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ARTICLE

Long-Term Colorectal Cancer Incidence and Mortality After Colonoscopy Screening According to Individuals' Risk Profiles

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Abstract

Background: It remains unknown whether the benefit of colonoscopy screening against colorectal cancer (CRC) and the optimal age to start screening differ by CRC risk profile. **Methods:** Among 75 873 women and 42 875 men, we defined a CRC risk score (0-8) based on family history, aspirin, height, body mass index, smoking, physical activity, alcohol, and diet. We calculated colonoscopy screening-associated hazard ratios and absolute risk reductions (ARRs) for CRC incidence and mortality and age-specific CRC cumulative incidence according to risk score. All statistical tests were 2-sided. **Results:** During a median of 26 years of follow-up, we documented 2407 CRC cases and 874 CRC deaths. Although the screening-associated hazard ratio did not vary by risk score, the ARRs in multivariable-adjusted 10-year CRC incidence more than doubled for individuals with scores 6-8 (ARR = 0.34%, 95% confidence interval [CI] = 0.26% to 0.42%) compared with 0-2 (ARR = 0.15%, 95% CI = 0.12% to 0.18%, $P_{trend} < .001$). Similar results were found for CRC mortality (ARR = 0.22%, 95% CI = 0.21% to 0.24% vs 0.08%, 95% CI = 0.07% to 0.08%, $P_{trend} < .001$). The ARR in mortality of distal colon and rectal cancers was fourfold higher for scores 6-8 than 0-2 (distal colon cancer: ARR = 0.08%, 95% CI = 0.07% to 0.08% vs 0.02%, 95% CI = 0.02% to 0.02%, $P_{trend} < .001$; rectal cancer: ARR = 0.08%, 95% CI = 0.08% to 0.09% vs 0.02%, 95% CI = 0.02% to 0.03%, $P_{trend} < .001$). When using age 45 years as the benchmark to start screening, individuals with risk scores of 0-2, 3, 4, 5, and 6-8 attained the threshold CRC risk level (10-year cumulative risk of 0.47%) at age 51 years, 48 years, 45 years, 42 years, and 38 years, respectively. **Conclusions:** The absolute benefit of colonoscopy screening is more than twice higher for individuals with the highest than lowest CRC risk profile. Individuals with a high- and low-risk profile may start screening up to 6-7 years earlier and later, respectively, than the recommended age of 45 years.

Colorectal cancer (CRC) is the third-leading cause of cancer death in the United States (1). Screening has been shown to decrease CRC incidence and mortality by identifying and removing precancerous polyps and early cancers (2-14). Among the available screening options (9,10), colonoscopy is most widely used in the United States (15). Despite an overall increase in the uptake of CRC screening, there remains a substantial disparity in the uptake (16-19) and approximately 40% screening-eligible adult Americans not complying with the recommendations (20,21). These data highlight the importance of tailored screening recommendations based on risk profile to optimize the benefit of screening and resource allocation at the population level.

Currently, CRC screening is recommended based only on age and family history. Although several studies have examined CRC risk prediction based on clinical, lifestyle, environmental, and genetic factors, those studies either aimed to develop screening recommendations based on the predicted CRC risk (22-26) or examined the joint effect of predictors and screening on CRC risk (27). To the best of our knowledge, no prior study

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has directly examined whether the benefit of screening differs by risk profile.

The optimal age to start screening is a critical component of screening recommendations. Since 2002, the US Preventive Services Task Force (USPSTF) recommended CRC screening to start at age 50 years in average-risk adults. Given the increasing incidence of early-onset CRC in recent years (28), in 2020, the USPSTF released the draft recommendation that average-risk adults may initiate routine screening at age 45 years instead of 50 years (29). A similar recommendation has been made by the American Cancer Society (30). These recommendations for earlier screening have spurred intensive debate about the risk-benefit balance and led to greater interest in developing risk-based screening strategies (22,31).

Therefore, in the current study, we prospectively assessed the relative and absolute risk of CRC incidence and mortality associated with colonoscopy screening according to individuals' risk profiles within 2 large cohorts in the United States, including the Nurses' Health Study (NHS) and Health Professionals Follow-up Study (HPFS). We also examined the age-specific CRC cumulative incidence and identified the ages when the threshold CRC risk at age 45 years and 50 years, respectively, was attained among individuals with different CRC risk profiles.

Methods

Detailed information about the study methods is provided in the Supplementary Methods (available online).

Study Population

The NHS and HPFS are 2 ongoing US cohorts that included 121 700 registered female nurses aged 30-55 years at enrollment in 1976 and 51 529 male health professionals aged 40-75 years at enrollment in 1986, respectively (32,33). In both cohorts, participants completed a detailed biennial questionnaire regarding lifestyle and medical history, and health-related questions with over 90% of follow-up. In the current study, we defined baseline as the year 1988, for both the NHS and HPFS, when we started to collect detailed information of colonoscopy. We excluded participants with a baseline history of cancer (except nonmelanoma skin cancer), inflammatory bowel disease, and those with missing information on diet and major lifestyle factors (Supplementary Figure 1, available online). As a result, 75 873 women and 42 875 men were included in the analysis. The study protocol was approved by the institutional review board of the Brigham and Women's Hospital and Harvard T.H. Chan School of Public Health and by those of participating registries as required.

Assessment of Colonoscopy Screening

In both cohorts, beginning in 1988 and continuing through 2014, participants were asked biennially whether they had undergone a colonoscopy in the past 2 years and, if so, the reason for the colonoscopy. We defined a colonoscopy screening as those for routine, age-related CRC screening or because of a family history of CRC, but not for positive symptoms. Participants were considered unscreened until the first time when they reported undertaking a colonoscopy screening and were considered screened thereafter for the remainder of follow-up.

Assessment of CRC Risk Profile

We selected the CRC risk factors constituting the risk profile based on the established evidence for their role in CRC. In detail, we included 8 prevalent risk factors in the general adult population, including first-degree relatives with CRC (34,35), cigarette smoking (36-38), body mass index (BMI) (39,40), physical activity (41,42), alcohol consumption (43,44), aspirin use (45-47), height (48,49), and diet (50-53). Alcohol consumption and diet were assessed every 4 years using validated food-frequency questionnaires (54,55) and the other factors through biennial questionnaires. Diet quality was assessed with the 6 major dietary recommendations in the World Cancer Research Fund/American Institute for Cancer Research Third Expert Report released in 2018 (53). For each of the 8 factors, we defined a high-risk criterion, by which the participants received a risk score of 1 if they met the criterion and 0 otherwise (Supplementary Table 1, available online). An overall CRC risk score (range = 0-8) was then defined as the sum of the 8 scores, with a higher score indicating a higher CRC risk.

Ascertainment of Cases and Deaths of CRC

Participants reported CRC diagnoses on each biennial questionnaire. CRC deaths were identified through the National Death Index or report by family members (56). For the reported CRC cases or deaths, we obtained medical records to confirm the diagnosis or cause of death by study physicians.

Statistical Analysis

Data were analyzed from February 26, 2020, to June 20, 2020. Participants contributed person-time from return of the baseline questionnaire (1988) until the date of CRC diagnosis (for CRC incidence analysis only), death, loss to follow-up, or end of the follow-up period (June 30, 2014, for the NHS and January 31, 2014, for the HPFS), whichever came first. First, we used time-varying and age-, questionnaire cycle–, and cohort-stratified Cox proportional hazards regression models to estimate the multivariable hazard ratios and 95% confidence intervals (CIs) for the association of colonoscopy screening with CRC incidence and mortality according to CRC risk score. We tested the trend in the hazard ratios across CRC risk scores by including in the model the main effects of CRC risk score (continuous) and colonoscopy screening (binary) as well as their product term, whose P value was considered as the P_{trend}.

Second, to examine the absolute benefit of colonoscopy screening according to CRC risk score, we assessed the multivariable-adjusted cumulative incidence and mortality of CRC according to the CRC risk score and colonoscopy screening status at baseline using Cox regression models. We calculated the cumulative risks of 10, 20, and throughout the follow-up of up to 28 years separately. In each CRC risk score group, we calculated the absolute risk reductions (ARRs) associated with colonoscopy screening by subtracting the cumulative risk in the screening group from that in the nonscreening group. We assessed the trend in the ARRs across CRC risk scores by regressing the multivariable-adjusted 10-year cumulative risk on baseline colonoscopy screening status and CRC risk score as well as their product term. The P value of the product term was derived as the P_{trend} in the ARRs across CRC risk scores.

Then, to estimate the risk-adapted starting age of screening, we calculated the age-specific multivariable-adjusted 10-, 20-,

and 28-year cumulative incidence of CRC in the overall cohorts and each risk score group that was defined at baseline. Risk-adapted starting age of screening was defined as the age at which individuals with a particular CRC risk score at baseline attained the threshold level of CRC cumulative incidence at which the general population is usually advised to initiate screening (57).

The analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC). All statistical tests were 2-sided, and *P* values less than .05 were considered statistically significant.

Results

Mean age at baseline was 54 years (SD = 8). In the 2 cohorts of 118 748 participants with a median of 26 years (up to 28 years and 2 388 051 person-years) of follow-up, we documented 2407 incident CRC cases and 874 CRC deaths, among which 1039 cases (43.2%) and 258 deaths (29.5%) occurred in the first 10 years, and 1729 cases (71.8%) and 745 deaths (85.2%) occurred in the first 20 years. By subsite, 910 cases (37.8%) and 304 deaths (34.8%) were of proximal colon cancer, 633 cases (26.3%) and 208 deaths (23.8%) of distal colon cancer, and 514 cases (21.4%) and 180 deaths (20.6%) of rectal cancer, with the remaining (14.5% cases and 20.8% deaths) having no confirmed subsite information. Throughout the follow-up, 57.0% of the participants reported a history of colonoscopy screening. As shown in Table 1, based on person-years, the prevalence of the CRC risk score of 0-2, 3, 4, 5, and 6-8 was 13.9%, 22.6%, 29.6%, 22.6%, and 11.3%, respectively; within each risk score group, the prevalence of colonoscopy screening was 22.7% to 31.3%. Compared with the score of 0-2, those with the score of 3, 4, 5, and 6-8 had 19.1%, 50.8%, 77.3%, and 145.2% higher risk of CRC, respectively (Supplementary Table 1, available online).

Table 2 shows the association of colonoscopy screening with CRC incidence and mortality according to CRC risk score. For CRC incidence, colonoscopy screening was associated with a hazard ratio of 0.59 (95% CI = 0.42 to 0.83), 0.56 (95% CI = 0.42 to 0.73), 0.50 (95% CI = 0.40 to 0.63), 0.55 (95% CI = 0.44 to 0.70), and 0.58 (95% CI = 0.44 to 0.76) among individuals with a CRC risk score of 0-2, 3, 4, 5, and 6-8, respectively (P_{trend} = .68). Similar results were observed for CRC mortality (P_{trend} = .71) and subsite-specific CRC ($P_{trend} \geq .17$) in individuals without and with family history of CRC separately, respectively, and when individuals were classified according to each of the 8 factors individually (Supplementary Tables 2-4, available online).

We then examined the 10- and 28-year multivariable-adjusted cumulative CRC incidence and mortality by screening status and calculated the ARRs associated with colonoscopy screening according to CRC risk score. As shown in Figure 1, the ARR associated with screening increased with the risk score (0-2: 0.15%, 95% CI = 0.12% to 0.18%; 3: 0.22%, 95% CI = 0.19% to 0.25%; 4: 0.23%, 95% CI = 0.20% to 0.26%; 5: 0.29%, 95% CI = 0.25% to 0.33%; 6-8: 0.34%, 95% CI = 0.26% to 0.42%; $P_{trend} < .001$). For mortality, the corresponding ARR increased from 0.08% (95% CI = 0.07% to 0.08%) with a score of 0-2 to 0.22% (95% CI = 0.21% to 0.24%) with a score of 6-8 ($P_{trend} < .001$). When assessed by CRC subsites, for cancer mortality of proximal colon, distal colon, and rectum, the ARRs increased from 0.01% (95% CI = 0.01% to 0.02%) to 0.03% (95% CI = 0.02% to 0.03%), from 0.02% (95% CI = 0.02% to 0.02%) to 0.08% (95% CI = 0.07% to 0.08%), and from 0.02% (95% CI = 0.02% to 0.03%) to 0.08% (95% CI = 0.08% to 0.09%), respectively (all $P_{trend} < .001$) (Figure 2). Similar results were found for incidence by CRC subsites (Supplementary Figure 2, available online), when person-years were excluded when a symptomatic colonoscopy was reported (Supplementary Figure 3, available online) and when we used the 28-year cumulative CRC incidence and mortality (Supplementary Figure 4, available online).

Finally, we plotted the age-specific multivariable-adjusted 10-, 20-, and 28-year cumulative incidence of CRC in the overall cohorts and in each of the risk score groups. We observed a cumulative incidence of 0.47% in the overall cohorts at the benchmark age of 45 years (Figure 3). This threshold risk level was attained at age 51 years, 48 years, 45 years, 42 years, and 38 years for individuals with the CRC risk score of 0-2, 3, 4, 5, and 6-8, respectively. When we used age 50 years as the benchmark, the cumulative incidence was 0.68% and corresponding ages were 56 years, 53 years, 51 years, 48 years, and 44 years. Similar results were observed in individuals without and with a family history of CRC separately (Supplementary Figure 5, available online), in men and women separately (Supplementary Figure 6, available online), and when we used the 20- and 28-year cumulative incidence of CRC (1.62% and 2.51%, respectively, in the overall cohorts) to plot the curves (Supplementary Figure 7, available online).

Discussion

In 2 large prospective cohorts, we found that, although colonoscopy screening was associated with a similar relative risk of CRC among individuals with different risk profiles, the absolute benefit of colonoscopy screening was more than twice higher for individuals with the highest CRC risk score compared with the lowest score. We also observed that individuals with a high or low CRC risk profile may start colonoscopy screening for up to 6-7 years earlier and later, respectively, than the recommended age of 45 years or 50 years. These findings provide evidence for the development of tailored colonoscopy screening recommendations based on individuals' risk profiles.

A number of prior studies have assessed the benefit of colonoscopy screening (2-14,58) and developed risk prediction models for CRC (22-26,59). However, no prior studies have examined how the benefit of colonoscopy screening may be modified by CRC risk profile. In a recent study focusing on the additional benefit of a healthy lifestyle on top of a predefined genetic risk and colonoscopy status (27), as a secondary finding, the authors observed a consistent CRC risk reduction by colonoscopy across all groups jointly defined by genetic risk and healthy lifestyle status. However, that study did not examine how colonoscopy-related CRC risk reduction might be modified by individuals' CRC risk profile. Addressing this question has the potential to inform risk-based screening recommendations through a direct assessment of the benefit of screening against CRC rather than via implications for the intent to screen in the risk prediction models. Given that risk stratification may enable a more efficient use of limited colonoscopy resources (60), our study has important implications for tailored CRC screening.

Colonoscopy screening protects against incident CRC through detection and removal of colorectal precancerous lesions, whereas the factors constituting our CRC risk score, that is, family history of CRC, aspirin use, height, weight, BMI, smoking, alcohol use, physical activity, and diet, influence CRC risk through various biological pathways, including genetic susceptibility, hyperinsulinemia, systemic inflammation, and modulation of gene expression and the gut microbiota (34,48,51,61-64). Due to the largely independent pathways through which

Table 1. Age- and sex-standardized characteristics[a] of study participants according to CRC risk score[b] and colonoscopy screening status

	CRC risk score									
	0-2		3		4		5		6-8	
Characteristic	Screening	No screening	Screening	No screening	Screening	No screening	Screening	No screening	Screening	No screening
Person-years (% in overall study sample)	330 867 (13.9)		539 624 (22.6)		706 919 (29.6)		539 380 (22.6)		271 261 (11.3)	
Person-years (% within risk score group)	103 645 (31.3)	227 221 (68.7)	138 610 (25.7)	401 014 (74.3)	164 882 (23.3)	542 037 (76.7)	122 569 (22.7)	416 811 (77.3)	63 476 (23.4)	207 786 (76.6)
Age, y	71.9	62.0	71.7	61.7	71.6	61.7	71.5	61.8	71.3	62.0
Male sex, %	61.6	37.4	58.5	32.3	56.0	29.8	54.4	29.3	52.5	29.8
White race, %	94.3	94.1	95.4	94.7	96.2	95.5	96.2	96.2	97.3	96.8
Family history of CRC in first-degree relatives, %	8.0	3.3	15.2	6.3	25.0	10.4	35.8	18.0	55.7	35.8
Regular aspirin use, %	59.7	53.6	41.8	37.1	30.5	24.6	19.8	14.9	10.3	6.5
Current multivitamin use, %	63.5	53.0	55.4	46.0	53.2	41.3	52.6	37.9	50.2	35.0
Height, inches	66.0	65.7	66.2	65.9	66.6	66.2	67.2	66.9	68.0	67.9
Body mass index, kg/m^2	23.7	23.5	24.8	24.8	26.0	26.2	27.0	27.2	27.9	27.9
Current smoker, %	1.1	1.9	2.0	5.2	3.8	9.6	7.7	15.7	10.8	22.5
Pack-years of smoking[c]	11.1	14.6	16.2	20.4	19.3	24.5	23.1	28.3	26.0	31.3
Alcohol intake, g/d	5.6	4.8	5.9	5.4	6.8	6.3	9.2	8.8	13.9	15.0
Physical activity, min/d	41.2	39.4	29.1	26.1	21.0	18.4	17.0	13.9	13.1	11.0
Dietary intake										
Red meat, serving/wk	2.8	3.0	3.7	3.9	4.0	4.4	4.2	4.6	4.5	4.8
Processed meat, serving/wk	1.1	1.3	1.6	1.9	2.0	2.3	2.2	2.5	2.5	2.8
Dietary fiber, g/wk	160.1	155.6	141.6	137.1	132.3	127.8	127.1	121.7	122.2	115.7
Dairy products, serving/wk	15.6	16.5	15.8	16.3	15.9	16.0	15.9	16.0	15.7	16.1
Whole grain, g/wk	221.6	200.8	179.9	157.1	159.3	133.7	142.3	119.8	134.0	107.2
Ratio of whole grains/total grains in weight	0.4	0.3	0.3	0.3	0.3	0.3	0.3	0.2	0.3	0.2
Calcium supplement, %	68.2	60.3	61.4	48.9	55.8	41.2	50.8	36.6	44.4	33.4

[a]Updated information throughout follow-up was used to calculate the means for continuous variables and percentage for categorical variables. All variables were age- and sex-standardized except person-years, age, and sex; age and sex were mutually standardized. CRC = colorectal cancer.

[b]CRC risk score (range = 0-8) was defined as the number of the 8 CRC high-risk factors: having a family history of CRC among the first-degree relatives, no regular use of aspirin (<2 tablets or times per week), tall stature (upper 50% of height in each cohort), overweight or obesity (body mass index ≥25.0 kg/m^2), current smoker or past smoker with 5 or more pack-years, low physical activity (<30 min/d of moderate-to-vigorous intensity activity), heavy alcohol intake (≥1 drink [14 g alcohol] per day for women and ≥2 drinks per day for men), and unhealthy diet (meeting <3 of the 6 dietary recommendations by the World Cancer Research Fund/American Institute for Cancer Research Report 2018, which included red meat <0.5 serving per day, processed meat <0.2 serving per day, dietary fiber ≥30 g/d, dairy products ≥3 servings per day, whole grains ≥48 g/d or account for at least one-half of total grains, and calcium supplement use).

[c]Among ever-smokers only.

Table 2. Association of colonoscopy screening with incidence and mortality of CRC according to CRC risk score[a]

Subgroup model	CRC risk score 0-2	3	4	5	6-8	P_{trend}[f]
Incidence						
No. of cases						
Colonoscopy screening	58	79	111	105	80	
Nonscreening	167	333	579	525	370	
Incidence rate, per 100 000 py[b]						
Colonoscopy screening	56	57	67	86	126	
Nonscreening	74	83	107	126	178	
Age-adjusted HR (95% CI)[c]	0.58 (0.41 to 0.81)	0.56 (0.43 to 0.74)	0.50 (0.40 to 0.62)	0.55 (0.44 to 0.69)	0.60 (0.46 to 0.78)	.57
MV-adjusted HR (95% CI)[d]	0.59 (0.42 to 0.83)	0.58 (0.44 to 0.76)	0.51 (0.41 to 0.64)	0.57 (0.45 to 0.71)	0.60 (0.46 to 0.78)	.64
MV-adjusted HR (95% CI)[e]	0.59 (0.42 to 0.83)	0.56 (0.42 to 0.73)	0.50 (0.40 to 0.63)	0.55 (0.44 to 0.70)	0.58 (0.44 to 0.76)	.68
Mortality						
No. of deaths						
Colonoscopy screening	15	25	35	49	29	
Nonscreening	41	94	221	209	156	
Mortality rate, per 100 000 pys[b]						
Colonoscopy screening	18	19	20	35	37	
Nonscreening	22	26	40	45	61	
Age-adjusted HR (95% CI)[c]	0.44 (0.23 to 0.86)	0.42 (0.26 to 0.68)	0.25 (0.17 to 0.37)	0.44 (0.32 to 0.62)	0.35 (0.23 to 0.53)	.66
MV-adjusted HR (95% CI)[d]	0.52 (0.26 to 1.01)	0.52 (0.32 to 0.85)	0.29 (0.20 to 0.43)	0.51 (0.37 to 0.72)	0.41 (0.27 to 0.63)	.68
MV-adjusted HR (95% CI)[e]	0.50 (0.25 to 0.98)	0.52 (0.32 to 0.85)	0.29 (0.20 to 0.42)	0.52 (0.37 to 0.73)	0.41 (0.27 to 0.64)	.71

[a]CRC risk score (range = 0-8) was defined as the number of the 8 CRC-high risk factors: having a family history of CRC among the first-degree relatives, no regular use of aspirin (<2 tablets or times per week), tall stature (upper 50% of height in each cohort), overweight or obesity (body mass index ≥25.0 kg/m^2), current smoker or past smoker with 5 or more pack-years, low physical activity (<30 min/d of moderate-to-vigorous intensity activity), heavy alcohol intake (≥1 drink [14 g alcohol] per day for women and ≥2 drinks per day for men), and unhealthy diet (meeting <3 of the 6 dietary recommendations by the World Cancer Research Fund/American Institute for Cancer Research Report 2018, which included red meat <0.5 serving per day, processed meat <0.2 serving per day, dietary fiber ≥30 g/d, dairy products ≥3 servings per day, whole grains ≥48 g/d or account for at least one-half of total grains, and calcium supplement use). CI = confidence interval; CRC = colorectal cancer; HR = hazard ratio; MV = multivariable; pys = person-years.

[b]Incidence and mortality rates were age- and sex-standardized.

[c]Cox proportional hazards models were stratified by age, questionnaire cycle, and cohort.

[d]Cox proportional hazards models were stratified by age, questionnaire cycle, and cohort and were further adjusted for ethnicity, current multivitamin use, menopausal status, and hormone use (women only).

[e]Cox proportional hazards models were stratified by age, questionnaire cycle, and cohort and were further adjusted for ethnicity, current multivitamin use, menopausal status, and hormone use (women only) and 8 individual risk factors constituting the CRC risk score in continuous form (except aspirin use and CRC family history as binary variables) to account for residual confounding.

[f]The linear trend was assessed by including main effects of colonoscopy screening and CRC risk score and their product term in the models, and the P value for the product term was used as the P_{trend}. We additionally assessed the potential quadratic trend in the hazard ratios across the CRC risk score groups by including a quadratic term of CRC risk score and a product term between colonoscopy screening and the quadratic CRC risk score. For CRC incidence, the P_{trend} was .73, .80, and .80 for the 3 models, respectively, and the corresponding P_{trends} were .76, .77, and .76 for CRC mortality.

screening and the risk factors influence CRC risk, it is not surprising that we observed relatively consistent hazard ratios of colonoscopy screening for CRC incidence and mortality across the CRC risk score groups. However, given the effect of these risk factors for CRC development and death, individuals with a higher CRC risk score are at a higher risk of developing colorectal precancerous lesions and CRC (65,66). It is thus understandable that colonoscopy screening may confer a greater ARR of CRC incidence and mortality among individuals with higher risk scores compared with lower risk scores.

Our findings have important clinical and public health implications. First, although relative risk is important to determine the effect of screening, ARR is a clinically more important indicator for decision making owing to its indication for determining priorities in health-care services (67). Our findings provide empirical evidence for setting screening priorities among individuals at high risk of CRC. Such evidence is particularly valuable given individuals at a higher risk of CRC tend to have a worse health consciousness and are less likely to undergo screening (68). These data indicate the need for developing actionable risk-based screening strategies to improve health-care delivery for better prevention of CRC. Second, we found that the difference in screening-associated ARR across individuals with different risk profiles was more pronounced for mortality of distal colon and rectal cancers compared with proximal colon cancer. Because the protective effect of endoscopic screening against cancer substantially decreases from the rectum to proximal colon (69), our finding suggests a particular merit of risk-based recommendations for colonoscopy screening for prevention of distal colon and rectal cancers.

The optimal age to start screening represents an important aspect of screening recommendation. The recent recommendations for lowering the starting age of CRC screening in average-risk adults from 50 to 45 years from both the USPSTF and American Cancer Society are based on population-level modeling analysis without accounting for the substantial variations in CRC risk among individuals with different risk profiles (29,30). Given that more than 80% of CRC cases have no family history of CRC (22) and 20% to 70% of CRC cases and deaths could potentially be prevented by modifiable factors, for example, aspirin, BMI, smoking, alcohol, physical activity, and diet (65,70,71), a more comprehensive CRC risk profile including more than

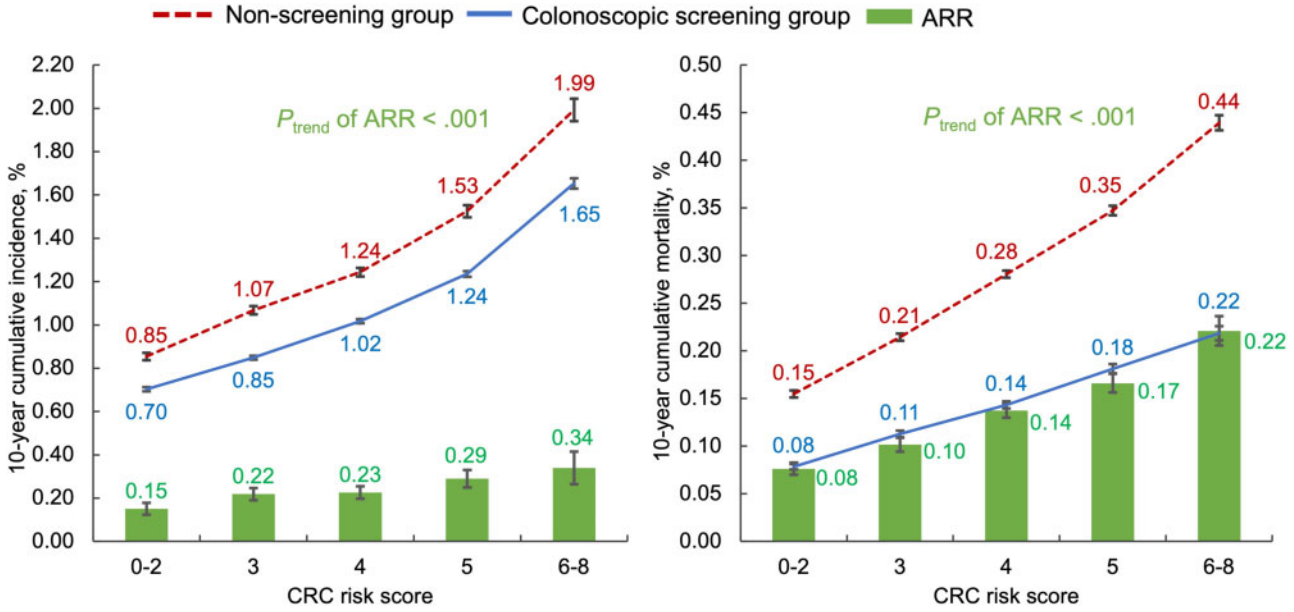

Figure 1. Multivariable-adjusted 10-year cumulative incidence (**left panel**) and mortality (**right panel**) of colorectal cancer (CRC) and the corresponding absolute risk reduction (ARR) according to CRC risk score. CRC risk score (range = 0-8) was defined as the number of the 8 CRC high-risk factors: having a family history of CRC among the first-degree relatives, no regular use of aspirin (<2 tablets or times per week), tall stature (upper 50% of height in each cohort), overweight or obesity (body mass index ≥25.0 kg/m^2), current smoker or past smoker with 5 or more pack-years, low physical activity (<30 min/d of moderate-to-vigorous intensity activity), heavy alcohol intake (≥1 drink [14 g alcohol] per day for women and ≥2 drinks per day for men), and unhealthy diet (meeting <3 of the 6 dietary recommendations by the World Cancer Research Fund/American Institute for Cancer Research Report 2018, which included red meat <0.5 serving per day, processed meat <0.2 serving per day, dietary fiber ≥30 g/d, dairy products ≥3 servings per day, whole grains ≥48 g/d or account for at least one-half of total grains, and calcium supplement use). Trend in the ARRs across CRC risk scores was examined by regressing the multivariable-adjusted cumulative risk on baseline colonoscopy screening status and CRC risk score as well as their product term, whose *P* value was derived as the P_{trend}. The tests were 2-sided. Error bars indicate 95% confidence intervals.

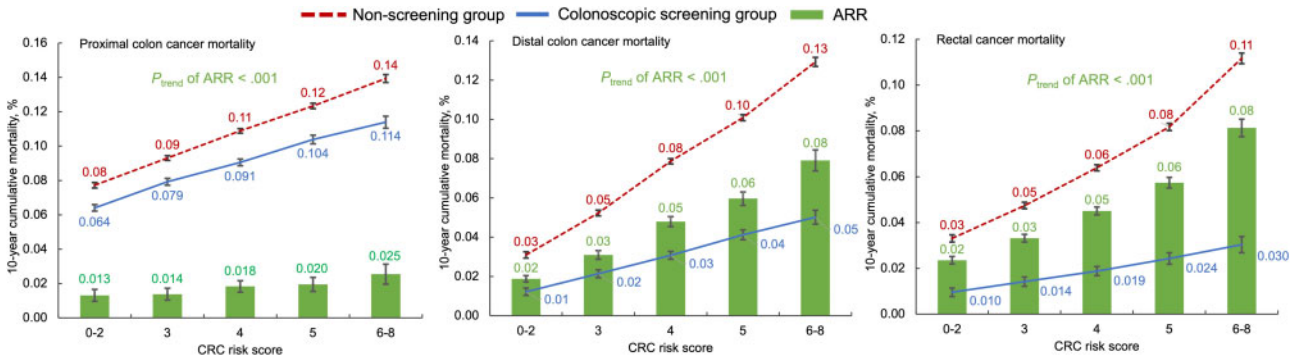

Figure 2. Multivariable-adjusted 10-year cumulative mortality of colorectal cancer (CRC) by subsite and corresponding absolute risk reduction according to CRC risk score. CRC risk score (range = 0-8) was defined as the number of the 8 CRC high-risk factors: having a family history of CRC among the first-degree relatives, no regular use of aspirin (<2 tablets or times per week), tall stature (upper 50% of height in each cohort), overweight or obesity (body mass index ≥25.0 kg/m^2), current smoker or past smoker with 5 or more pack-years, low physical activity (<30 min/d of moderate-to-vigorous intensity activity), heavy alcohol intake (≥1 drink [14 g alcohol] per day for women and ≥2 drinks per day for men), and unhealthy diet (meeting <3 of the 6 dietary recommendations by the World Cancer Research Fund/American Institute for Cancer Research Report 2018, which included red meat <0.5 serving per day, processed meat <0.2 serving per day, dietary fiber ≥30 g/d, dairy products ≥3 servings per day, whole grains ≥48 g/d or account for at least one-half of total grains, and calcium supplement use). Trend in the ARRs across CRC risk scores was examined by regressing the multivariable-adjusted cumulative risk on baseline colonoscopy screening status and CRC risk score as well as their product term, whose *P* value was derived as the P_{trend}. The tests were 2-sided. Error bars indicate 95% confidence intervals.

just family history of CRC may inform more personalized recommendations for the age to start CRC screening. In our current study, individuals with the highest and lowest CRC risk profile may start screening 6-7 years earlier and later, respectively, than age 45 years as recently recommended. This finding has implications for determining the optimal age to start CRC screening among individuals with different risk profiles in the context of the increasing incidence of early-onset CRC (30,72-74). Indeed, there has been an increasing body of evidence by our group and others indicating the potential contribution of lifestyle factors to early-onset CRC (75-79). Further research is needed to evaluate the cost-benefit of the risk profile-based recommendations for earlier or later screening.

Our study has several strengths, including the large sample size, long-term follow-up, and repeated assessments of medical and lifestyle factors and colonoscopy screening. Several limitations should also be noted. First, the information of lifestyle factors and colonoscopy screening was self-reported and thus

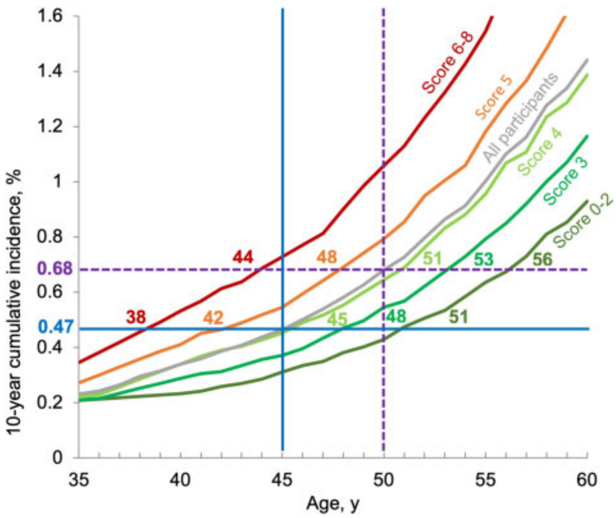

Figure 3. Multivariable-adjusted 10-year cumulative incidence of colorectal cancer (CRC) by age in all participants and according to CRC risk score. The **crossed solid straight lines** indicate the 10-year cumulative incidence of CRC of 0.47% in the whole study population at age 45 years, when CRC screening is recommended to start. The **crossed dash straight lines** indicate the corresponding incidence of 0.68% at age 50 years. Individuals with a CRC risk score of 0-2, 3, 4, 5, and 6-7 reached the age 45 years threshold risk at age 51 years, 48 years, 45 years, 42 years, and 38 years, respectively. CRC risk score (range = 0-8) was defined as the number of the 8 CRC high-risk factors: having a family history of CRC among the first-degree relatives, no regular use of aspirin (<2 tablets or times per week), tall stature (upper 50% of height in each cohort), overweight or obesity (body mass index ≥25.0 kg/m^2), current smoker or past smoker with 5 or more pack-years, low physical activity (<30 min/d of moderate-to-vigorous intensity activity), heavy alcohol intake (≥1 drink [14 g alcohol] per day for women and ≥2 drinks per day for men), and unhealthy diet (meeting <3 of the 6 dietary recommendations by the World Cancer Research Fund/American Institute for Cancer Research Report 2018, which included red meat <0.5 serving per day, processed meat <0.2 serving per day, dietary fiber ≥30 g/d, dairy products ≥3 servings per day, whole grains ≥48 g/d or account for at least one-half of total grains, and calcium supplement use).

subject to measurement error. However, the accuracy of these self-reported data within our cohorts has been well documented (6,80-84). Second, our study participants are health professionals and predominantly Whites, thereby limiting the generalizability of our findings. Nonetheless, because our participants tend to have a healthier risk profile (65), the difference in the absolute benefit of screening across risk profiles is likely to have been underestimated. Third, in the calculation of risk-adapted starting age of screening, we used our cohort population to generate the threshold CRC risk. Because our cohort participants have a healthier profile compared with the general population, we may have underestimated the threshold CRC risk. Also, we acknowledge that there may be possible cohort differences in the effect of lifestyle or screening on CRC, although this should not have influenced our findings for the differences in ages when the threshold risk was reached in different risk groups. Moreover, it is unlikely that the biological effect of the risk factors would be different between our cohort participants and the general population. Nevertheless, further studies in more recent birth cohorts are needed to better investigate the optimal starting age for CRC screening for prevention of early-onset CRC. Additionally, with an ultimate goal of CRC precision prevention, we believe that further efforts are needed to improve the risk assessment tools (to minimize the false negatives), integrate the tool into the electronic health record system (to facilitate the use in the primary care setting), and assess the cost-effectiveness of the risk-based approach compared with the current approach. We acknowledge that there is a long way ahead to realize the promises of CRC precision prevention while believing that our current study provides the proof of principle for that path.

In conclusion, the absolute benefits of colonoscopy screening for the prevention of CRC and related death are more than twice higher for individuals with the highest than lowest CRC risk profile. Individuals with a high and low CRC risk profile may start CRC screening up to 6-7 years earlier and later, respectively, than the recommended age of 45 years or 50 years. Our data support the importance of risk-based screening recommendations.

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Author contributions: Drs. Wang and Song have full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: Chan, Song, Wang. Acquisition, analysis, or interpretation of data: Wang, Song, Chan. Drafting of the manuscript: Wang. Critical revision of the manuscript for important intellectual content: Ma, Wu, Ogino, Giovannucci. Statistical analysis: Wang. Obtained funding: Chan, Song. Administrative, technical, or material support: Chan, Song, Giovannucci. Supervision: Chan, Song.

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Data Availability

The data underlying this article will be shared on reasonable request to the corresponding author. Because of the sensitive nature of the data collected for this study, requests to access the dataset from qualified researchers trained in human subject confidentiality protocols may be sent to Brigham and Women's/Harvard Cohorts at https://docs.google.com/forms/d/e/1FAIpQLScAPV23ZIBpkk9CyEJ1OcFJjMol9elKEpL YnPu7g3PgBL57XA/viewform.

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