SUPPLEMENTARY MATERIALS

Supplementary Methods

Harmonization of lifestyle and environmental data
Data harmonization procedures using a standardized protocol were carried out at the coordinating center at the Fred Hutchinson Cancer Center in Seattle, WA. The iterative data harmonization process took into account all individual study protocols and data collection methodologies. In summary, the first step of the data harmonization process consisted of defining common data elements (CDEs), which were used to map study-specific data elements. These CDEs were then transformed and grouped into one common dataset with uniform definitions and coding, and standardized values within a predefined range. Outlying values were reclassified according to the minimum or maximum permissible value for each respective variable. The final dataset was reviewed for quality assurance.

Assessment of Lifestyle and Environmental Variables
Information on demographics, lifestyle, dietary, and pharmacological factors were ascertained through self-report by means of in-person interviews and/or structured questionnaires. All self-reported variables were collected at the reference time of each respective study, defined as blood collection or participant selection for cohort studies, and approximately 1-2 years preceding participant selection for case-control studies. Among studies that captured height and BMI through direct measurement, these variables were ascertained at the reference time for each corresponding study. In order to ensure congruence of risk factors across studies, a multi-phase, iterative harmonization process was undertaken for all included data. Lastly, we performed sex- and study-specific mean imputation to address any missing data for the included risk factors.

Height
Height was estimated in centimeters using data from self-report, and was rescaled to represent increments of 10 cm.

Body mass index
Body mass index (BMI) was defined using data from self-report of body weight (kg) and height (m^2). BMI was rescaled to represent increments of 5 kg/m^2 (i.e., BMI/5), and BMI estimates <18.5 were recategorized as missing.

Educational attainment
Highest level of educational attainment was defined based on the highest level achieved, and categorized as follows: less than high school degree, high school degree or completed GED, some college or technical school, and college or graduate degree.

Diabetes
Type 2 diabetes was defined as a binary yes/no variable based on self-report.

Sedentary lifestyle
Sedentary lifestyle was retrospectively calculated by summing the hours per week of moderate and/or vigorous physical exercise, activity during leisure-time, and undifferentiated activities. Undifferentiated activities consisted of the following tasks: housework, gardening, walking, cycling, and physical exercise (e.g., aerobics, swimming, jogging, tennis, line dancing). After summation, the variable was categorized as "no" if the total sum was ≥1 hour/week, and "yes" if total sum was <1 hour/week.

Pack-years of smoking

Pack-years of smoking were estimated by multiplying the mean number of cigarette packs smoked per day by smoking duration in years, and were harmonized across studies using sex- and study-specific quartiles. Quartile cutoffs were based on study-specific distribution within the sex-specific controls. This variable was categorized as follows: "0" assigned for never-smokers, "1" assigned for ≤ first quartile, "2" assigned for > first quartile but ≤ second quartile, "3" assigned for > second quartile but ≤ third quartile, and "4" assigned for > third quartile. In all analyses, pack-years of smoking was modelled as continuous variable.

Alcohol consumption

Alcoholic beverage consumption, represented by the grams of alcohol intake per day (g/day), was estimated by summing the daily intake of alcohol content per beverage. Individuals were subsequently categorized as follows: non- and occasional drinkers (< 1 g/day), light-to-moderate drinkers (1-28 g/day), and heavy drinkers (>28 g/day).

Aspirin use

Aspirin use was a binary variable and grouped as "yes" if an individual regularly used aspirin in the reference time period, and "no" otherwise.

Nonsteroidal anti-inflammatory drug use

Nonsteroidal anti-inflammatory drug (NSAID) use was a binary variable and grouped as "yes" if an individual regularly used non-aspirin NSAIDs in the reference time period, and "no" otherwise.

Dietary factors

Dietary variables were evaluated according to food frequency questionnaires (FFQs) or diet history. Fruit, vegetable, red meat, and processed meat consumption were measured by servings per day. While, fiber intake was expressed in terms of grams per day (g/day), total folate intake as micrograms per day (μg/day), and total calcium intake as milligrams per day (mg/day). Total calcium intake (mg/day) was determined using both the mg/day of calcium consumption in foods (i.e., dietary) and through dietary supplements (i.e., single, multivitamins, and antacids), when available. Among studies that registered dietary supplement data as "regular user" versus "nonuser", regular use of calcium supplements was assumed to be 500 mg/day, 500 mg/single tablet, or 130 mg/multivitamin tablet (i.e., the generic dose in supplements). Folate and folic acid consumption were determined based on μg/day of folate from foods (i.e., dietary folate) and μg/day of folic acid through dietary supplements (i.e., single or multivitamins), when available. In order to account for the greater bioavailability of synthetic folic acid compared with dietary folate intake, we estimated total folate intake using dietary folate equivalents (DFE), in which total μg DFE were equal to the sum of μg of dietary folate and 1.7 times the μg folic acid from dietary supplements. Further, since enrollment periods for several studies coincided or followed the inception period of folic acid fortification (1996-1998), these studies accounted for folic acid fortification when calculating DFE by entering dietary folate intake as the sum of μg of dietary folate due to natural sources and 1.7 times the μg folic acid from fortified foods. Among studies that registered dietary supplement data as "regular user" versus "nonuser", regular use of folic acid supplements was assumed to be 400 μg/day or 400 μg/multivitamin tablet (i.e., the generic dose in supplements). Dietary variables were harmonized across studies using sex- and study-specific quartiles, with quartile cutoffs based on the distribution within the sex-specific controls of each respective study, and modelled as continuous factors. For studies with reduced variation in dietary intake, likely resulting from fewer dietary-related questions, dietary factors were only assigned to the 2nd and 3rd quartiles. Lastly, total energy consumption was defined as a continuous variable in in kcal/day and rescaled using its standard error.

Family history of CRC

A positive family history of CRC was characterized as having one or more first-degree relatives diagnosed with CRC.

Supplementary Tables

Supplementary Table 1. Study descriptions[a]

Study Name	Design	Country	Reference Time	Cases	Controls
Colon Cancer Family Registry (CCFR[b])	Case-control	Canada, Australia, and United States	1996-2009	1,934	986
Colorectal Cancer Genetics & Genomics, Spanish Study (CRCGEN)	Case-control	Spain	1996-2015	54	97
Darmkrebs: Chancen der Verhütung durch Screening (DACHS[c,d])	Case-control	Germany	2003-2015	163	118
Diet, Activity and Lifestyle Study (DALS[e])	Case-control	United States	1990-1993	83	89
European Prospective Investigation into Cancer and Nutrition (EPIC)	Cohort	France, Germany, Greece, Italy, Netherlands, Spain, Sweden, and United Kingdom	1992-1999	84	26
Kentucky Case-Control Study (Kentucky[f])	Case-control	United States	2001-2010	94	62
Leeds Colorectal Cancer Study (LCCS)	Case-control	United Kingdom	1997-2011	83	24
Molecular Epidemiology of Colorectal Cancer (MECC[g])	Case-control	Israel	1998-2015	376	209
North Carolina Colon Cancer Studies I (NCCCS I)	Case-control	United States	1997-2000	19	30
North Carolina Colon Cancer Studies II (NCCCS II)	Case-control	United States	2002-2010	84	59
Newfoundland Case-Control Study (NFCCR)	Case-control	Canada	2000-2004	17	68
Nurses' Health Study (NHS[h])	Cohort	United States	1978-2013	36	60
UK Biobank (UKB)	Cohort	United Kingdom	2006-2010	459	2,062

[a]Reference time for each study was defined as patient selection or blood collection for cohort studies, and 1-2 years prior to selection for case-control studies. Only the years for included participants were reported

[b]Newcomb PA, et al. Colon Cancer Family Registry. Colon Cancer Family Registry: an international resource for studies of the genetic epidemiology of colon cancer. Cancer Epidemiol Biomarkers Prev. 2007 Nov;16(11):2331-43. UK = United Kingdom.

[c]Brenner H, at al. Protection from colorectal cancer after colonoscopy: a population-based, case-control study. Ann Intern Med. 2011 Jan 4;154(1):22-30.

[d]Lilla C, et al. Effect of NAT1 and NAT2 genetic polymorphisms on colorectal cancer risk associated with exposure to tobacco smoke and meat consumption. Cancer Epidemiol Biomarkers Prev. 2006 Jan;15(1):99-107.

[e]Slattery ML, et al. Energy balance and colon cancer--beyond physical activity. Cancer Res. 1997 Jan 1;57(1):75-80.

[f]Nock NL, et al. Associations between obesity and changes in adult BMI over time and colon cancer risk. Obesity (Silver Spring). 2008 May;16(5):1099-104.

[g]Poynter JN, et al. Statins and the risk of colorectal cancer. N Engl J Med. 2005 May 26;352(21):2184-92.
[h]Belanger CF, et al. The nurses' health study. Am J Nurs. 1978 Jun;78(6):1039-40.

Supplementary Table 2. Associations between environmental and lifestyle variables and risk of both early- late-onset colorectal cancer

	Men		Women	
Variable[a]	Log-odds ratio[b]	Odds ratio[b]	Log-odds ratio[b]	Odds ratio[b]
Anthropometric				
BMI (per 5 kg/m^2)	0.226	1.25	0.107	1.11
Height (per 10 cm)	-0.008	0.99	0.074	1.08
Lifestyle				
Pack-years of smoking	0.056	1.06	0.067	1.07
Sedentary lifestyle	-0.015	0.99	-0.215	0.81
Alcohol use				
0 g/d	0.080	1.08	0.120	1.13
>28 g/d	0.356	1.43	0.102	1.11
Lower educational attainment, highest level completed				
High school graduate or completed GED	0.012	1.01	-0.064	0.94
Some college or technical school	-0.230	0.79	-0.139	0.87
≥ College graduate	-0.294	0.75	-0.129	0.88
History of diabetes	0.103	1.11	0.330	1.39
Dietary				
Lower total folate intake (mcg/day)[c]	-0.02	0.98	-0.023	0.98
Lower fruit intake (servings/day)[c]	-0.033	0.97	-0.003	1.00
Lower vegetable intake (servings/day)[c]	0.097	1.10	0.045	1.05
Greater red meat intake (servings/day)[c]	0.056	1.06	0.163	1.18
Greater processed meat intake (servings/day)[c]	0.060	1.06	-0.052	0.95
Lower total fiber intake (g/day)[c]	0.045	1.05	0.009	1.01
Lower total calcium intake (mg/day)[c]	0.043	1.04	0.063	1.07
Pharmacological				
No aspirin use	0.359	1.43	0.258	1.29
No NSAID use	0.206	1.23	0.116	1.12

[a]The reference category was chosen in a way that it represents the lowest risk based on a minimally adjusted model. The referent category for each categorical factor was defined as the following: presence of a sedentary lifestyle (no), alcohol intake (1-28 g/day), educational attainment (< high school graduate), history of diabetes (no), aspirin use (yes), and NSAID use (yes). BMI = body mass index; GED = general educational development; NSAID = non-steroidal anti-inflammatory drug.

[b]The estimated weights, log-odds ratios, for the 16 variables used to construct the ERS were from a multivariable logistic regression model developed using 9,748 CRC cases and 10,590 controls without age restrictions (see Jeon J, Du M, Schoen RE, et al. Determining risk of colorectal cancer and starting age of screening based on lifestyle, environmental, and genetic factors. Gastroenterology. 2018;154(8):2152-64.e19). The ERS was built using the following 19 risk factors: height, body mass index, education, history of type 2 diabetes mellitus, smoking status, alcohol, regular aspirin use, regular NSAID use, regular use of post-menopausal hormones (women only), sex- and study-specific quartiles of smoking pack-years and dietary factors (intake of fiber, calcium, folate, processed meat, red meat, fruit, vegetable), total-energy consumption, and sedentary lifestyle. In addition, models were adjusted for study, age, family history, and endoscopy history. Notably, two lifestyle and environmental risk factors that were incorporated in the external multivariable model used for constructing the weights were excluded in the early-onset ERS: a) a dichotomous smoking variable, given that pack-years was already accounted for, and b) use of post-menopausal hormones, since this variable was not applicable to young individuals.

[c]Dietary variables were harmonized across studies by sex- and study-specific quartiles, and assigned values 0,1,2,3 in the order of increasing risk. These variables were treated as continuous variables in the analysis.

Supplementary Table 3. Associations between environmental and lifestyle variables and risk of early-onset colorectal cancer estimated using ridge regression

	Men	Women
Variable[a]	Log-odds ratio	Log-odds ratio
Anthropometric		
BMI (per 5 kg/m^2)	0.003	0.004
Height (per 10 cm)	0.033	0.032
Lifestyle		
Pack-years of smoking	0.022	0.023
Sedentary lifestyle	-0.280	-0.278
Alcohol use (0 g/d)	0.220	0.220
Alcohol use (>28 g/d)	0.071	0.070
Lower educational attainment, highest level completed	0.043	0.043
History of diabetes	0.122	0.122
Dietary		
Lower total folate intake (mcg/day)[b]	0.031	0.030
Lower fruit intake (servings/day)[b]	-0.009	-0.009
Lower vegetable intake (servings/day)[b]	0.055	0.055
Greater red meat intake (servings/day)[b]	0.025	0.025
Greater processed meat intake (servings/day)[b]	-0.098	-0.098
Lower total fiber intake (g/day)[b]	-0.091	-0.090
Lower total calcium intake (mg/day)[b]	0.047	0.046
Pharmacological		
No aspirin use	-0.073	-0.072
No NSAID use	0.338	0.336

[a]The referent category for each categorical factor was defined as the following: presence of a sedentary lifestyle (no), alcohol intake (1-28 g/day), history of diabetes (no), aspirin use (yes), and NSAID use (yes). BMI = body mass index; NSAID = non-steroidal anti-inflammatory drug.
[b]Dietary variables were harmonized across studies by sex- and study-specific quartiles, and assigned values 0,1,2,3 in the order of increasing risk. These variables were treated as continuous variables in the analysis.

Supplementary Table 4. Odds ratio (95% CI) of ERS and PRS associated with early-onset CRC risk using repeated k-fold cross-validation (CV) and an ERS with weights derived from ridge regression in early-onset CRC[a]

Model	OR (95% CI)	*P*[b]	K-fold CV Accuracy (SD)
Models with ERS as the predictor			
Model 1: ERS per 1 SD[c]	1.15 (1.09, 1.21)	<0.001	0.725 (0.020)
Model 2: ERS per quartile[d]			0.722 (0.021)
1	Referent	–	–
2	1.16 (1.00, 1.35)	0.06	–
3	1.28 (1.10, 1.48)	0.001	–
4	1.47 (1.26, 1.71)	<0.001	–
Models with both ERS and PRS as predictors			
Model 3[e]:			0.738 (0.022)
ERS per 1 SD	1.13 (1.07, 1.20)	<0.001	–
PRS per 1 SD	1.59 (1.50, 1.68)	<0.001	–
Model 4[f]:			0.735 (0.008)
ERS per quartile			
1	Referent	–	–
2	1.19 (1.01, 1.39)	0.03	–
3	1.27 (1.09, 1.49)	0.002	–
4	1.44 (1.23, 1.69)	<0.001	–
PRS per quartile			
1	Referent	–	–
2	1.50 (1.28, 1.75)	<0.001	–
3	2.07 (1.77, 2.42)	<0.001	–
4	3.53 (3.01, 4.15)	<0.001	–

[a]Risks for early-onset CRC linked to the ERS and PRS were evaluated by ridge regression in 3,486 cases and 3,890 controls less than 50 years of age. CI = confidence interval; CV = cross-validation; ERS = environmental risk score; OR = odds ratio; PRS = polygenic risk score; SD = standard deviation.
[b]2-sided *P* values per the Wald test.
[c]The model includes age, sex, total energy consumption, study, family history, and a continuous z-transformed ERS.
[d]The model includes age, sex, total energy consumption, study, family history, and the ERS in quartiles.
[e]The model includes age, sex, total energy consumption, study, family history, principal components, genotype platform, and continuous z-transformed ERS and PRS.
[f]The model includes age, sex, total energy consumption, study, family history, principal components, genotype platform, and the ERS and PRS in quartiles.

Supplementary Table 5. Odds ratio (95% CI) of ERS and PRS associated with early-onset CRC risk using repeated k-fold cross-validation (CV) in the CCFR study

Model	OR (95% CI)	*P*[a]	K-fold CV Accuracy (SD)
Models with ERS as the predictor			
Model 1: ERS per 1 SD[b]	1.23 (1.13, 1.34)	<0.001	0.729 (0.012)
Model 2: ERS by quartile[c]			0.729 (0.013)
1	Referent	–	–
2	0.98 (0.77, 1.25)	0.87	–
3	1.24 (0.98, 1.57)	0.08	–
4	1.71 (1.33, 2.18)	<0.001	–
Models with PRS as the predictor			
Model 3: PRS per 1 SD[d]	1.52 (1.39, 1.66)	<0.001	0.736 (0.011)
Model 4: PRS by quartile[e]			0.735 (0.298)
1	Referent	–	–
2	1.41 (1.12, 1.77)	0.004	–
3	2.09 (1.65, 2.66)	<0.001	–
4	3.14 (2.43, 4.06)	<0.001	–
Models with both ERS and PRS as predictors			
Model 5[f]:			0.740 (0.013)
ERS per 1 SD	1.20 (1.10, 1.32)	<0.001	–
PRS per 1 SD	1.53 (1.40, 1.67)	<0.001	–
Model 6[g]:			0.733 (0.023)
ERS by quartile			
1	Referent	–	–
2	0.95 (0.74, 1.22)	0.69	–
3	1.21 (0.95, 1.55)	0.12	–
4	1.61 (1.25, 2.07)	<0.001	–
PRS by quartile			
1	Referent	–	–
2	1.39 (1.09, 1.75)	0.007	–
3	2.13 (1.67, 2.72)	<0.001	–
4	3.09 (2.38, 4.02)	<0.001	–

[a]2-sided *P* values per the Wald test. CI = confidence interval; CV = cross-validation; ERS = environmental risk score; OR = odds ratio; PRS = polygenic risk score; SD = standard deviation.

[b]The model includes age, sex, total energy consumption, family history, and a continuous z-transformed ERS.

[c]The model includes age, sex, total energy consumption, family history, and the ERS in quartiles.

[d]The model includes age, sex, genotype platform, family history, principal components, and a continuous z-transformed PRS.

[e]The model includes age, sex, genotype platform, family history, principal components, and the PRS in quartiles.

[f]The model includes age, sex, total energy consumption, family history, principal components, genotype platform, and continuous z-transformed ERS and PRS.

[g]The model includes age, sex, total energy consumption, family history, principal components, genotype platform, and the ERS and PRS in quartiles.

Supplementary Table 6. Associations between 141 risk variants and risk of colorectal cancer in the study population

SNP	Locus	Risk/other allele	Risk allele freq	PMID	P[a]	Unadjusted log-odds ratio (95% CI)	Adjusted log-odds ratio (95% CI)[b]
rs72647484	1p36.12	T/C	0.9107	25990418	0.002	0.0504 (0.0192, 0.0816)	--
rs4360494	1p34.3	G/C	0.4539	30510241	<0.001	0.0523 (0.0349, 0.0697)	0.0379 (0.0013, 0.0689)
rs12144319	1p32.3	C/T	0.2548	30510241	<0.001	0.0665 (0.0469, 0.0861)	0.0661 (0.0338, 0.0861)
rs7542665	1p31.3	C/T	0.273	30529582	<0.001	0.0770 (--, --)	--
rs6678517	1q25.3	A/G	0.5898	24737748	<0.001	0.0730 (0.0556, 0.0904)	--
rs17011141	1q41	G/A	0.2087	20972440	<0.001	0.0877 (0.0665, 0.1089)	--
rs7606562	2p16.3	T/A	0.813	30529582	<0.001	0.0953 (--, --)	--
rs11692435	2q11.2	G/A	0.9	31089142	<0.001	0.1133 (--, --)	--
rs448513	2q24.2	C/T	0.326	30510241	<0.001	0.0511 (0.0329, 0.0693)	0.0054 (0.0008, 0.0578)
rs11884596	2q33.1	C/T	0.3823	30510241	<0.001	0.0535 (0.0355, 0.0715)	0.0342 (0.0012, 0.0330)
rs983402	2q33.1	T/C	0.3312	30510241	<0.001	0.0627 (0.0441, 0.0813)	0.0622 (0.0300, 0.0813)
rs3731861	2q35	T/C	0.6295	27005424	<0.001	0.0613 (0.0435, 0.0791)	--
rs35470271	3p22.1	G/A	0.154	26151821	<0.001	0.0994 (0.0759, 0.1229)	--
rs9831861	3p21.1	G/T	0.59	31089142	<0.001	0.0677 (--, --)	--
rs6781752	3p14.1	A/G	0.205	26151821	<0.001	0.0597 (0.0379, 0.0815)	--
rs13086367	3q13.2	A/G	0.5262	30510241	<0.001	0.0474 (0.0302, 0.0646)	0.0463 (0.0106, 0.0646)
rs12635946	3q13.2	C/T	0.62	31089142	<0.001	0.0770 (--, --)	--
rs72942485	3q13.2	G/A	0.9802	30510241	<0.001	0.1761 (0.1153, 0.2369)	0.0545 (0.0028, 0.2254)
rs10049390	3q22.2	A/G	0.7353	30510241	<0.001	0.0597 (0.0399, 0.0795)	0.0455 (0.0017, 0.0788)
rs113569514	3q22.2	T/C	0.62	30529582	<0.001	0.0953 (--, --)	--
rs9876206	3q26.2	C/T	0.7507	20972440	<0.001	0.0453 (0.0255, 0.0651)	--
rs13149359	4q22.2	A/C	0.3663	29917119	<0.001	0.0520 (0.0342, 0.0698)	--
rs1391441	4q24	A/G	0.672	30510241	<0.001	0.0522 (0.0342, 0.0702)	0.0148 (0.0008, 0.0667)
rs11727676	4q31.21	C/T	0.098	30510241	<0.001	0.0842 (0.0544, 0.1140)	0.0093 (0.0013, 0.0990)
rs78368589	5p15.33	T/C	0.0597	30510241	<0.001	0.1119 (0.0745, 0.1493)	0.0786 (0.0027, 0.1474)
rs2735940	5p15.33	G/A	0.4952	29917119	<0.001	0.0865 (0.0691, 0.1039)	--
rs7708610	5p13.1	A/G	0.3564	30510241	<0.001	0.0545 (0.0363, 0.0727)	0.0384 (0.0013, 0.0718)
rs12514517	5p13.1	A/G	0.288	29917119	<0.001	0.1013 (0.0819, 0.1207)	--
rs145364999	5q21.1	T/A	0.9969	30510241	<0.001	0.5559 (0.3683, 0.7435)	0.3496 (0.0118, 0.7297)
rs755229494	5q22.2	G/A	0.0011	29917119	<0.001	0.6286 (0.4534, 0.8038)	--
rs12659017	5q23.2	G/A	0.232	30529582	<0.001	0.0862 (--, --)	--
rs4976270	5q31.1	C/T	0.5501	23263487	<0.001	0.0693 (0.0521, 0.0865)	--
rs2070699	6p24.1	T/G	0.48	31089142	<0.001	0.0677 (--, --)	--
rs1476570	6p22.1	A/G	0.376	30529582	<0.001	0.1133 (--, --)	--
rs3131043	6p21.33	G/A	0.43	31089142	<0.001	0.0677 (--, --)	--
rs116353863	6p21.33	C/T	0.0165	30510241	<0.001	0.1545 (0.0932, 0.2158)	0.1202 (0.0062, 0.2144)

rs116685461	6p21.33	G/A	0.8755	30510241	<0.001	0.0698 (0.0435, 0.0961)	0.0655 (0.0057, 0.0960)
rs2516420	6p21.33	C/T	0.9263	30510241	<0.001	0.1118 (0.0775, 0.1461)	0.1091 (0.0931, 0.1460)
rs3830041	6p21.32	T/C	0.14	30529582	<0.001	0.1484 (--, --)	--
rs9271695	6p21.32	G/A	0.7954	30510241	<0.001	0.0889 (0.0658, 0.1120)	0.0889 (0.0649, 0.0930)
rs16878812	6p21.31	A/G	0.8861	29917119	<0.001	0.0778 (0.0502, 0.1054)	--
rs9470361	6p21.2	A/G	0.2488	22634755	<0.001	0.0540 (0.0342, 0.0738)	--
rs62396735	6p21.1	C/T	0.2908	26965516	<0.001	0.0330 (0.0142, 0.0518)	--
rs2079660	6q21	C/A	NA	31089142	<0.001	0.0322 (--, --)	--
rs13204733	6p12.1	G/A	0.141	30510241	<0.001	0.0680 (0.0425, 0.0935)	0.0643 (0.0060, 0.0934)
rs62404966	6p12.1	C/T	0.7623	29917119	<0.001	0.0724 (0.0514, 0.0934)	--
rs12672022	7p13	T/C	0.8345	30510241	<0.001	0.0650 (0.0417, 0.0883)	0.0067 (0.0010, 0.0714)
rs80077929	7p12.3	T/C	0.1107	30510241	<0.001	0.0643 (0.0359, 0.0927)	0.0093 (0.0017, 0.0764)
rs10951878	7p12.3	C/T	0.49	31089142	<0.001	0.0583 (--, --)	--
rs3801081	7p12.3	G/A	0.68	31089142	<0.001	0.0770 (--, --)	--
rs16892766	8q23.3	C/A	0.0829	26965516	<0.001	0.2099 (0.1723, 0.2475)	--
rs6469654	8q23.3	G/C	0.2288	18372905	<0.001	0.0677 (0.0436, 0.0918)	--
rs117079142	8q24.11	A/C	0.0432	26965516	<0.001	0.1139 (0.0688, 0.1590)	--
rs6983267	8q24.21	G/T	0.5228	17618284	<0.001	0.1052 (0.0795, 0.1309)	--
rs7013278	8q24.21	T/C	0.3761	30510241	<0.001	0.0606 (0.0341, 0.0871)	0.0091 (0.0016, 0.0748)
rs4313119	8q24.21	G/T	0.7486	30510241	<0.001	0.0608 (0.0410, 0.0806)	0.0518 (0.0023, 0.0803)
rs1537372	9p21.3	G/T	0.5692	30510241	<0.001	0.0504 (0.0330, 0.0678)	0.0120 (0.0008, 0.0641)
rs34405347	9q22.33	T/G	0.9034	30510241	<0.001	0.0818 (0.0528, 0.1108)	0.0089 (0.0013, 0.0952)
rs10980628	9q31.3	C/T	0.2106	30510241	<0.001	0.0637 (0.0427, 0.0847)	0.0511 (0.0020, 0.0841)
rs12217641	10p14	C/T	0.6981	30510241	<0.001	0.0462 (0.0260, 0.0664)	0.0069 (0.0012, 0.0569)
rs11255841	10p14	T/A	0.703	18372905	<0.001	0.1064 (0.0864, 0.1264)	--
rs10821907	10q11.23	C/T	0.8276	29917119	<0.001	0.0730 (0.0501, 0.0959)	--
rs704017	10q22.3	G/A	0.5846	24836286	<0.001	0.0765 (0.0589, 0.0941)	--
rs1250567	10q22.3	C/T	0.4405	30510241	<0.001	0.0483 (0.0307, 0.0659)	0.0470 (0.0097, 0.0659)
rs10786560	10q24.2	G/A	0.762	30510241	<0.001	0.0514 (0.0293, 0.0735)	0.0082 (0.0013, 0.0659)
rs11190164	10q24.2	G/A	0.2626	24737748	<0.001	0.0889 (0.0685, 0.1093)	--
rs12246635	10q25.2	C/T	0.0983	25105248	<0.001	0.0975 (0.0693, 0.1257)	--
rs11196170	10q25.2	A/G	0.2178	24836286	<0.001	0.0527 (0.0319, 0.0735)	--
rs4450168	11p15.4	C/A	0.17	31089142	<0.001	0.0953 (--, --)	--
rs174533	11q12.2	G/A	0.6739	24836286	<0.001	0.0636 (0.0452, 0.0820)	--
rs7121958	11q13.4	G/T	0.5105	22634755	<0.001	0.0780 (0.0608, 0.0952)	--
rs7946853	11q13.4	C/T	0.8624	30510241	<0.001	0.0603 (0.0348, 0.0858)	0.0119 (0.0016, 0.0807)
rs61389091	11q13.4	C/T	0.9606	30510241	<0.001	0.1934 (0.1469, 0.2399)	0.1934 (0.1469, 0.2399)
rs55864876	11q22.1	G/A	0.9184	30510241	<0.001	0.0774 (0.0447, 0.1101)	0.0150 (0.0020, 0.1035)
rs2186607	11q22.1	T/A	0.5178	30510241	<0.001	0.0537 (0.0365, 0.0709)	0.0483 (0.0028, 0.0708)
rs3087967	11q23.1	T/C	0.2911	18372901	<0.001	0.1122 (0.0934, 0.1310)	--

rs35808169	12p13.32	C/T	0.1721	23263487	<0.001	0.0890 (0.0661, 0.1119)	--
rs3217810	12p13.32	T/C	0.1253	24737748	<0.001	0.1181 (0.0891, 0.1471)	--
rs3217874	12p13.32	T/C	0.4282	30510241	<0.001	0.0550 (0.0370, 0.0730)	0.0453 (0.0019, 0.0726)
rs10849433	12p13.31	C/T	0.267	30510241	<0.001	0.0510 (0.0316, 0.0704)	0.0468 (0.0034, 0.0703)
rs2250430	12p13.31	T/A	0.7095	24836286	<0.001	0.0597 (0.0399, 0.0795)	--
rs2710310	12p13.2	C/T	0.7596	27145994	0.16	0.0145 (-0.0057, 0.0347)	--
rs77969132	12p11.21	T/C	0.015	30529582	<0.001	0.3646 (--, --)	--
rs11610543	12q12	G/A	0.5013	30510241	<0.001	0.0530 (0.0359, 0.0701)	0.0474 (0.0026, 0.0699)
rs12372718	12q13.12	G/A	0.3924	20972440	<0.001	0.0896 (0.0720, 0.1072)	--
rs4759277	12q13.3	A/C	0.3546	30510241	<0.001	0.0530 (0.0350, 0.0710)	0.0285 (0.0010, 0.0692)
rs597808	12q24.12	G/A	0.5166	26151821	<0.001	0.0737 (0.0561, 0.0913)	--
rs1427760	12q24.21	C/T	0.5268	30510241	<0.001	0.0456 (0.0284, 0.0628)	0.0424 (0.0034, 0.0628)
rs7300312	12q24.21	C/T	0.5719	29917119	<0.001	0.0660 (0.0488, 0.0832)	--
rs55990915	12q24.22	A/C	0.1222	26151821	<0.001	0.0640 (--, --)	--
rs377429877	13q13.2	C/T	0.6117	29917119	<0.001	0.0468 (0.0288, 0.0648)	--
rs7333607	13q13.3	G/A	0.235	30510241	<0.001	0.0758 (0.0552, 0.0964)	0.0758 (0.0527, 0.0964)
rs45597035	13q22.1	A/G	0.6506	30510241;31089142	<0.001	0.0505 (0.0323, 0.0687)	0.0495 (0.0135, 0.0687)
rs78341008	13q22.1	C/T	0.0719	30510241	<0.001	0.0982 (0.0635, 0.1329)	0.0109 (0.0015, 0.1163)
rs1924816	13q22.1	A/G	0.7737	30510241	<0.001	0.0544 (0.0338, 0.0750)	0.0506 (0.0040, 0.0749)
rs1330889	13q22.3	C/T	0.87	31089142	<0.001	0.1044 (--, --)	--
rs8000189	13q34	T/C	0.6401	30510241	<0.001	0.0549 (0.0371, 0.0727)	0.0473 (0.0022, 0.0725)
rs1951864	14q22.2	A/G	0.3722	30510241	<0.001	0.0407 (0.0227, 0.0587)	0.0059 (0.0011, 0.0480)
rs35107139	14q22.2	C/A	0.4235	19011631	<0.001	0.0912 (0.0734, 0.1090)	--
rs4901473	14q22.2	G/A	0.378	21655089	<0.001	0.0465 (0.0287, 0.0643)	--
rs17094983	14q23.1	G/A	0.8773	30510241	<0.001	0.0691 (0.0415, 0.0967)	0.0062 (0.0013, 0.0424)
rs8020436	14q23.1	A/G	0.4016	30510241	<0.001	0.0454 (0.0270, 0.0638)	0.0294 (0.0015, 0.0629)
rs12708491	15q13.3	G/A	0.5872	21655089	<0.001	0.0464 (0.0278, 0.0650)	--
rs2293581	15q13.3	A/G	0.2116	21655089	<0.001	0.1248 (0.1030, 0.1466)	--
rs17816465	15q13.3	A/G	0.2055	30510241	<0.001	0.0705 (0.0489, 0.0921)	0.0690 (0.0238, 0.0680)
rs12594720	15q22.31	C/G	0.7218	30510241;31089142	<0.001	0.0476 (0.0280, 0.0672)	0.0246 (0.0014, 0.0656)
rs56324967	15q22.33	C/T	0.6757	30510241	<0.001	0.0689 (0.0505, 0.0873)	0.0689 (0.0490, 0.0873)
rs745213	15q23	G/T	0.8102	30510241	<0.001	0.0490 (0.0274, 0.0706)	0.0072 (0.0013, 0.0591)
rs7495132	15q26.1	T/C	0.12	31089142	<0.001	0.1044 (--, --)	--
rs9924886	16q22.1	A/C	0.7321	19011631	<0.001	0.0550 (0.0356, 0.0744)	--
rs9930005	16q23.2	C/A	0.4303	30510241	<0.001	0.0498 (0.0324, 0.0672)	0.0061 (0.0008, 0.0610)
rs12447408	16q24.1	A/G	0.2535	30510241	<0.001	0.0472 (0.0270, 0.0674)	0.0079 (0.0012, 0.0616)
rs12149163	16q24.1	T/C	0.4976	29917119	<0.001	0.0487 (0.0315, 0.0659)	--
rs62042090	16q24.1	T/C	0.2164	25990418	<0.001	0.0481 (0.0271, 0.0691)	--
rs4968127	17p13.3	G/A	0.3684	24836286	<0.001	0.0514 (0.0328, 0.0700)	--
rs73975586	17p13.3	A/T	0.8732	30510241	<0.001	0.0680 (0.0408, 0.0952)	0.0497 (0.0025, 0.0944)

rs1078643	17p12	A/G	0.7636	30510241	<0.001	0.0748 (0.0534, 0.0962)	0.0747 (0.0452, 0.0765)
rs983318	17q24.3	A/G	0.2526	30510241	<0.001	0.0595 (0.0395, 0.0795)	0.0397 (0.0013, 0.0783)
rs373585858	17q25.3	A/G	0.0016	30510241	<0.001	0.6995 (0.3977, 1.0013)	0.1103 (0.0183, 0.8932)
rs75954926	17q25.3	G/A	0.6568	30510241	<0.001	0.0882 (0.0684, 0.1080)	0.0882 (0.0684, 0.0923)
rs11874392	18q21.1	A/T	0.545	17934461	<0.001	0.1606 (0.1434, 0.1778)	--
rs34797592	19p13.11	T/C	0.1182	30510241	<0.001	0.0868 (0.0596, 0.1140)	0.0824 (0.0139, 0.1139)
rs28840750	19q13.11	T/G	0.948	19011631	<0.001	0.1939 (0.1555, 0.2323)	--
rs1963413	19q13.2	A/G	0.6119	24836286	<0.001	0.0441 (0.0265, 0.0617)	--
rs12979278	19q13.33	T/C	0.53	31089142	<0.001	0.0677 (--, --)	--
rs73068325	19q13.43	T/C	0.1826	30510241	<0.001	0.0632 (0.0407, 0.0857)	0.0066 (0.0010, 0.0716)
rs189583	20p12.3	G/C	0.3298	19011631	<0.001	0.0795 (0.0607, 0.0983)	--
rs994308	20p12.3	C/T	0.5939	30510241	<0.001	0.0627 (0.0449, 0.0805)	0.0626 (0.0385, 0.0805)
rs4813802	20p12.3	G/T	0.3561	21655089	<0.001	0.0819 (0.0635, 0.1003)	--
rs28488	20p12.3	T/C	0.6388	30510241	<0.001	0.0714 (0.0530, 0.0898)	0.0714 (0.0525, 0.0747)
rs11087784	20p12.3	G/A	0.1523	23263487	<0.001	0.0874 (0.0639, 0.1109)	--
rs556532366	20p12.3	T/C	0.0029	30510241	<0.001	0.4760 (0.2682, 0.6838)	0.0715 (0.0126, 0.5885)
rs6058093	20q11.22	C/A	0.4942	29917119	<0.001	0.0450 (0.0278, 0.0622)	--
rs6031311	20q13.12	T/C	0.7591	30510241	<0.001	0.0597 (0.0395, 0.0799)	0.0362 (0.0012, 0.0350)
rs6066825	20q13.13	A/G	0.6448	26151821	<0.001	0.0719 (0.0539, 0.0899)	--
rs6067417	20q13.13	C/T	0.5635	30510241	<0.001	0.0446 (0.0268, 0.0624)	0.0331 (0.0017, 0.0619)
rs6063514	20q13.13	C/T	0.6086	29917119	<0.001	0.0547 (0.0367, 0.0727)	--
rs6091189	20q13.13	T/C	0.1529	30510241	<0.001	0.0620 (0.0381, 0.0859)	0.0549 (0.0035, 0.0857)
rs13831	20q13.32	G/A	0.684	30529582	<0.001	0.0770 (--, --)	--
rs1741640	20q13.33	C/T	0.7652	20972440	<0.001	0.1146 (0.0936, 0.1356)	--
rs2738783	20q13.33	T/G	0.2029	30510241	<0.001	0.0593 (0.0379, 0.0807)	0.0060 (0.0009, 0.0637)

[a]2-sided *P* values per the Wald test. CI = confidence interval; SNP = single nucleotide polymorphism; PMID = PubMed identification.

[b]Adjusted for "winner's curse" (Zhong H, Prentice RL. Bias-reduced estimators and confidence intervals for odds ratios in genome-wide association studies. Biostatistics. 2008 Oct;9(4):621-34) given that these variants were initially discovered in GECCO and CORECT studies, which provides conservatively attenuated estimates for these risk variants.

Supplementary Table 7. CRC incidence (cases per 100,000) for non-Hispanic White individuals in SEER13 (1992-2005)[a]

	CRC incidence (cases per 100,000)	
Age, years	Men	Women
0	0	0
1	0	0
2	0	0
3	0	0
4	0	0.1
5	0	0
6	0	0
7	0	0
8	0	0
9	0.2	0
10	0	0
11	0.1	0.1
12	0.1	0.1
13	0.1	0.2
14	0.2	0.2
15	0.3	0.3
16	0.2	0.3
17	0.3	0.4
18	0.5	0.4
19	0.6	0.5
20	0.4	0.5
21	0.9	0.8
22	1	1.4
23	1.1	1.1
24	0.9	1.4
25	1.6	1.8
26	1.8	1.7
27	1.4	2
28	2.5	2.3
29	3.1	2.3
30	3.1	2.8
31	3	3.5
32	3.8	3.4
33	5.6	5
34	5	4.8
35	5.9	5.5
36	6.3	5.4
37	7.9	6.4
38	9	7.3
39	10.6	8.8
40	11.4	10.6
41	12.2	12.1
42	14.9	14.3
43	17.4	14.6
44	18.8	16.2
45	21.8	19.1
46	24.9	21.5
47	28.3	24.2
48	33.2	25.5
49	34.8	28.6

50	54.2	41.5
51	55.4	42.5
52	53.7	39.7
53	56.7	42.3
54	63.1	44.9
55	68.3	49.8
56	76.7	50.6
57	77.4	57.2
58	86.3	59.6
59	93.9	67.5
60	106.9	71.1
61	113.1	78.7
62	121.9	79.5
63	131.4	88.4
64	140.4	98.7
65	163	112.5
66	172.1	116.5
67	184.3	123.5
68	193.8	130.4
69	207.9	148.5
70	225.6	158.5
71	234	169
72	255.4	185.1
73	272.7	194.1
74	280.3	213.5
75	284.5	218
76	316.8	227.9
77	320.3	245.7
78	337.6	266.1
79	341.9	264.1
80	358	283.2
81	365.5	296.9
82	373.6	309
83	395.1	323.2
84	408	321.9
85+	400.7	339.9

[a]CRC = colorectal cancer; SEER = surveillance, epidemiology, and end results.

Supplementary Table 8. Colorectal cancer (CRC) mortality (deaths per 100,000) for non-Hispanic White individuals in SEER13 (1992-2005)

	CRC mortality (deaths per 100,000)			
	Men		Women	
Age, years	CRC	Other-causes[a]	CRC	Other-causes[a]
0	0	650.6	0	531.1
1-4	0	32.1	0	25.6
5-9	0	15.6	0	12.3
10-14	0	20.8	0	14
15-19	0	82.1	0	36.2
20-24	0	127.5	0	44
25-29	0	131.6	0	51.9
30-34	0.1	153.4	0.1	68.4
35-39	0.2	194.8	0.2	98.4
40-44	0.4	271.4	0.4	147.9
45-49	0.8	396.8	0.6	226.2
50-54	1.3	590.4	0.8	344.2
55-59	1.8	878.8	1.1	521.2
60-64	2.7	1330.9	1.5	815.2
65-69	4.3	2024.5	2.3	1281.3
70-74	6	3168.5	3.4	2060.7
75-79	6.8	4992.9	4.1	3354.1
80-84	5.9	8077.9	3.9	5689.8
85+	5.4	16170.8	4.6	13791.7

[a]The other-cause mortality was computed by subtracting the CRC mortality from the all-cause mortality. SEER = surveillance, epidemiology, and end results.

Supplementary Table 9. Odds ratio (95% CI) of ERS and PRS associated with early-onset CRC risk across anatomic subsites using multinomial logistic regression

Anatomic Site	ERS per 1 SD	PRS per 1 SD
Proximal Colon Cancer[a]		
OR (95% CI)	1.13 (1.04, 1.22)	1.38 (1.27, 1.50)
P[b]	0.003	<0.001
Covariate-adjusted AUC (95% CI)	0.542 (0.499, 0.584)[d]	0.592 (0.554, 0.630)[e]
Distal Colon Cancer[a]		
OR (95% CI)	1.12 (1.04, 1.20)	1.73 (1.60, 1.87)
P[b]	0.004	<0.001
Covariate-adjusted AUC (95% CI)	0.530 (0.495, 0.564)[d]	0.643 (0.614, 0.671)[e]
Rectal Cancer[a]		
OR (95% CI)	1.13 (1.05, 1.21)	1.67 (1.55, 1.80)
P[b]	<0.001	<0.001
Covariate-adjusted AUC (95% CI)	0.531 (0.504, 0.559)[d]	0.654 (0.630, 0.680)[e]
Proximal Colon vs. Distal Colon		
P[c]	0.78	<0.001
Proximal Colon vs. Rectum		
P[c]	0.99	<0.001
Distal Colon vs. Rectum		
P[c]	0.76	0.43

[a]The model includes age, sex, total energy consumption, study, family history, principal components, and the z-transformed ERS and PRS. AUC = area under the ROC curve; CI = confidence interval; ERS = environmental risk score; OR = odds ratio; PRS = polygenic risks core.
[b]2-sided *P* values per the Wald test.
[c]Chi-square test for contrasts in multinomial models. All tests were 2-sided.
[d]The model for estimating the AUC includes a z-transformed ERS as the predictor, adjusting for age, sex, total energy consumption, study, and family history.
[e]The model for estimating the AUC includes a z-transformed PRS as the predictor, adjusting for age, sex, family history, genotype platform, and principal components.

Supplementary Table 10. Assessment for the presence of biological interaction between the ERS and PRS[a]

Measure of Additive Interaction	Estimate (95% CI)
RERI	0.134 (-0.004, 0.271)
AP	1.259 (1.187, 1.336)
S	0.081 (0.025, 0.137)

[a]AP = proportion attributable to interaction; CI = confidence interval; ERS = environmental risk score; PRS = polygenic risks core; RERI = relative excess risk due to interaction; S = synergy index.

Supplementary Table 11. 5-year absolute risk estimates for early-onset CRC with varying risk factor profiles

			Men[a]	Women[a]
Age, years	ERS Percentile	PRS Percentile	Risk (95% CI), %	Risk (95% CI), %
25	Average Risk[b]		0.01 (--)	0.01 (--)
25	1%	1%	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)
25	10%	10%	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)
25	50%	50%	0.01 (0.01, 0.01)	0.01 (0.01, 0.01)
25	90%	90%	0.02 (0.02, 0.02)	0.02 (0.02, 0.02)
25	99%	99%	0.03 (0.03, 0.03)	0.03 (0.02, 0.03)
30	Average Risk[b]		0.02 (--)	0.02 (--)
30	1%	1%	0.01 (0.01, 0.01)	0.01 (0.01, 0.01)
30	10%	10%	0.01 (0.01, 0.01)	0.01 (0.01, 0.01)
30	50%	50%	0.02 (0.02, 0.02)	0.02 (0.02, 0.02)
30	90%	90%	0.05 (0.04, 0.05)	0.04 (0.04, 0.04)
30	99%	99%	0.06 (0.05, 0.06)	0.05 (0.05, 0.05)
35	Average Risk[b]		0.04 (--)	0.03 (--)
35	1%	1%	0.01 (0.01, 0.01)	0.01 (0.01, 0.01)
35	10%	10%	0.01 (0.01, 0.01)	0.01 (0.01, 0.01)
35	50%	50%	0.04 (0.04, 0.04)	0.03 (0.03, 0.03)
35	90%	90%	0.09 (0.09, 0.09)	0.07 (0.07, 0.07)
35	99%	99%	0.11 (0.10, 0.11)	0.09 (0.08, 0.09)
40	Average Risk[b]		0.07 (--)	0.07 (--)
40	1%	1%	0.02 (0.02, 0.02)	0.02 (0.02, 0.02)
40	10%	10%	0.03 (0.03, 0.03)	0.03 (0.03, 0.03)
40	50%	50%	0.07 (0.07, 0.07)	0.06 (0.06, 0.06)
40	90%	90%	0.16 (0.16, 0.17)	0.14 (0.14, 0.15)
40	99%	99%	0.20 (0.19, 0.21)	0.17 (0.17, 0.18)
45	Average Risk[b]		0.14 (--)	0.12 (--)
45	1%	1%	0.04 (0.04, 0.04)	0.04 (0.04, 0.04)
45	10%	10%	0.05 (0.05, 0.05)	0.05 (0.05, 0.05)
45	50%	50%	0.13 (0.13, 0.13)	0.11 (0.11, 0.11)
45	90%	90%	0.31 (0.30, 0.32)	0.25 (0.24, 0.26)
45	99%	99%	0.38 (0.37, 0.40)	0.30 (0.29, 0.32)

[a]Models were adjusted for age, study, total energy consumption, family history, genotype platform, and principal components. CI = confidence interval; ERS = environmental risk score; PRS = polygenic risks core.

[b]Average risks in general population were calculated based on SEER incidence rates for men and women separately.