Evaluating the Use of Environmental and Polygenic Risk Scores to Inform Colorectal Cancer Risk-Based Surveillance Intervals

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INTRODUCTION: **United States Multi-Society Task Force colonoscopy surveillance intervals are based solely on adenoma characteristics, without accounting for other risk factors. We investigated whether a risk model including demographic, environmental, and genetic risk factors could individualize surveillance intervals under an "equal management of equal risks" framework.**

METHODS: **Using 14,069 individuals from the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial who had a diagnostic colonoscopy following an abnormal flexible sigmoidoscopy, we modeled the risk of colorectal cancer, considering the diagnostic colonoscopy finding, baseline risk factors (e.g., age and sex), 19 lifestyle and environmental risk factors, and a polygenic risk score for colorectal cancer. Ten-year absolute cancer risks for each diagnostic colonoscopy finding (advanced adenomas [N = 2,446], ≥3 non-advanced adenomas [N = 483], 1–2 non-advanced adenomas [N = 4,400], and no adenoma [N = 7,183]) were used as implicit risk thresholds for recommended surveillance intervals.**

RESULTS: **The area under the curve for the model including colonoscopy findings, baseline characteristics, and polygenic risk score was 0.658. Applying the equal management of equal risks framework, 28.2% of individuals with no adenoma and 42.7% of those with 1–2 non-advanced adenomas would be considered high risk and assigned a significantly shorter surveillance interval than currently recommended. Among individuals who developed cancer within 10 years, 52.4% with no adenoma and 48.3% with 1–2 non-advanced adenomas would have been considered high risk and assigned a shorter surveillance interval.**

DISCUSSION: **Using a personalized risk-based model has the potential to identify individuals with no adenoma or 1–2 non-advanced adenomas, who are higher risk and may benefit from shorter surveillance intervals.**

KEYWORDS: colorectal cancer; PLCO; surveillance; adenoma; guidelines

INTRODUCTION

Colorectal cancer (CRC) screening in asymptomatic individuals reduces CRC incidence and mortality through the identification and removal of precancerous adenomatous polyps and through early detection of cancer, leading to better prognosis (1,2). Current guidelines recommend starting screening between ages 45–50 years (3–5). For surveillance following detection of an adenoma, the 2020 United States Multi-Society Task Force (USMSTF) (6) recommend individuals with an adenoma ≥ 10 mm in diameter, tubulovillous or villous histology, or high-grade dysplasia (advanced adenoma) undergo repeat colonoscopy at 3 years, whereas individuals with tubular adenomas < 10 mm in diameter (non-advanced adenoma) are recommended to be re-examined in 3–10 years, depending on the number of adenomas. However, adherence to these guidelines is poor (7), in part due to the presence of other suspected risk factors (e.g.,

family history), the fear of missed polyps or interval cancers, and uncertainty in the strength of evidence for the recommendations.

The inclusion of other risk factors, including genetic and environmental factors, into surveillance recommendations could provide a more individualized risk assessment, with the potential to improve outcomes, efficiency, and cost-effectiveness. Known lifestyle, environmental, and genetic risk factors for CRC have been combined into models for cancer risk (8–11), but it is unclear how to apply these risk models to recommend surveillance intervals following CRC screening. To be consistent with existing practice, one approach is to utilize implicit risk thresholds to inform surveillance intervals; this approach has been successfully implemented for cervical cancer screening (12,13). The 10-year absolute CRC risk for colonoscopy findings (i.e., advanced adenoma, ≥ 3 non-advanced adenomas, 1–2 non-advanced adenomas, and no adenoma) can serve as implicit risk thresholds for recommended surveillance intervals. Using the risk model, one can calculate each person's CRC risk and assign them to an interval consistent with their risk. This allows equal management of equal risks (14), such that the surveillance interval assigned based on the risk computed by a risk model that includes environmental and lifestyle and/or genetic factors is consistent with the surveillance interval that would be assigned to someone with the same estimated risk from adenoma characteristics alone.

We therefore aimed to determine whether lifestyle and environmental and/or genetic risk factors predicted future CRC risk among individuals with an abnormal flexible sigmoidoscopy screen who completed a diagnostic colonoscopy examination. We used a previously validated lifestyle and environmental score (e-score) based on known CRC risk factors (11) and a polygenic risk score (PRS) derived from genome-wide association studies to predict risk. Our goal was to evaluate the potential utility of using these environmental and genetic risk scores to inform surveillance intervals.

METHODS
This study included individuals from the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial (15,16), which enrolled approximately 155,000 individuals aged 55–74 years from 10 centers in the United States between 1993 and 2001. The National Cancer Institute and each center's Institutional Review Board approved the protocol, and all study participants provided written informed consent. Information on demographic, lifestyle, environmental, and dietary risk factors was collected at baseline using questionnaires. Individuals randomized to the intervention arm (N = 77,465) were offered a flexible sigmoidoscopy at baseline and at either 3 years (before April 1995) or 5 years after randomization. Individuals with an abnormal flexible sigmoidoscopy were referred to their physician for follow-up, and their medical records were abstracted for subsequent diagnostic workup. Individuals with an inadequate flexible sigmoidoscopy (<50-cm depth of insertion or visual inspection limited to < 90% of the mucosal surface due to inadequate bowel preparation, with no detection of a polyp or mass) were invited for a repeat flexible sigmoidoscopy (17); approximately 8.1% of PLCO participants had an inadequate screen (18). This study was limited to participants with an abnormal flexible sigmoidoscopy, defined as a screen with visible or palpable evidence of mucosal abnormality, rectal nodules, rectal or colon masses, and rectal or colon polyp(s). Individuals with screen-detected abnormalities were referred to their physician for follow-up (with colonoscopy referral optional for diverticulosis and other noncancer-related abnormalities); their medical records were abstracted for subsequent diagnostic workup (15,17). In total, 15,512 participants in the intervention arm completed a baseline questionnaire, had an abnormal flexible sigmoidoscopy at either the baseline or follow-up screen, and underwent a follow-up diagnostic colonoscopy. Adenomas were classified as non-advanced (tubular adenomas < 10 mm in size) or advanced (tubulovillous or villous histology, high-grade dysplasia, or ≥ 10 mm in size). Participants were classified according to their worst finding on the colonoscopy.

Follow-up
Cancer incidence was ascertained from annual study questionnaires and confirmed by medical record abstraction for cancer diagnoses through 2009, after which information on cancer incidence was collected via passive linkage to cancer registries through December 31, 2016 (19). Mortality was assessed through linkage to the National Death Index through December 31, 2018.

Genotyping and PRS
As described previously (20), PLCO participants were genotyped on a high density single nucleotide polymorphism (SNP) array and imputed to the TOPMed reference panel. Because of limited statistical power to evaluate risk in other ancestries, this analysis was restricted to individuals of European ancestry with genotyping available (N = 14,313).

A genome-wide PRS for CRC was generated using GCTB SBayesR (v2.03beta) (21,22) and genome-wide association study (GWAS) summary statistics from the GECCO Consortium (23), excluding individuals from PLCO to generate unbiased weights. This PRS, which included 455,995 SNPs, was applied to the PLCO cohort. As a sensitivity analysis, we additionally considered a PRS based only on published loci (23) (including 194 of 205 reported SNPs). PRS quartiles were based on the distribution in the full cohort.

Lifestyle and environmental risk score
Using data collected from baseline risk factor and dietary questionnaires, a lifestyle and environmental risk score (e-score) was calculated for each individual based on the model developed by Jeon et al (11). The Supplement contains details on the variables included and how they were combined to form the e-score (Supplementary Table 1, Supplementary Digital Content 1, http://links.lww.com/CTG/B219). Sex-specific quartile cut points for the e-score were generated using the distribution of the entire cohort.

Statistical methodology
Kaplan-Meier survival analyses for CRC risk were performed to examine crude associations with screening colonoscopy result, PRS, and e-score. Cox proportional hazard models were used to model CRC risk, adjusting for age, sex, previous self-reported CRC screening in the past 3 years, family history of CRC, and genotyping platform (baseline characteristics). Individuals were censored at the earliest of CRC diagnosis, death, or end of follow-up. Five models were developed for CRC risk based on (i) colonoscopy findings, (ii) colonoscopy findings + baseline characteristics, (iii) colonoscopy findings + baseline characteristics + e-score, (iv) colonoscopy findings + baseline

characteristics + PRS, and (v) colonoscopy findings + baseline characteristics + e-score + PRS. The area under the curve (AUC) was calculated for each model to assess the models' ability to discriminate between individuals who did and did not develop CRC within 10 years. A two-sided P value < 0.05 was considered statistically significant.

To inform whether a different surveillance interval would be assigned based on the modeled risk compared with their colonoscopy result, we first determined each participant's recommended surveillance interval based on their colonoscopy results under the USMSTF recommendations. Because of small sample size, participants with ≥ 3 non-advanced adenomas were combined. We used Kaplan-Meier models to estimate the 10-year CRC risk for individuals with each colonoscopy finding (i.e., no adenoma, 1–2 non-advanced adenomas, ≥ 3 non-advanced adenomas, or advanced adenoma). These 10-year risks were then used as thresholds to assign surveillance intervals to each individual based on the USMSTF recommendations (Supplementary Table 2, Supplementary Digital Content 1, http://links.lww.com/CTG/B219). Individuals whose modeled risk was below the estimated risk of individuals with no adenoma (very low risk) were assigned a 10-year surveillance interval; individuals with a risk between the risk of individuals with no adenoma and individuals with 1–2 non-advanced adenomas (low risk) were assigned a 7-10-year surveillance interval; individuals with a risk between the risk of individuals with 1–2 non-advanced adenomas and ≥ 3 non-advanced adenomas (moderate risk) were assigned a 3-7-year surveillance interval; individuals with a risk between the risk of individuals with ≥ 3 non-advanced adenomas and an advanced adenoma (high risk) were assigned a 3-yearly interval, and individuals with a risk above individuals with an advanced adenoma (very high risk) were assigned a 1-3-year surveillance interval. The proportion of individuals assigned a different surveillance interval was calculated for all individuals in the study and for individuals who developed CRC within 10 years.

Levels of missing data were low ($< 7\%$), so median and mean imputation was performed for categorical and continuous variables, respectively (see Supplement for more details, including levels of missing data for each variable, Supplementary Table 3, Supplementary Digital Content 1, http://links.lww.com/CTG/B219). A complete case analysis was performed as a sensitivity analysis.

RESULTS

Of the 14,313 individuals with an abnormal flexible sigmoidoscopy result who attended colonoscopy, 244 were excluded because they were diagnosed with CRC within 60 days of their sigmoidoscopy (N = 28) or had > 12 months between their sigmoidoscopy and diagnostic colonoscopy (N = 216), leaving 14,069 individuals for analysis (Figure 1, Table 1). Approximately 17% (N = 2,446) had an advanced adenoma detected on their colonoscopy, 32% (N = 4,440) had a non-advanced adenoma (N = 3,957 [28%] with 1–2 adenomas and N = 483 [3%] with ≥ 3 adenomas), and 51% had no adenoma (N = 7,183).

The median follow-up for CRC incidence after colonoscopy was 15.3 years (IQR: 12.2–18.7 years). A total of 116 individuals (1.6%) were diagnosed with CRC within 10 years, with 40% (N = 46) diagnosed within 5 years of their initial diagnostic colonoscopy following an abnormal flexible sigmoidoscopy. Among those who developed CRC within 10 years, 35% (N = 41) had an advanced adenoma, 28% (N = 33) had a non-advanced adenoma (including 25% [N = 29] with 1–2 non-advanced adenomas), and 36% (N = 42) had no adenoma on their initial colonoscopy.

CRC risk varied by diagnostic colonoscopy finding (log-rank test $P < 0.001$), with a higher risk observed for individuals with advanced adenomas (Figure 2a); individuals with a higher PRS were also at increased risk ($P = 0.002$, Figure 2b); however, no significant difference in CRC risk was observed by e-score quartile ($P = 0.7$, Figure 2c).

In multivariate models including baseline characteristics and baseline colonoscopy result, there was no significant association between e-score and risk of CRC; however, higher PRS was associated with an increased risk of CRC ($HR_{per\ quartile\ increase}$ = 1.22, 95% CI: 1.08–1.38, Table 2), resulting in an hazard ratio (HR) of 1.81 for individuals in the highest PRS quartile compared with the lowest quartile. When PRS was considered as a continuous variable, standardized to have a mean of 0 and SD of 1, each SD increase in PRS was associated with an HR of 1.29 (95% CI: 1.11–1.50). The 10-year AUC for the model including only colonoscopy findings was 0.606; adding baseline characteristics increased the AUC to 0.648. The AUC was slightly higher for the models including PRS (0.658). There was no difference between the AUCs of the models including and excluding the e-score (0.649 vs 0.648). Complete case results were very similar, with AUCs approximately 0.02 higher (Supplementary Table 4, Supplementary Digital Content 1, http://links.lww.com/CTG/B219).
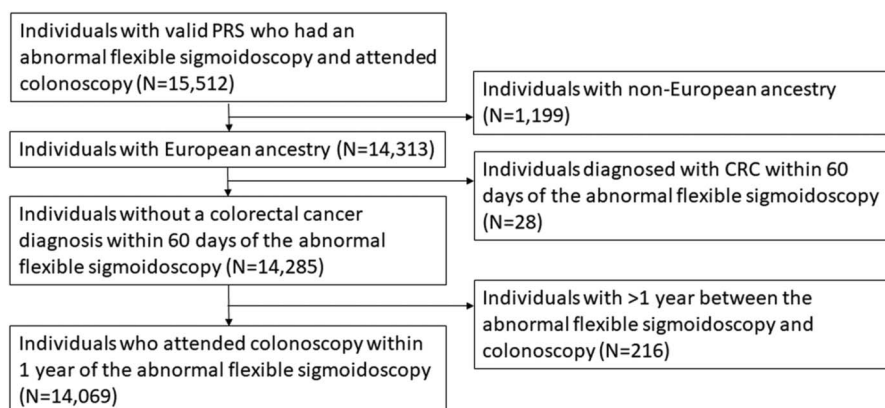
Figure 1. Consolidated Standards of Reporting Trials flowchart for inclusion in the study population. CRC, colorectal cancer; PLCO, Prostate, Lung, Colorectal, and Ovarian; PRS, polygenic risk score.
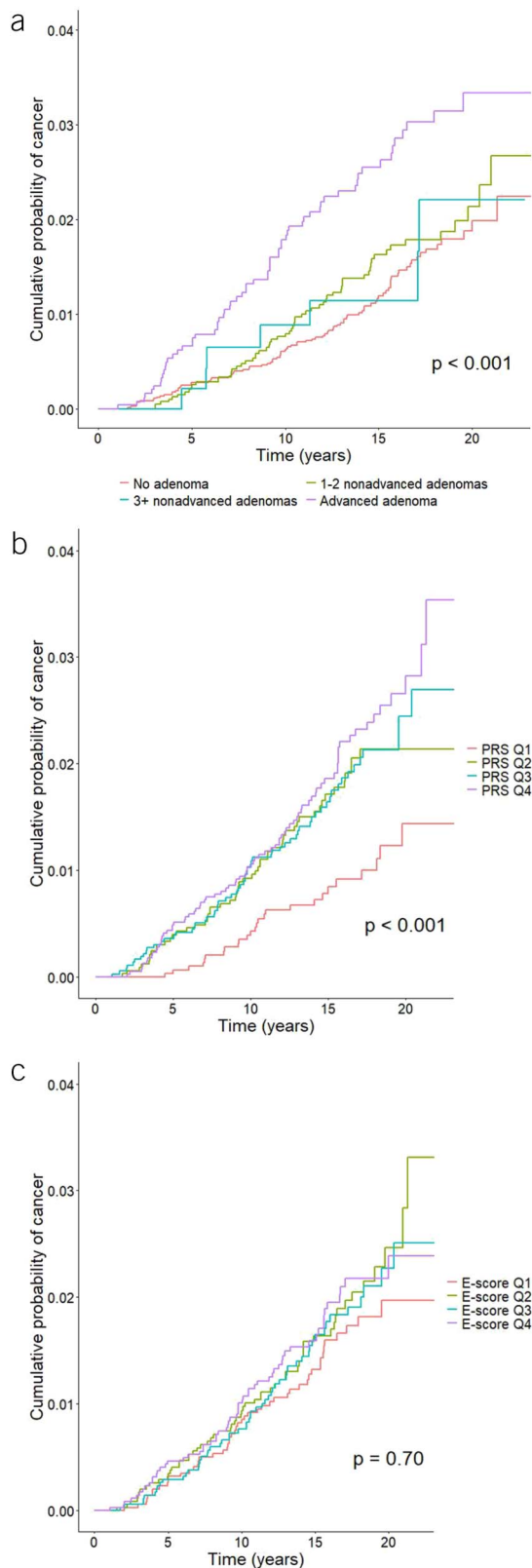
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Figure 2. Cumulative probability of colorectal cancer by (**a**) colonoscopy result, (**b**) PRS quintile, and (**c**) lifestyle and environmental risk score (e-score) quartile. PRS, polygenic risk score.

In our study, the 10-year CRC risk for individuals who had no adenoma, 1–2 non-advanced adenomas, ≥ 3 non-advanced adenomas, and an advanced adenoma were 0.62% (95% CI: 0.43%–0.81%), 0.79% (95% CI: 0.50%–1.08%), 0.89% (95% CI: 0.02%–1.75%), and 1.79% (95% CI: 1.12%–2.23%), respectively. Under an equal management of equal risks framework and using the model with PRS (Model 4), over a quarter (28.2%) of individuals with no adenoma would be considered high or very high risk and assigned a shorter surveillance interval of ≤ 3 years, since their 10-year estimated absolute CRC risk exceeded those with ≥ 3 non-advanced adenomas (i.e., ≥ 0.89%), compared with 10 years under the USMSTF Recommendations (Figure 3, Supplementary Table 5, Figure S1, Supplementary Digital Content 1, http://links. lww.com/CTG/B219). Similarly, 42.7% of individuals with 1–2 non-advanced adenomas would be considered high or very high risk and assigned a shorter surveillance interval of ≤ 3 years, compared with 7–10 years under the USMSTF Recommendations. Over half the individuals with ≥ 3 non-advanced adenomas (51.8%) had a 10-year estimated absolute risk < 0.79% and would therefore be considered low or very low risk and assigned a longer surveillance interval of 7–10 years. One in 8 individuals (12.6%) with an advanced adenoma would be considered low or very low risk (10-year estimated absolute risk < 0.79%) and assigned a longer surveillance interval of 7–10 years. The results were similar for the model with baseline characteristics (Model 2, Supplementary Tables 4 and 5, Supplementary Digital Content 1, http://links.lww.com/CTG/B219), as well as for the complete case analyses (Supplementary Tables 4 and 6, Supplementary Digital Content 1, http://links.lww.com/CTG/B219).

To understand how these changes in surveillance intervals might affect CRC, we restricted our analysis to the 116 individuals who developed CRC within 10 years (Figure S3, Supplementary Digital Content 1, http://links.lww.com/CTG/B219). Overall, 33.6% of these individuals would have been considered higher risk than their colonoscopy result alone suggested (Supplementary Table 7, Supplementary Digital Content 1, http://links.lww. com/CTG/B219) and would therefore have been assigned a shorter surveillance interval under the risk model including PRS (Model 4) as well as the model with only baseline characteristics (Model 2). Approximately 13.8% would have been assigned a longer surveillance interval under the risk model with PRS (Model 4), with slightly fewer (11.2%) for the baseline risk model (Model 2) (Supplementary Table 7, Supplementary Digital Content 1, http://links.lww.com/CTG/B219).

Under the model with PRS (Model 4), 52.4% of CRC cases with no adenoma on colonoscopy and 48.3% of CRC cases with 1–2 non-advanced adenomas would have been considered high or very high risk (10-year estimated absolute risk ≥ 0.89%) and assigned a shorter surveillance interval of ≤ 3 years (Figure S2, Supplementary Table 5, Supplementary Digital Content 1, http:// links.lww.com/CTG/B219). In addition, 90.2% of individuals with advanced adenomas who subsequently developed cancer within 10 years would have been considered high or very high risk and assigned a surveillance interval of ≤ 3 years under the model with PRS (Model 4). No individuals with advanced adenomas assigned to 10-year surveillance interval developed CRC within 10 years. Similar results were observed for the model containing only baseline characteristics (Model 2).

Table 1. Descriptive characteristics of the 14,069 individuals from the PLCO Cancer Screening Trial, who had a diagnostic colonoscopy and met the inclusion criteria for this study

	Advanced adenoma		3+ non-advanced adenoma		1–2 non-advanced adenoma		No adenoma		Total	
	N	%	N	%	N	%	N	%	N	%
Total	2,446	17	483	3	3,957	28	7,183	51	14,069	100
Sex										
Male	1,652	68	360	75	2,514	64	3,927	55	8,453	60
Female	794	32	123	25	1,443	36	3,256	45	5,616	40
Age at colonoscopy (yr)										
55–59	518	21	81	17	791	20	1,410	20	2,800	20
60–64	796	33	191	40	1,373	35	2,602	36	4,962	35
65–69	668	27	128	27	1,069	27	1,918	27	3,783	27
70–74	396	16	70	14	591	15	1,016	14	2073	15
≥75	68	3	13	3	133	3	237	3	451	3
Family history										
Yes	310	13	59	12	438	11	785	11	1,592	11
No	2,059	84	406	84	3,376	85	6,146	86	11,987	85
Unknown	77	3	18	4	143	4	252	4	490	3
Smoking status										
Never	903	37	163	34	1,575	40	2,799	39	5,440	39
Current	366	15	77	16	548	14	1,015	14	2,006	14
Former	1,177	48	243	50	1,834	46	3,369	47	6,623	47
BMI, median (IQR)	27.2 (24.6, 30.3)		27.3 (24.7, 30.3)		27.6 (25.1, 30.7)		27.1 (24.4, 30.1)		27.1 (24.6, 30.2)	
Aspirin and/or ibuprofen use in past 12 mo										
Yes	1,376	56	283	59	2,376	60	4,354	61	8,389	60
No	1,070	44	200	41	1,581	40	2,829	39	5,680	40
Prior self-reported endoscopy[a]										
Yes	746	30	184	38	1,695	43	3,447	48	6,072	43
No	1,700	70	299	62	2,262	57	3,736	52	7,997	57
First positive FSG										
Baseline	1,814	74	338	70	2,509	63	4,171	58	8,832	63
Year 3	128	5	25	5	267	7	468	7	888	6
Year 5	504	21	120	25	1,181	30	2,544	35	4,349	31
e-score										
Quartile 1 (lowest)	556	23	117	24	967	24	1,877	26	3,517	25
Quartile 2	586	24	106	22	1,034	26	1,791	25	3,517	25
Quartile 3	627	26	121	25	990	25	1,779	25	3,517	25
Quartile 4 (highest)	677	28	139	29	966	24	1,736	24	3,518	25
PRS										
Quartile 1 (lowest)	454	19	99	20	969	24	1,972	27	3,494	25
Quartile 2	509	21	124	26	1,060	27	1,932	27	3,625	26
Quartile 3	590	24	149	31	1,110	28	1,959	27	3,808	27
Quartile 4 (highest)	893	37	111	23	818	21	1,320	18	3,142	22
Length of follow-up, median (IQR) (yr)	15.9 (12.1–19.0)		15.5 (12.2–18.7)		15.4 (12.5–18.9)		15.1 (12.2–18.5)		15.3 (12.2–18.7)	

BMI, body mass index; e-score, environmental risk score; FSG, flexible sigmoidoscopy; IQR, interquartile range; PLCO, Prostate, Lung, Colorectal, and Ovarian; PRS, polygenic risk score.

[a]Individuals whose first positive flexible sigmoidoscopy was at year 3 or 5 and attended the baseline screen in PLCO were considered to have a prior endoscopy.

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Table 2. Hazard ratios (95% CI) of risk factors associated with colorectal cancer under different models[a]

	Model 1: Colonoscopy result			Model 2: Model 1 + baseline characteristics			Model 3: Model 2 + e-score			Model 4: Model 2 + PRS			Model 5: Model 2 + e-score + PRS		
	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value
PRS quartile										1.22	1.08, 1.38	0.002	1.22	1.08, 1.38	0.002
e-score quartile							1.06	0.95, 1.20	0.308				1.06	0.94, 1.20	0.314
Age				1.06	1.03, 1.08	<0.001	1.06	1.03, 1.09	<0.001	1.06	1.03, 1.09	<0.001	1.06	1.03, 1.09	<0.001
Sex															
Male					1 (ref)			1 (ref)			1 (ref)			1 (ref)	
Female				0.98	0.74, 1.29	0.870	0.98	0.74, 1.29	0.859	0.97	0.73, 1.28	0.818	0.97	0.73, 1.28	0.810
Prior self-reported endoscopy[b]															
No					1 (ref)			1 (ref)			1 (ref)			1 (ref)	
Yes				0.97	0.72, 1.30	0.829	0.97	0.73, 1.31	0.858	0.98	0.73, 1.31	0.879	0.98	0.73, 1.32	0.906
Family history of colorectal cancer															
No					1 (ref)			1 (ref)			1 (ref)			1 (ref)	
Yes				1.17	0.79, 1.72	0.436	1.16	0.79, 1.71	0.448	1.13	0.77, 1.66	0.547	1.12	0.76, 1.65	0.558
Unsure				0.82	0.36, 1.86	0.638	0.81	0.36, 1.84	0.621	0.81	0.36, 1.84	0.619	0.81	0.36, 1.82	0.601
Diagnostic colonoscopy result															
Advanced adenoma	2.56	1.70, 3.85	<0.001	2.45	1.62, 3.69	<0.001	2.43	1.61, 3.67	<0.001	2.32	1.53, 3.50	<0.001	2.30	1.52, 3.48	<0.001
Adenoma: 3+	1.13	0.52, 2.44	0.752	1.12	0.52, 2.41	0.781	1.11	0.51, 2.40	0.789	1.07	0.49, 2.31	0.872	1.06	0.49, 2.30	0.881
Adenoma: 1-2	1.20	0.87, 1.66	0.272	1.19	0.86, 1.65	0.301	1.19	0.86, 1.65	0.297	1.16	0.84, 1.61	0.368	1.16	0.84, 1.61	0.365
No adenoma		1 (ref)			1 (ref)			1 (ref)			1 (ref)			1 (ref)	
AUC at 10 yr[c]		0.606			0.648		0.649			0.658			0.658		

AUC, area under the curve; HR, hazard ratio; PLCO, Prostate, Lung, Colorectal, and Ovarian; PRS, polygenic risk score.
[a]All models were additionally adjusted for genotyping platform.
[b]Individuals whose first positive flexible sigmoidoscopy was at year 3 or 5 and attended the baseline screen in PLCO were considered to have a prior endoscopy.
[c]The AUCs at 10 yr exclude genotyping platform.

Among all individuals in this study (Supplementary Table 7, Supplementary Digital Content 1, http://links.lww.com/CTG/B219), both those who did and did not develop CRC within 10 years, 31.0% would be assigned a shorter surveillance interval when PRS was included in the risk model (Model 4), with similar results for the baseline risk model (Model 2). Using the midpoint of each surveillance interval, the mean time until the first surveillance visit among all individuals in this study would be 6.32 years when PRS was included in the risk model (Model 4) compared with 8.13 years under the USMSTF Recommendations, implying more surveillance colonoscopies would be carried out using risk-based surveillance intervals.

We additionally constructed a model using a PRS based only the published loci (23) (Model 6); results were very similar (Supplementary Table 8, Supplementary Digital Content 1, http://links.lww.com/CTG/B219). Among individuals who developed CRC within 10 years, 34.5% would be assigned a shorter surveillance interval under the model using PRS with published loci (Supplementary Table 7, Supplementary Digital Content 1, http://links.lww.com/CTG/B219), compared with 33.6% for the original genome-wide PRS model (Model 4).

DISCUSSION

Our study explored the potential benefit of including genetic and lifestyle/environmental risk factors as well as other baseline characteristics into a risk assessment model to recommend colorectal surveillance intervals following colonoscopy. PRS was a statistically significant predictor of CRC risk after accounting for colonoscopy result, with a hazard ratio of 1.81 for individuals in the highest quartile compared with the lowest, whereas the lifestyle and environmental risk score was not significant. Although the discrimination was moderate for all models evaluated, including baseline characteristics (e.g., age) and, to a lesser extent, PRS, improved the model's ability to discriminate between individuals who did and did not develop CRC compared with the model only containing colonoscopy findings. Using either the PRS or baseline risk model, a substantial proportion of individuals would be moved to more frequent surveillance because of an estimated increase in risk (e.g., 28.2% of individuals with no adenoma would be assigned a surveillance interval of ≤3 years using the PRS model). A small portion of individuals under the PRS model had substantially lower estimated risk than their colonoscopy result would imply (e.g., 4.4% of individuals with advanced adenomas were classified as very low risk), and a long surveillance interval would be recommended under this model.

Risk-stratified screening and/or surveillance using genetic or lifestyle/environmental factors has the potential to improve efficiency and cost-effectiveness, as well as reduce harms among low-risk individuals and allow limited resource settings to make the best use of their resources (24,25). In this study, if individuals were assigned surveillance intervals based on their estimated cancer risk, many more people would be assigned a shorter surveillance interval, which may not always be feasible; however, different risk thresholds could be used for determining
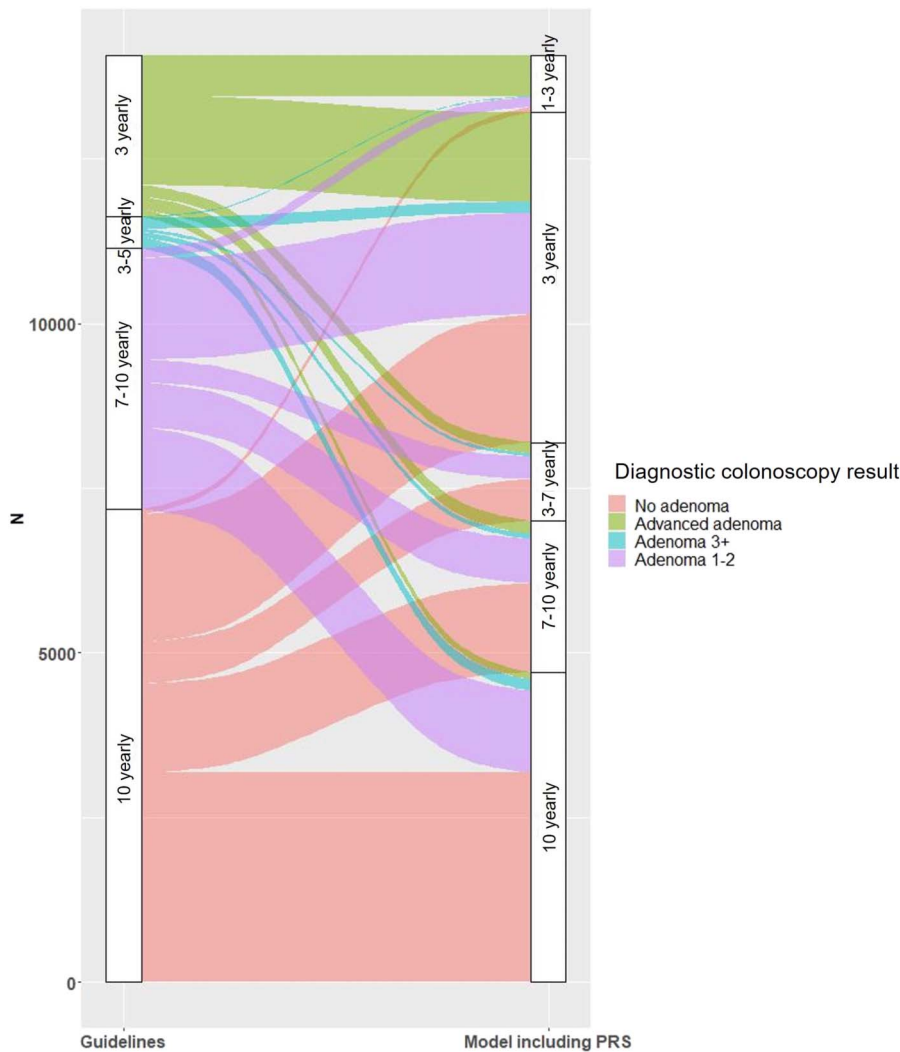
Figure 3. Screening intervals for the full population under the US Multi-Society 2020 Task Force Recommendations on the left and the model containing colonoscopy findings, baseline characteristics, and PRS on the right. PRS, polygenic risk score.

surveillance intervals based on available resources. We used implicit risk thresholds from current surveillance guidelines to demonstrate the principle of risk-based surveillance, but these may not be the optimal thresholds for guiding clinical management. Previous work considered what proportion of colorectal cancers in the PLCO intervention arm which were not screen-detected could have been detected at screening; with a mean follow-up of 11.5 years, they estimated that almost half the cancers could not have been detected at screening, with another 27% considered prevalent but not detected (26).

Current surveillance recommendations in the United States depend only on characteristics of adenomas identified at colonoscopy (6); however, CRC risks have been shown to differ by PRS among individuals with low-risk and high-risk adenomas (27). Although cohort studies have suggested that individuals with low-risk adenomas do not have an increased risk of CRC compared with individuals with no adenoma (28–30), these studies cannot account for surveillance colonoscopy and adenoma removal, which reduces CRC incidence (31,32). Randomized trials of surveillance colonoscopy at 5 and 10 vs 10 years in individuals with 1–2 non-advanced adenomas are underway (33,34) which should help clarify CRC risk in the absence of

surveillance. We found that 3.8% of individuals with 1–2 non-advanced adenomas have an estimated 10-year absolute risk that exceeds the average risk for individuals with advanced adenoma, suggesting substantial heterogeneity in risk among those with non-advanced adenoma. We note that family history was not a significant predictor in this model, despite being associated with CRC incidence and mortality in the PLCO in an earlier study (35). This was also true when family history was the only variable in the model (HR = 1.18, 0.80–1.74), which suggests that among individuals with an abnormal flexible sigmoidoscopy, family history is not a strong predictor of cancer risk. There may be benefits of incorporating other risk factors into the risk assessment to identify those at high risk; however, the benefits of shortening surveillance intervals for individuals traditionally considered to be low risk must be balanced against harms, as the majority will not develop cancer.

In practice, any advantage of including PRS in models may be outweighed by the logistical and financial challenges involved with generating genetic scores in the population eligible for CRC surveillance; however, genotyping costs have substantially decreased over the last decade and the same genetic data can be used to predict many common complex diseases and inform

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preventive interventions, such as statin treatment, diabetes prevention, or screening for other cancers (36). As such, PRS may be broadly used in health care in the next decade.

Our study has some limitations. For most participants, we do not know what screening or polypectomies took place following the trial. These practices can reduce the risk of CRC; previous work showed a 44% reduction in cancer incidence from a single surveillance visit (31). However, our data represent real-life clinical practice in the United States. In addition, individuals who had no adenoma detected on colonoscopy in this study are not necessarily representative of all individuals without adenoma since they all had an abnormal flexible sigmoidoscopy prior to colonoscopy. However, the 10-year CRC risk among PLCO intervention arm participants who had a negative flexible sigmoidoscopy at baseline was 0.81%, comparable with the 0.62% observed among individuals with no adenoma with abnormal sigmoidoscopy in this analysis. Because of small numbers of racial and ethnic minority individuals in the PLCO, we were unable to accurately assess risk in these populations and had to limit our analysis to individuals with European ancestry. As a result, the generalizability of our study to other populations is limited; future studies involving more diverse populations are warranted.

Our study had many strengths. We prospectively followed > 14,000 individuals who underwent colonoscopy for a median of 15.3 years, allowing us to compare the predictive ability of a lifestyle and environmental risk score and PRS together with baseline questionnaire data. The detailed information on adenomas allowed us to accurately categorize individuals according to risk, and the high-quality long-term follow-up for CRC incidence and death allowed us to assess 10-year risks. PLCO participants were healthy individuals recruited across the United States and randomly assigned to screening, making the PLCO more representative of the general population than a clinical-based study. We provided absolute risk estimates, in addition to relative risks, allowing the comparison of surveillance intervals based on adenoma characteristics with those based on risk estimates. Finally, we were able to show, using an equal management of equal risks framework, how an individualized risk assessment using baseline characteristics and PRS may be beneficial in identifying those at high risk for more frequent surveillance.

In conclusion, we have demonstrated that the use of a risk model containing additional information beyond colonoscopy findings has the potential to change surveillance recommendations for a substantial proportion of individuals. Our study is one of the first to demonstrate the potential utility of using baseline characteristics as well as PRS to guide colorectal surveillance intervals after CRC screening. More prospective studies and randomized trials are required before clinical implementation of personalized risk-based surveillance decisions, but this study suggests that the incorporation of individual risk factors may be beneficial.

CONFLICTS OF INTEREST

Study Highlights

WHAT IS KNOWN

✓ Current surveillance guidelines for individuals with colorectal adenomas depend only on adenoma characteristics such as number and size.

WHAT IS NEW HERE

✓ Adding age, sex, colonoscopy history, and family history improves colorectal cancer risk prediction beyond colonoscopy findings.

✓ This could be useful for assigning surveillance intervals.

✓ Adding a genetic risk score slightly further improves colorectal cancer risk prediction, whereas the lifestyle and environmental risk score does not contribute additional information.

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