaneous risk assessment for various diseases.

Comparing the one-time use of PRS and FIT has its merits. First, the discovery of new SNPs might warrant an updated PRS, and second, performing a single FIT with subsequent risk-adapted screening intervals might improve adherence rates to regular FIT screening.

The large sample size of our study enabled precise estimation of AUCs even within subgroups. This study was conducted in a screening setting, with a colonoscopy performed in all participants. However, participants aged <50 years were not included because CRC screening is not offered for them. Results might differ from other FITs and PRSs. Our study was restricted to a population of European ancestry. Lastly, the risk of developing CRC could not be directly determined. However, observed AUCs of PRS for CRC were comparable to those from large-scale cohort and case-control studies with CRC endpoints[1, 10].

In conclusion, a single FIT outperformed PRS in risk assessment for the presence of AN, a strong indicator for those with a substantial risk of developing CRC in the following years who would most likely benefit from screening. Applying a quantitative FIT, paying attention to hemoglobin concentrations below the commonly employed cutoffs, might be more informative, economical and feasible for CRC risk assessment than genetic testing with currently available PRS. Further research should evaluate refined strategies of risk assessment for CRC screening.

DECLARATIONS

AUTHOR CONTRIBUTIONS

Hermann Brenner and Tobias Niedermaier designed the study. Tobias Niedermaier conducted the statistical analyses and drafted the manuscript. Data acquisition: Tobias Niedermaier, Elizabeth Alwers, Hermann Brenner. All authors contributed to important intellectual content, critically reviewed the manuscript and approved the final draft submitted.

ACKNOWLEDGMENT

None.

CONFLICTS OF INTEREST STATEMENT

The authors declare no potential conflicts of interest.

MedRxiv preprint https://doi.org/10.1101/2022.07.22.22277924

FUNDING INFORMATION

This study was partly funded by grants from the German Research Council (DFG, grant No. BR1704/16-1), the Federal Ministry of Education and Research (BMBF, grant no. 01GL1712), and the German Cancer Aid (No. 70113330). The funding source had no role in any aspect pertaining to the study.

ETHICS APPROVAL

The study was conducted following the Declaration of Helsinki and Good Clinical Practice guidelines. The study was approved by the ethics committees of Heidelberg University (178/2005) and the state medical

chambers of Baden-Württemberg (M118-05-f), Saarland (217/13), Rhineland Palatinate (837.047.06(5145)) and Hesse (MC 254/2007). All participants provided written informed consent to participate in the study.

CONSENT FOR PUBLICATION

Not applicable.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request. However, it should also be noted that these data can also be obtained from the ECRIN data center upon reasonable request.

Tobias Niedermaier[1]
Elizabeth Alwers[1]
Xuechen Chen[1,2]
Thomas Heisser[1,2]
Michael Hoffmeister[1]
Hermann Brenner[1,3,4]

[1]*Division of Clinical Epidemiology and Aging Research, German Cancer Research Center (DKFZ), Heidelberg, Baden-Württemberg, Germany*
[2]*Medical Faculty Heidelberg, Heidelberg University, Heidelberg, Baden-Württemberg, Germany*
[3]*Division of Preventive Oncology, German Cancer Research Center (DKFZ), Heidelberg, Baden-Württemberg, Germany*
[4]*German Cancer Consortium (DKTK), German Cancer Research Center (DKFZ), Heidelberg, Baden-Württemberg, Germany*

Correspondence
Tobias Niedermaier, Division of Clinical Epidemiology and Aging Research (C070), German Cancer Research Center (DKFZ), Im Neuenheimer Feld 581, Heidelberg D-69120, Baden-Württemberg, Germany.
Email: t.niedermaier@dkfz-heidelberg.de

ORCID

Tobias Niedermaier https://orcid.org/0000-0001-7990-3437
Xuechen Chen https://orcid.org/0000-0003-2476-7110

REFERENCES

1. Thomas M, Sakoda LC, Hoffmeister M, Rosenthal EA, Lee JK, van Duijnhoven FJB, et al. Genome-wide Modeling of Polygenic Risk Score in Colorectal Cancer Risk. Am J Hum Genet. 2020;107(3):432–44.
2. Gies A, Cuk K, Schrotz-King P, Brenner H. Direct Comparison of Diagnostic Performance of 9 Quantitative Fecal Immunochemical Tests for Colorectal Cancer Screening. Gastroenterology. 2018;154(1):93–104.
3. Amitay EL, Cuk K, Niedermaier T, Weigl K, Brenner H. Factors associated with false-positive fecal immunochemical tests in a large German colorectal cancer screening study. Int J Cancer. 2018;144(10):2419–27.
4. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. Biometrics. 1988;44(3):837–45.
5. Chen LS, Yen AM, Chiu SY, Liao CS, Chen HH. Baseline faecal occult blood concentration as a predictor of incident colorectal neoplasia: longitudinal follow-up of a Taiwanese population-based colorectal cancer screening cohort. Lancet Oncol. 2011;12(6):551–8.
6. Buron A, Roman M, Auge JM, Macia F, Grau J, Sala M, et al. Changes in FIT values below the threshold of positivity and short-term risk of advanced colorectal neoplasia: Results from a population-based cancer screening program. Eur J Cancer. 2019;107:53–9.
7. Zhong GC, Sun WP, Wan L, Hu JJ, Hao FB. Efficacy and cost-effectiveness of fecal immunochemical test versus colonoscopy in colorectal cancer screening: a systematic review and meta-analysis. Gastrointest Endosc. 2020;91(3):684-97 e15.
8. Peterse EFP, Meester RGS, de Jonge L, Omidvari AH, Alarid-Escudero F, Knudsen AB, et al. Comparing the Cost-Effectiveness of Innovative Colorectal Cancer Screening Tests. J Natl Cancer Inst. 2021;113(2):154–61.
9. Naber SK, Kundu S, Kuntz KM, Dotson WD, Williams MS, Zauber AG, et al. Cost-Effectiveness of Risk-Stratified Colorectal Cancer Screening Based on Polygenic Risk: Current Status and Future Potential. JNCI Cancer Spectr. 2020;4(1):pkz086.
10. Saunders CL, Kilian B, Thompson DJ, McGeoch LJ, Griffin SJ, Antoniou AC, et al. External Validation of Risk Prediction Models Incorporating Common Genetic Variants for Incident Colorectal Cancer Using UK Biobank. Cancer Prev Res (Phila). 2020;13(6):509–20.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.