Effects of Screenings in Reducing Colorectal Cancer Incidence and Mortality Differ by Polygenic Risk Scores

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INTRODUCTION: **Colorectal cancer (CRC) screening reduces CRC incidence and mortality. However, it is unclear whether the reduction in CRC risk may differ by genetic susceptibility.**

METHODS: **We evaluated this question in a cohort of 304,740 participants of European descent aged 50 years and older. Genetic susceptibility was measured using a polygenic risk score (PRS) constructed with risk variants identified in genomewide association studies. Cox models were used to estimate hazard ratios and 95% confidence intervals of CRC risk.**

RESULTS: **Over a median follow-up of 7.0 years, 2,261 incident CRC cases and 528 CRC deaths were identified. CRC screening was associated with a significantly reduced CRC incidence among individuals with a high (hazard ratio, 0.80; 95% confidence interval, 0.71–0.92) and intermediate PRS (0.84, 0.71–0.98) but not among those with a low PRS (1.03, 0.86–1.25; $P_{interaction}$, 0.005). A similar but more evident difference was observed for mortality ($P_{interaction}$, 0.046), with more than 30% reduced mortality observed in the high PRS group (0.69, 0.52–0.91). Among the younger group (age 50–60 years), CRC screenings were associated with a slightly (but nonsignificantly) elevated incidence and mortality in the low PRS group but a reduced risk in the high PRS group ($P_{interaction}$, 0.043 [incidence]; 0.092 [mortality]). No significant interaction was observed in the older group (age > 60 years).**

DISCUSSION: **Individuals with a higher genetic risk benefited more substantially from CRC screenings than those with a lower risk. Our findings suggest that PRS may be used to develop personalized CRC screening to maximize its effect on CRC prevention.**

SUPPLEMENTARY MATERIAL accompanies this paper at http://links.lww.com/CTG/A611.

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INTRODUCTION

Colorectal cancer (CRC) is the third most commonly diagnosed malignancy and second leading cause of cancer death globally (1). Most CRC is known to arise from precancerous lesions according to the adenoma-carcinoma sequence (2). CRC screenings, such as the use of fecal occult-blood testing and endoscopies, can reduce CRC incidence by detecting and removing precancerous lesions through endoscopic resection. They can also decrease CRC mortality by detecting cancer at an early, and thus more curable, stage (3–7). Screenings using fecal occult-blood testing have been shown to reduce CRC incidence by approximately 17%–20% (3) and CRC mortality by approximately 22%–32% (4). Compared with fecal occult blood tests, use of colonoscopy and sigmoidoscopy in CRC screenings has resulted in a more significant reduction in CRC incidence by 43%–56% (6) and CRC mortality by 41%–68% (6).

Genomewide association studies (GWAS) have identified large numbers of common genetic variants associated with CRC risk. Although each of these risk variants confers a small to moderate risk of CRC, a combination of these variants measured by polygenic risk scores (PRSs) is strongly associated with CRC risk (8–10). We showed in a recent cohort study that, compared with individuals in the lowest PRS quintile, those in the highest quintile had a greater than 3-fold risk of CRC (8). However, despite several lines of evidence for the clinical utility of PRS, the level of CRC risk reduction by screening according to genetic susceptibility has not been adequately evaluated. In this study, we investigated the association of screening with reduced CRC

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incidence and mortality using a CRC PRS derived from GWAS-identified risk variants.

METHODS

Study population

The UK Biobank is a population-based cohort study which has recruited more than 500,000 adults across England, Scotland, and Wales. Its design and methods have been previously described (11). At UK Biobank enrollment, information was collected on screening, demographic characteristics, and lifestyle risk factors associated with CRC, including body mass index, waist-to-hip ratio, physical activity, processed and red meat intake, vegetable and fruit intake, alcohol consumption, and tobacco smoking using a self-administered touchscreen questionnaire (http://www.ukbiobank.ac.uk/resources/) and nurse-led interviews. The question addressing CRC screening was as follows: "Have you ever had a screening test for bowel (colorectal) cancer? (Please include tests for blood in the stool/feces or a colonoscopy or a sigmoidoscopy.)" People who answered yes to this question were categorized as the screening group, and those who answered no were placed into the nonscreening group. During the interviews, trained staff used standardized procedures to measure the participants' body weight, waist and hip circumferences, and height.

The National Health Service Information Center (for participants from England and Wales; follow-up through March 31, 2016) and the National Health Service Central Register Scotland (for participants from Scotland; follow-up through October 31, 2015) provided the diagnoses and dates diagnosed on site-specific incident cancers. Cancers were coded by the *International Classification of Diseases, Ninth Revision* (*ICD-9*), or the *ICD, Tenth Revision* (*ICD-10*). The outcomes for this study were incident CRC and death due to CRC (*ICD-9* = 153, 154.0, and 154.1 or *ICD-10* = C18, C19, and C20). All participants provided written informed consent.

We included participants aged 50 years and older, the recommended age at which screening starts for average-risk individuals in the United Kingdom. Because the PRS was constructed using GWAS conducted in European descendants, we included only participants of European ancestry in the current study, based on information gathered by projecting the genotype data of all samples on the first 2 major principal components of 4–1,000 genome populations (CEU, YRI, CHB, and JPT). We excluded participants who had missing values for the screening questions. After all exclusions, 304,740 participants (141,554 men and 163,186 women) remained for the study, including 113,231 screened and 191,509 not screened.

Polygenic risk scores

We built a PRS using 95 risk variants identified in previous GWAS conducted among populations of European ancestry (see Table 1, Supplementary Digital Content 1, http://links.lww.com/CTG/A611 which demonstrates the list of SNPs included in the PRS) (12). We used previously reported regression coefficients as variant-specific weights and calculated the PRS as the sum of the product of the weight and the number of risk alleles (0, 1, and 2) for each risk variant across all selected risk variants per individual. Details for the derivation of this genetic risk score are described in our recently published article (8) using risk variants reported in the study conducted by Huyghe et al. (10). We categorized the PRS as low (score: $\leq$ 7.6625), intermediate (7.6626–8.0589), and high ($\geq$ 8.0590), according to the tertile distribution of PRS in all participants.

Statistical analyses

We compared demographic characteristics and known CRC risk factors by screening status using χ^2 tests (for categorical variables) or *t* tests (for continuous variables). We used the Cox proportional hazards models to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) of CRC risk associated with screening and PRS, with age as the underlying timescale, left-truncated at the age at baseline interview. We categorized education into 4 levels (college or university degree, some professional qualifications, secondary education, and none of the above) and the Townsend deprivation index into quintiles. We divided each lifestyle factor into 2 categories, those who met the recommendations and those who did not, based on the American Cancer Society Guidelines on Nutrition and Physical Activity for Cancer Prevention and the guideline to "Stay Away from Tobacco" (see Table 2, Supplementary Digital Content 1, http://links.lww.com/CTG/A611 which provides descriptions of categories used) (13,14). Multivariate Cox regression models were adjusted for age at enrollment, sex, education, community socioeconomic status (based on the Townsend deprivation index), family history of CRC, body mass index, waist-to-hip ratio, physical activity, processed and red meat intake, vegetable and fruit intake, alcohol consumption, tobacco smoking, the top 5 principal components for ancestry, and genotyping batches. All covariates had less than 2% of the missing values except for physical activity (8.2% missing) and vegetable and fruit intake (2.5% missing). Missing data for covariates were set to sex-specific medians. The Cox models were stratified by birth cohorts, defined according to the year of birth as follows: $\leq$ 1941, 1942–1951, 1952–1956, 1957–1961, 1962–1966, and $>$ 1966. The assumptions of proportionality of the Cox models were verified using the Schoenfeld residuals. We estimated adjusted HRs for CRC incidence or CRC mortality by the joint distribution of screening and PRS groups. We test interactions between screening and PRS in the same Cox model with the Wald test. We also estimated the cumulative incidence and mortality risk of CRC from age 50 to 75 years as the complement of the survivals (i.e., 1-survivals), adjusted to the medians or modes of the covariates. We calculated the attributable fraction because of screening by taking the risk difference (cumulative risk among nonscreeningcumulative risk among screening), dividing it by the cumulative risk among nonscreening. In addition, we conducted subgroup analyses stratified by family history of CRC (negative vs positive) and age groups ($>$60 years vs 50–60 years) and performed interaction tests of PRS, CRC screenings, and family history of CRC or age. All statistical analyses were conducted as 2-sided on a 0.05 significance level using SAS software, version 9.4 (SAS Institute, Cary, NC) and R v. 3.6.0 software (https://www.r-project.org/).

RESULTS

Over a median follow-up of 7.0 years, 2,261 incident CRC cases and 528 CRC deaths were observed in the cohort. Baseline characteristics of the cohort between the screening and nonscreening groups are presented in Table 1. Compared with the nonscreening group, the screening group was more likely to be older, male, have a family history of CRC, reside in more privileged areas, have a higher processed and red meat intake, and have a higher PRS.

Table 1. Baseline characteristics of study participants by CRC screening status in the UK Biobank

Characteristic	Screening[a]	Nonscreening[a]	*P* value[b]
No. of participants	113,231	191,509	—
Male sex, %	48.5	45.3	<0.0001
Age at enrollment (yr): Median (IQR)	63 (6)	59 (9)	<0.0001
> 60 yr, %	69.0	38.5	
50–60 yr, %	31.0	61.5	
Family history of CRC, %	15.7	9.9	<0.0001
Education, %			<0.0001
College or university degree	29.8	31.0	
Some professional qualifications	26.7	27.2	
Secondary education	20.3	21.7	
None of the above	22.1	19.0	
Living in the most deprived[c], %	21.3	21.9	<0.0001
Body mass index, %			<0.0001
< 18.5 kg/m^2	0.5	0.5	
18.5–24.9 kg/m^2	30.3	31.5	
25.0–29.9 kg/m^2	44.3	42.9	
≥ 30.0 kg/m^2	24.6	24.8	
Waist-to-hip ratio: median (IQR)	0.89 (0.13)	0.88 (0.14)	<0.0001
≥ 0.85 for women, ≥ 0.90 for men, %	54.9	50.6	<0.0001
Low physical activity[d], %	78.2	78.7	0.22
High processed and red meat intake[e], %	86.4	85.6	<0.0001
Low vegetable and fruit intake[f], %	66.2	68.2	<0.0001
High alcohol consumption[g], %	71.7	71.9	0.24
Smoking, %			<0.0001
Never	50.2	53.3	
Former	41.5	36.1	
Current	7.9	10.3	
PRS, %			0.0005
Low	33.0	33.5	
Intermediate	33.3	33.4	
High	33.7	33.1	

CRC, colorectal cancer; IQR, interquartile range; PRS, polygenic risk score.
[a]Percentages do not always sum to 100 because of missing data.
[b]Subjects with missing data not included in this analysis.
[c]Top quartile of the Townsend deprivation index.
[d]Defined as being physically active 10 + min for moderate activity < 6 d/wk or vigorous activity < 3 d/wk.
[e]Defined as eating either processed meat or red meat ≥ 4 times per week.
[f]Defined as eating vegetables and fruits ≤ 5 servings per day.
[g]Defined as drinking alcoholic beverages > 1–2 times per week.

We evaluated the association of CRC incidence and mortality with CRC screening stratified by the PRS tertiles (Table 2). A significant reduced risk of CRC was associated with receiving a screening among individuals with a high PRS (HR, 0.80; 95% CI, 0.71–0.92) and intermediate PRS (0.84, 0.71–0.98) but not among those with a low PRS (1.03, 0.86–1.25) compared with those who did not receive a CRC screening before the baseline survey; there was a significant heterogeneity in these associations ($P_{interaction}$, 0.005). A similar but more evident heterogeneity was observed for mortality ($P_{interaction}$, 0.046; HR, 0.69 [95% CI, 0.52–0.91] for those with a high PRS, 0.74 [0.52–1.05] for those with an intermediate PRS, and 0.98 [0.67–1.43] for those with a low PRS). HRs for CRC incidence and mortality associated with screenings for all participants combined were 0.86 (95% CI, 0.79–0.95) and 0.77 (0.64–0.93), respectively. Similar to the results described above, we showed that the attributable fraction due to screening of developing or dying from CRC was more apparent for those with a high PRS than those with a low PRS.

Table 2. Association of CRC risk with receiving CRC screenings according to CRC PRS in the UK Biobank

	CRC incidence				CRC mortality			
	Screening		Nonscreening		Screening		Nonscreening	
PRS category	Cases (N)	Noncases (N)	Cases (N)	Noncases (N)	Cases (N)	Noncases (N)	Cases (N)	Noncases (N)
Low	203	37,147	279	63,942	50	37,300	72	64,149
Intermediate	260	37,420	437	63,464	51	37,629	102	63,799
High	383	37,818	698	62,689	79	38,122	174	63,213
Overall	846	112,385	1,414	190,095	180	113,051	348	191,161

	HR (95% CI)[a]			HR (95% CI)[a]		
	By screening and PRS jointly		Association with screening by PRS	By screening and PRS jointly		Association with screening by PRS
	Screening	Nonscreening		Screening	Nonscreening	
Low	1.00 (reference)	0.97 (0.80–1.17)	1.03 (0.86–1.25)	1.00 (reference)	1.02 (0.70–1.49)	0.98 (0.67–1.43)
Intermediate	1.27 (1.06–1.52)	1.53 (1.29–1.83)	0.84 (0.71–0.98)	1.02 (0.69–1.50)	1.44 (1.01–2.05)	0.74 (0.52–1.05)
High	1.86 (1.56–2.20)	2.32 (1.98–2.73)	0.80 (0.71–0.92)	1.58 (1.11–2.25)	2.29 (1.65–3.18)	0.69 (0.52–0.91)
Overall	1.00 (reference)	1.17 (1.07–1.28)	0.86 (0.79–0.95)	1.00 (reference)	1.31 (1.08–1.58)	0.77 (0.64–0.93)
	P for interaction = 0.005			*P* for interaction = 0.046		

	Cumulative risk (95% CI, %)[b]		Attributable fraction due to screening (%)	Cumulative risk (95% CI, %)[b]		Attributable fraction due to screening (%)
	Screening	Nonscreening		Screening	Nonscreening	
Low	1.81 (1.40–2.21)	1.69 (1.35–2.03)	−7.10	0.59 (0.29–0.89)	0.56 (0.30–0.82)	−5.36
Intermediate	2.28 (1.79–2.77)	2.66 (2.16–3.17)	14.29	0.60 (0.29–0.90)	0.80 (0.44–1.16)	25.00
High	3.31 (2.64–3.97)	4.25 (3.48–5.01)	22.12	0.92 (0.47–1.36)	1.37 (0.78–1.96)	33.58
Overall	2.46 (1.99–2.92)	2.85 (2.35–3.34)	13.68	0.70 (0.38–1.02)	0.90 (0.53–1.28)	22.22

CI, confidence interval; CRC, colorectal cancer; HR, hazard ratio; PRS, polygenic risk score.
[a]Adjusted for age at enrollment, sex, family history of CRC, education, Townsend deprivation index, body mass index, waist-to-hip ratio, physical activity, processed and red meat intake, vegetable and fruit intake, alcohol consumption, tobacco smoking, top 5 principal components for ancestry, and genotyping batch, and stratified by birth cohort.
[b]Cumulative incidence or mortality of CRC from age 50 to 75 years by CRC screening and PRS. Adjusted to the median of continuous covariates and modes of categorical variables.

Further stratified analyses by family history of CRC showed a similar pattern of association regardless of family history, although some estimates were unstable because of a smaller sample size (Figure 1). When we stratified analyses by age, we found that in the younger age group (age 50–60 years) CRC screenings were associated with a slightly, although nonsignificantly, elevated incidence and mortality among those with a low PRS but a reduced risk among those with a high PRS ($P_{interaction}$, 0.043 for incidence and 0.092 for mortality; Figure 2). In the older age group (older than 60 years), CRC screenings were associated with an overall reduced incidence (HR, 0.79; 95% CI, 0.72–0.88) and mortality (HR, 0.72; 95% CI, 0.58–0.90), although the risk estimates were statistically significant only for CRC incidence in the high and intermediate PRS groups and for mortality in the high PRS group, and tests for interactions were not statistically significant ($P_{interaction}$, 0.131 for incidence and 0.276 for mortality).

DISCUSSION

This is the first large prospective cohort study to examine the effects of CRC screenings on reducing CRC incidence and mortality according to genetic risk of CRC. We found that individuals with a high PRS of CRC benefited substantially more from a CRC screening than those with a low PRS. These results suggest that genetic susceptibility to CRC could modify the level of CRC risk reduction by CRC screenings. This information, if confirmed, could be used to guide personalized screening strategies to reduce CRC incidence and mortality.

Several studies have demonstrated the potential of using PRS for risk stratification, either by itself or along with environmental and/or lifestyle risk factors (15–20). For example, Balavarca et al. reported that a joint environmental-genetic score showed higher predictive values for CRC risk (area under the receiver operating

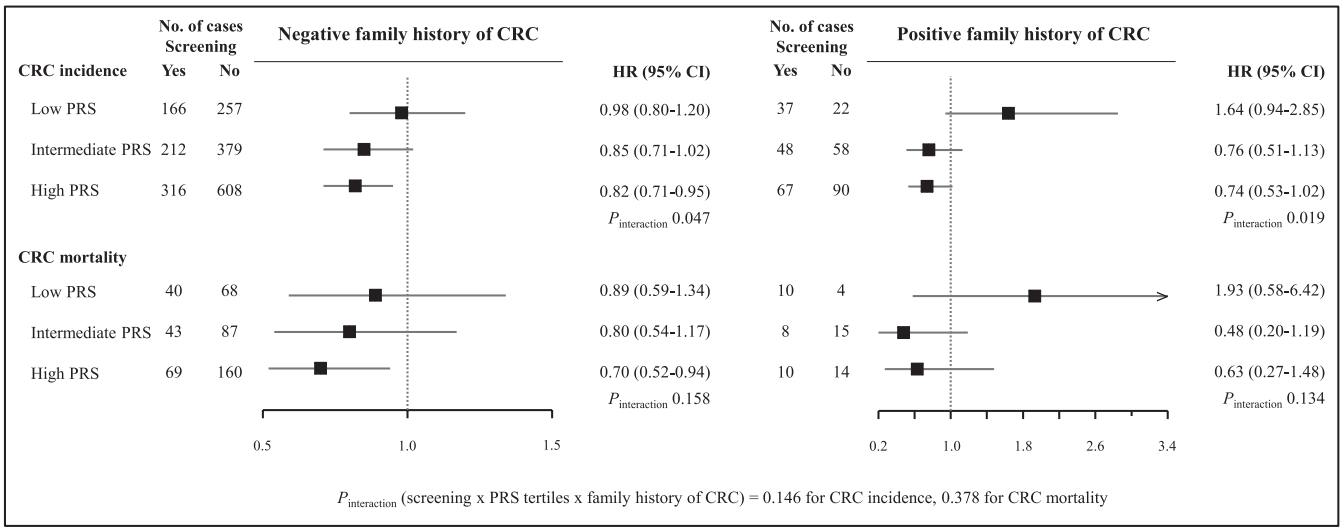

Figure 1. Hazard ratios for the associations of colorectal cancer incidence and mortality with screenings, according to polygenic risk score groups and family history of colorectal cancer. CRC, colorectal cancer; CI, confidence interval; HR, hazard ratio; PRS, polygenic risk score.

characteristic curve, 0.64; 95% CI, 0.60–0.67) than the environmental score alone (0.58, 0.55–0.62) (19). Using data from 2 large international consortia, Jeon et al. (20) suggested that starting ages for CRC screening should be earlier, by 12 years for men and 14 for women, based on a combined polygenic and environmental score, for individuals in the highest vs the lowest 10% of risk. However, to the best of our knowledge, no research has been conducted that uses PRS to assess the overall effects of bowel screening on reducing CRC incidence and mortality using a large cohort study.

In our study, age-stratified analyses showed that in the younger age group (age 50–60 years), a CRC screening was associated with slightly elevated incidence and mortality among those with a low PRS, but with a reduced risk among those with a high PRS. The increased risk among the low PRS group might be due to overdiagnosis or just a chance finding, particularly since point estimates were not statistically significant. Recently, based on a systematic evidence review of the existing CRC screening literature and microsimulation modeling analyses, the American Cancer Society recommends that adults aged 45 years and older, with an average risk of CRC, undergo regular screenings. Although there is clear evidence of both the benefit and harm of screening, the balance of benefits and harms for administering it before the age of 50 years, which is when screening starts for average-risk individuals, is not well understood (21). It was reported recently that CRC PRS is more strongly associated with early-onset (<50 years old) than late-onset (≥50 years old) cancer (22). However, we did not include participants younger than 50 years in this study because current UK guidelines recommend starting CRC screening at age 50. We did find that in the younger age group (age 50–60 years), there is a significant interaction between screening and PRS ($P_{interaction}$, 0.043 for incidence and marginal significance of 0.092 for mortality), suggesting that a CRC screening at a younger age might only

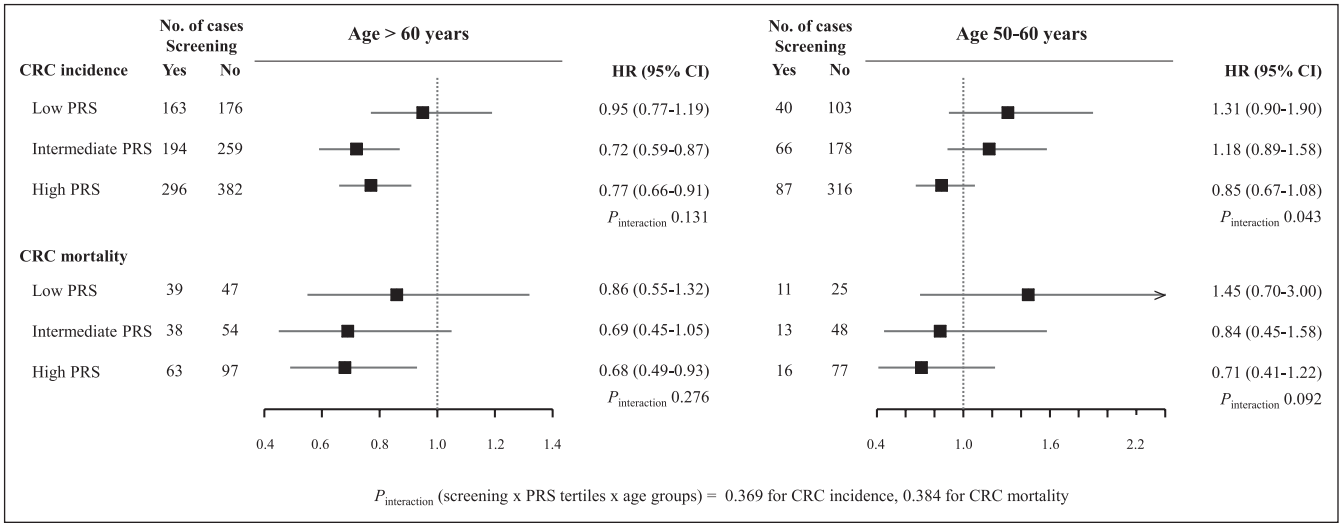

Figure 2. Hazard ratios for the associations of colorectal cancer incidence and mortality with screenings, according to polygenic risk score groups and age groups. CRC, colorectal cancer; CI, confidence interval; HR, hazard ratio; PRS, polygenic risk score.

benefit individuals with intermediate or higher genetic risk. However, future studies are needed to verify this result.

Different screening modalities may have different impacts on CRC incidence and mortality reduction, but several randomized controlled trials and cohort studies have demonstrated that all types of screening currently in practice could reduce CRC incidence and mortality (3–7,23–25). In our study, there were overall a 14% and 23% lower risk of CRC incidence and mortality, respectively, in the screening group compared with the non-screening group, which is similar to previous studies showing approximately 20%–30% reduction in CRC incidence and mortality by using fecal occult blood testing as the screening tool (3,4).

The major strengths of our study include a prospective study design, a large sample size, and the availability of extensive data on demographic and lifestyle factors, which enabled us to carefully adjust for potential influence of confounders on our study results. However, in our study, no information was available on the type, frequency, and date of screening interventions each participant received before the study enrollment. These limitations may have affected our estimates of the magnitude of screening effects on CRC incidence and mortality. Nevertheless, our findings for a modifying effect of PRS on CRC screening are significant, and there is no obvious reason to speculate that such an effect may differ by screening modalities. Also, no information on CRC screening during the follow-up period was available for our analyses. However, the follow-up time after study enrollment was relatively short (median = 7.0 years), so it should not have any major influence on our study results. In addition, several CRC risk factors were more prevalent in the screened group, which, if not properly controlled, could reduce the difference observed in our study. Although we have included them in our models as potential confounders, we could not entirely rule out the possibility of residual confounding effects. Future studies can be performed to quantify the size of this modifying effect by screening modalities.

In conclusion, we found that individuals with a lower genetic risk of CRC, as measured by PRS constructed using genetic risk variants identified in GWAS, may benefit less from CRC screenings than those with a higher genetic risk. Our study provides strong support for using PRS in risk stratification for personalized CRC screening.

CONFLICTS OF INTEREST

Guarantor of the article: Jungyoon Choi, MD, PhD, and Wei Zheng, MD, PhD, MPH.

Specific author contributions: J.C., G.J., and W.Z. were responsible for study conception and design; J.C., G.J., W.W., and W.Z. performed data analysis; J.C. and W.Z. prepared the manuscript. All authors approved the final version of the manuscript.

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Potential competing interests: The authors have no conflict of interest to declare.

Ethical approval: The study was approved by the relevant ethical committee for UK Biobank. All participants provided written informed consent.

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Study Highlights

WHAT IS KNOWN

- ✓ Colorectal cancer (CRC) screening can reduce CRC incidence and mortality.
- ✓ It is unclear whether the reduction in CRC risk may differ by CRC genetic susceptibility.

WHAT IS NEW HERE

- ✓ Individuals with a high genetic susceptibility to CRC benefit more substantially from CRC screenings than those with a low genetic risk.
- ✓ Our findings could be useful in recommending personalized strategies for CRC screening.

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