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LETTER TO THE EDITOR

Beyond familial risk: deriving risk-adapted starting ages of screening among people with a family history of colorectal cancer

Dear Editor,

Colorectal cancer (CRC) is the third most common cancer globally [1], even though a large proportion of those cancers would be preventable by screening. Among those with a family history (FH) of CRC, it is commonly recommended to start screening at younger ages, e.g., at age 40 or 10 years younger than the age at diagnosis of the youngest affected first-degree relative [2–5]. Even within the group of those with a FH, risk of CRC is not homogeneous and depends on factors such as the number of affected relatives and the age at which the relatives were diagnosed with CRC [6, 7], lifestyles, and genetic background profiles. However, these metrics except genetic factors may change over lifetime, which limits their use for defining starting ages of screening. The aim of this study was to evaluate whether a polygenic risk score (PRS), which combines information from CRC-related risk variants [8] and genetically determined sex (2 constant and established CRC risk factors), could effectively contribute to enhanced risk stratification. We also aimed to determine if it could assist in defining risk-adapted starting ages for CRC screening, even in individuals with a FH of CRC. The assessment was performed using the well-established metric of risk advancement periods (RAPs) [9], which measures the impact of an exposure on the relation of age to disease.

Data for the current analysis was obtained from white British participants of the UK Biobank cohort [10] with a self-reported FH of CRC (defined as mother, father, or siblings ever diagnosed with CRC) and without a prior CRC diagnosis (Supplementary Figure S1). Details regarding the study design and population are presented in Supplementary Materials and Methods. In brief, a PRS was calculated as the sum of the number of risk alleles in 139 of 140 single nucleotide polymorphisms (SNPs) that were found to be associated with CRC within individuals of European ancestry by a recent genome-wide association study [8] (Supplementary Table S1; rs377429877 was not measured in the UK Biobank and also not measured in the 1000G reference panel for further consideration of a potential proxy SNP. Therefore, it was not included in the current analysis). Sex was determined according to the relative intensity of markers on the Y and X chromosomes [10]. Incident CRC cases were identified through cancer registry data using the 10th revision of the International Classification of Diseases (ICD-10) codes C18-C20. Follow-up was censored at date of death or last date of follow-up (February 29, 2020 for England and Wales, and January 31, 2021 for Scotland), whichever occurred first.

Using Cox regression models, we estimated hazard ratios (HRs) of CRC risk according to age, sex, number of family members with CRC, and PRS. To define risk-adapted starting ages of screening among people with a FH of CRC, we derived the RAP metric which is applicable for diseases, such as CRC whose risk monotonically increases with age [9] and quantifies how many years earlier people with a specific risk factor reach the same risk as those without the risk factor. The derivation of RAPs and their 95% confidence intervals (CIs) have been described in detail elsewhere [9]. For the current analysis, RAPs were estimated as ratios of the regression coefficients for the respective risk factors (sex, PRS levels categorized according to the quintile distribution in the whole study population) and age. Then, using a defined starting age of men in the middle PRS quintile as reference, risk-adapted starting ages of CRC screening for women and men in different PRS quintiles were derived by adding or subtracting the respective RAPs.

Among 45,055 eligible participants (median follow-up time: 11 years; 792 incident CRC cases), 15.8%, 33.5%, and 50.8% were aged 40-49, 50-59, and 60-69 years,

List of abbreviations: CI, confidence interval; CRC, colorectal cancer; FH, family history; HR, hazard ratio; ICD-10, 10th revision of the International Classification of Diseases; PRS, polygenic risk score; RAP, risk advancement period; SNP, single nucleotide polymorphism.

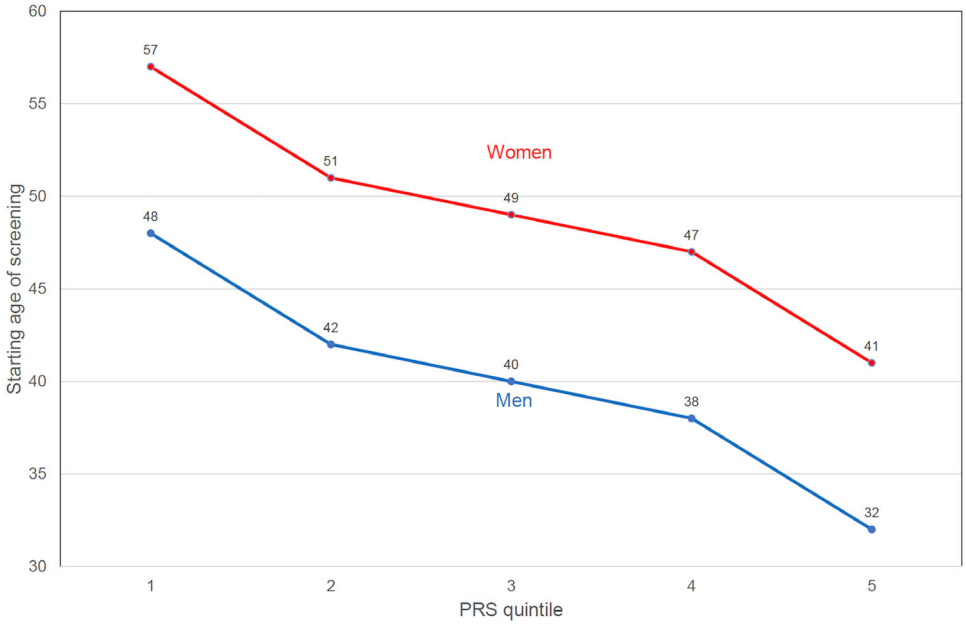

FIGURE 1 Calculation for risk-adapted starting age according to PRSs and sex as an alternative to the commonly recommended starting age of 40 for those with a FH.

Forty years was assigned as the starting age for screening for men in the middle PRS quintile. Then, risk-adapted starting ages of colorectal cancer screening for women and men in the different PRS quintiles were determined. Risk-adapted starting ages of screening would range from 32 years among men in the highest quintile of PRS to 57 years among women in the lowest quintile of PRS.

Abbreviation: PRS, polygenic risk score; FH, family history.

respectively, and 53.0% were female (Supplementary Table S2). Approximately 65% of incident CRC cases were identified in the 60-69 years age group. Most participants had one first-degree relative with CRC, and only 5.5% of the study population had two or more. HRs (95% CIs) were stronger for male sex (1.64, 1.43-1.90) and PRS (2.44, 1.95-3.05 for highest versus lowest quintile) than for the number of affected family members (≥ 2 versus 1: 1.33, 1.03-1.72) (Supplementary Table S3). This translated in RAPs (95% CIs) of 8.9 (5.8-12.0) years for males versus females and 15.9 (10.9-20.9) years for highest versus lowest PRS quintile (Supplementary Table S4). Besides, sex and PRS were independently associated with CRC risk ($P_{\text{interaction}}$ = 0.332, Supplementary Table S5). Sensitivity analyses using a weighted PRS, which was generated by summing up risk alleles with weights (log of odds ratio of respective SNP) [8], yielded very similar results (Supplementary Table S6).

In subgroup analyses by age, the number of first-degree relatives was significantly associated with CRC in the younger group (< 60 years at baseline) only ($P_{\text{interaction}}$ for age = 0.009), whereas no significant interactions with age were found for the associations of sex and PRS with CRC risk (Supplementary Table S7). In Figure 1, we present estimated risk-adapted starting ages according to PRS and sex as an alternative to the commonly recommended starting age of 40 for those with a FH. Results are shown for a base case scenario assigning 40 years as the starting age for screening for men in the middle PRS quintile. Risk-adapted starting ages of screening would range from 32 years among men in the highest quintile of PRS to 57 years among women in lowest quintile of PRS. Corresponding risk-adapted starting ages of CRC screening when assigning starting ages other than 40 years for men in the middle PRS quintile can be easily derived by increasing or decreasing presented ages accordingly.

Our analysis demonstrated a large potential for refinement of CRC risk stratification even within the high-risk group of people with a FH of CRC. We intentionally focused on a few highly predictive and relatively easily (FH and sex) or reliably obtainable (PRS) risk predictors. In contrast to current practice of derivation of starting ages of screening, which is essentially exclusively based on FH, risk-adapted starting ages of screening would strongly vary among people with a FH even with additional consideration of just these few key variables. Additional consideration of lifestyle factors, such as smoking, overweight, or obesity, might enable even more refined risk stratification even though reliable ascertainment of lifetime exposure to these factors is often considerably more challenging, and, like features of the FH, these exposures are subject to changes during the life course.

In conclusion, our findings suggested a great potential for using PRS and sex in informing decisions regarding CRC screening among persons with a FH. Risk-adapted starting ages may vary by as much as 25 years between men in the highest PRS quintile and women in the lowest PRS quintile. In men with a FH of CRC and a relatively high PRS, it may be worthwhile to start screening well before age 40, whereas women with a FH of CRC but a relatively low PRS might not need to start CRC screening earlier than the average risk population. Our results pertain to a population of European descent. Further research should aim for similar analyses in populations with different ancestries, and validation in even larger cohorts are warranted. Modelling studies, which may be informed by our results, should be conducted to assess effectiveness and cost-effectiveness of risk-adapted screening strategies compared to current screening recommendations for those with a FH of CRC.

DECLARATIONS

AUTHOR CONTRIBUTIONS

Xuechen Chen: formal analysis; methodology; writing-original draft; writing-review and editing. **Thomas Heisser**: writing-review and editing. **Rafael Cardoso**: writing-review and editing. **Julia Hibbert**: writing-review and editing. **Michael Hoffmeister**: data curation; formal analysis; methodology; project administration; resources; supervision; writing-review and editing. **Hermann Brenner**: conceptualization; data curation; formal analysis; funding acquisition; methodology; project administration; resources; supervision; writing-original draft; Writing-review and editing. All authors read and approved the final manuscript.

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Not applicable.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

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ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was based on the UK Biobank study that has obtained approval as a Research Tissue Bank (RTB) from the North West Multi-center Research Ethics Committee (renewed approval in 2021: 21/NW/0157). All participants provided electronic signed informed consent.

CONSENT FOR PUBLICATION

Not applicable.

DATA AVAILABILITY STATEMENT

This research has been conducted using the UK Biobank resource under application number 66591. This work used data provided by patients and collected by the NHS as part of their care and support. The UK Biobank is an open-access resource and bona fide researchers can apply to use the UK Biobank dataset by registering and applying at https://www.ukbiobank.ac.uk/enable-your-research/apply-for-access. Further information is available from the corresponding author upon request.

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SUPPORTING INFORMATION

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