Online-Only Supplements

eMethod 1. Harmonization of lifestyle and environmental data

To ensure all the variables are comparable across studies, all data were harmonized at the coordinating center at the Fred Hutch using a standardized protocol. Information on basic demographics lifestyle and environmental risk factors was collected by self-report using in-person interviews and/or structured questionnaires. Individual level data of all studies were centrally harmonized at the data coordinating center. We carried out a multi-step data harmonization procedure, reconciling each study's unique protocols and data-collection instruments. First, we defined common data elements (CDEs). We examined the questionnaires and data dictionaries for each study to identify study specific data elements that could be mapped to the CDEs. Through an iterative process, we communicated with each data contributor to obtain relevant data and coding information. The data elements were written to a common data platform, transformed, and combined into a single dataset with common definitions, standardized permissible values, and standardized coding. The mapping and resulting data were reviewed for quality assurance, and range and logic checks were performed to assess data and data distributions within and between studies. Outlying samples were truncated to the minimum or maximum value of established range for each variable. All variables were collected at the study reference time, which was defined as study entry or blood collection for cohort studies and one to two years before sample ascertainment for case-control studies to ensure exposures assessed before cancer diagnoses. Age at referent time was defined in years and modeled continuously.

Height and Body mass index

Height[1, 2] was defined in centimeters based on self-reports or direct measures. Body mass index (BMI)[1, 3, 4, 5] was calculated from self-reports or direct measures of body weight (kg) divided by height (m^2). In our analysis, the BMI/5 was used, and if the BMI<18.5, it was set as missing.

Family history

Family history was a yes/no variable for presence or absence of a first-degree relative with colorectal cancer.

Endoscopy history

Endoscopy history was coded as yes, no, or missing, depending on whether a participant had sigmoidoscopy or colonoscopy screening before the study reference time, or such information was missing.

Education

Highest level of education was defined in four categories: less than high school degree, high school degree or completed GED, some college or technical school, and college or graduate degree.

Diabetes and Physical activity

Self-reported type 2 diabetes was categorized as yes/no.26 Physical activity was calculated by summing hours per week of leisure-time or undifferentiated activities and categorized as active (>=1 hour/week) or inactive (<1 hour/week).[6]

Smoking Status

Smoking status was defined as never- and ever-smoking; it was defined as "yes" for current or former smokers and "no" for never smokers. Pack-years of smoking were calculated by multiplying the average number of packs of cigarettes smoked per day by smoking duration (years). Smoking pack-years among ever smokers was harmonized across studies by sex- and study-specific quartiles with quartile cutoffs determined within the controls of each study and sex. We assigned values 1 for lesser than equal to the fist quartile, 2 for between the first and second quartiles, 3 for the second and the third quartiles, 4 for greater than the third quarter. For never smokers, it was assigned as "0". This variable was treated as continuous variable in the analysis.[1, 3, 7, 8, 9, 10]

Alcohol consumption

We converted consumption of alcoholic beverages into grams of alcohol per day (g/day) by summing the alcohol content of each beverage consumed per day. We grouped study participants as non-/occasional drinkers (< 1 g/day); light-to-moderate drinkers (1-28 g/day); and heavy drinkers (>28 g/day, one standard drinking is approximately equal to 14 grams of alcohol).[1, 3, 8, 11]

Aspirin and NSAIDs use

We used dichotomous variable for regular use of aspirin and/or NSAIDs (yes or no). Aspirin use is defined as "yes" if a person used aspirin regularly in reference time period and "no" otherwise. NSAIDs use is defined as "yes" if a person used non-aspirin NSAIDs regularly in reference time period and "no" otherwise.[1, 3, 12, 13]

Post-menopausal hormone use

Post-menopausal hormone use (PMH) was considered either as any PMH use, Estrogen-only use or Estrogen+Progesterone use at reference time.[3, 14, 15]

Dietary variables

Intake of dietary factors was assessed using food frequency questionnaires (FFQs) or diet history (DALS only). The dietary variables fruits, vegetables, and red or processed meats were measured in servings/day; fiber as g/day; calcium as mg/day; and folate as µg/day. The dietary variables were coded as sex- and study-specific quartiles with quartile cutoffs determined within the controls of each study and sex. Some studies with less variation in dietary intake (primarily because of fewer questions) had less than 4 intake categories for certain factors. In these instances, we assigned intake to only the 2nd and 3rd quartiles.[1, 3, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25]

Calcium intake was measured in mg/day was determined from calcium in foods (i.e., dietary) or supplements (single + multivitamins + antacids) when available. Total calcium intake was calculated as dietary + supplemental calcium. For studies that entered supplement data as regular user vs. nonuser, we assumed regular use was 500 mg/day, 500 mg/single tablet, or 130 mg/multivitamin tablet [the generic dose in supplements[16]]. Folate and folic acid intake in each study was determined based on micrograms per day (mcg/day) of folate from foods (i.e., dietary folate) and mcg/day of folic acid from supplements (single or multivitamins) when available. To account for the higher bioavailability of synthetic folic acid vs. food folate, we calculated total folate intake as dietary folate equivalents (DFE): total mcg DFE = mcg of dietary folate + 1.7 x mcg folic acid from supplements.[19] Because the times of enrollment for some studies overlapped or followed the period of folic acid fortification (1996-1998), these studies accounted for folic acid fortification when calculating dietary folate intake and entered dietary folate intake as mcg of natural food folate + 1.7 x mcg folic acid from fortified food. If studies entered supplement data as regular user vs. nonuser, we assumed regular use was 400 mcg/day or 400 mcg/tablet (for multivitamins), which corresponds to the generic dose in supplements.[17, 24] Total energy consumption was calculated in kcal/day and modeled as a continuous variable scaled by its standard error.

eTable 1. Full list of variables included in modifiable and non-modifiable risk scores

Risk score	Variable name	Classification
Modifiable risk score	BMI	Continuous, kg/m^2
	Physical activity	Binary, sedentary y/n
	Smoking	Binary, Ever/Never; group linear, sex-study-specific quartiles of pack-years
	Alcohol intake	Categorical, non-drinkers, 1-28 g/day and >28 g/day
	Processed meat intake	Group linear, sex-study-specific quartiles
	Red meat intake	Group linear, sex-study-specific quartiles
	Fruit intake	Group linear, sex-study-specific quartiles
	Vegetable intake	Group linear, sex-study-specific quartiles
	Fiber intake	Group linear, sex-study-specific quartiles
	Total calcium intake	Group linear, sex-study-specific quartiles
	Total folate intake	Group linear, sex-study-specific quartiles
	Regular use of aspirin	Binary, y/n
	Regular use of non-aspirin NSAIDs	Binary, y/n
	PMH use in women	Binary, y/n
	Diabetes	Binary, y/n
Nonmodifiable risk score	Height	Continuous, m
	Family history of CRC	Binary, y/n
	Genetic risk score	Continuous

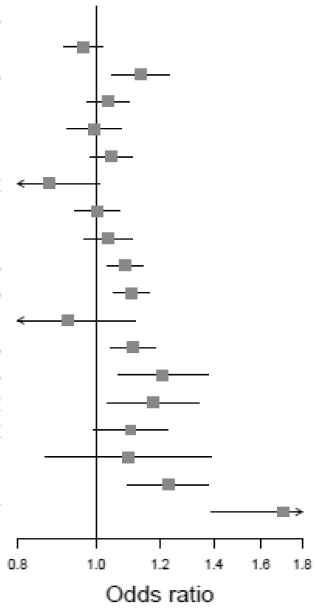
eMethod 2. Estimation of absolute risks of colorectal cancer

We estimated the 10-year absolute risk of developing CRC and corresponding 95% CIs for a given risk profile, as described previously[26]. We used external population incidence rates for non-Hispanic whites during 1992–2005 (reflective of the time period in which lifestyle and environmental risk factors were assessed across studies) from the Surveillance, Epidemiology, and End Results program registry [27] to calculate the baseline hazard function. This is achieved by multiplying the external incidence rate with one minus population attributable risk, which is estimated by taking the average of the inverse exponential of risk scores among cases [28]. We then pooled all studies to estimate the overall population attributable risk to improve efficiency. We also accounted for competing risks of death in the absolute risk estimation, where the mortality rates were obtained from the National Center for Health Statistics. We obtained the 95% CIs of the 10-year absolute risk estimates of CRC with 100 bootstrap samples.

eFigure 1. Estimated adjusted sex-specific beta (weight) for each risk factor in environmental risk score using one multivariable logistic regression model* in females (A) and males (B)

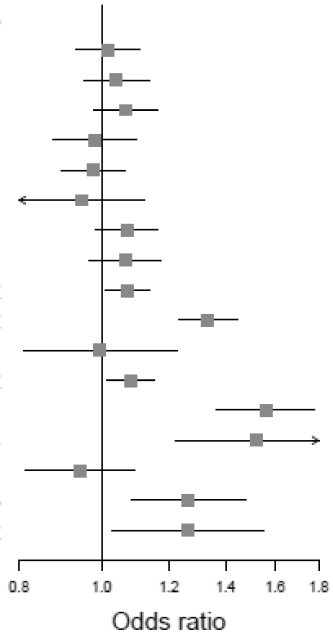
(A) Females

factor	beta	se	OR	p value
Total folate[a]	−0.036	0.03	0.96	2.2e−01
Height (per 10cm)	0.128	0.04	1.14	2.0e−03
Vegetable[a]	0.035	0.03	1.04	2.4e−01
Fiber[a]	−0.006	0.04	0.99	8.8e−01
Fruit[a]	0.044	0.03	1.05	1.5e−01
Sedentary	−0.133	0.07	0.88	6.6e−02
Processed meat[a]	0.004	0.03	1.00	9.1e−01
Red meat[a]	0.035	0.03	1.04	3.1e−01
Total calcium[a]	0.082	0.03	1.09	1.3e−03
BMI (per 5 kg/m^2)	0.101	0.03	1.11	8.6e−05
Ever smoking	−0.082	0.10	0.92	4.1e−01
Smoking (pack-years)	0.106	0.03	1.11	1.4e−03
No aspirin use	0.191	0.07	1.21	3.5e−03
No NSAIDs use	0.163	0.07	1.18	1.6e−02
Alcohol drink (0 g/d)	0.099	0.05	1.10	7.0e−02
Alcohol drink (>28 g/d)	0.093	0.12	1.10	4.4e−01
No PMH use	0.207	0.06	1.23	4.4e−04
Diabetes	0.533	0.11	1.70	3.9e−07



(B) Males

factor	beta	se	OR	p value
Total folate[a]	0.017	0.04	1.02	7.0e−01
Height (per 10cm)	0.039	0.05	1.04	3.8e−01
Vegetable[a]	0.066	0.04	1.07	1.3e−01
Fiber[a]	0.019	0.06	0.98	7.4e−01
Fruit[a]	0.022	0.04	0.98	6.0e−01
Sedentary	0.055	0.09	0.95	5.3e−01
Processed meat[a]	0.069	0.04	1.07	1.0e−01
Red meat[a]	0.064	0.05	1.07	1.9e−01
Total calcium[a]	0.069	0.03	1.07	2.3e−02
BMI (per 5 kg/m^2)	0.287	0.04	1.33	2.1e−12
Ever smoking	0.004	0.11	1.00	9.7e−01
Smoking (pack-years)	0.080	0.03	1.08	1.7e−02
No aspirin use	0.444	0.07	1.56	7.8e−11
No NSAIDs use	0.419	0.11	1.52	1.6e−04
Alcohol drink (0 g/d)	0.059	0.08	0.94	4.3e−01
Alcohol drink (>28 g/d)	0.235	0.08	1.26	2.9e−03
Diabetes	0.233	0.10	1.26	2.6e−02



*Adjusted for age, study, education, total energy consumption and history of screening.
[a] Odds ratios represent the effect per quartile increase in the intakes of dietary factors.

eTable 2. 10-year and 30-year absolute risk of colorectal cancer for a 50-year old individual by environmental risk scores[a,b]

A) 10-year absolute risk for a 50-year old individual by E score quartiles

		Environmental risk score[a,b]							
		Q1		Q2		Q3		Q4	
	Average 10-year AR	AR	95% CI	AR	95% CI	AR	95% CI	AR	95% CI
Overall	0.59	0.38	(0.35,0.39)	0.48	(0.47, 0.49)	0.64	(0.63, 0.65)	0.84	(0.80, 0.87)
Women	0.49	0.32	(0.29, 0.34)	0.41	(0.40, 0.42)	0.54	(0.53, 0.54)	0.70	(0.65, 0.73)
Men	0.68	0.41	(0.38, 0.44)	0.55	(0.53, 0.57)	0.74	(0.73, 0.75)	1.00	(0.93, 1.05)

AR: Absolute risk; 95% CI: 95% confidence interval
[a] Environmental risk score included BMI (kg/m^2), height (cm), smoking (ever/never, pack-years), alcohol consumption (non-drinkers, 1-28g/day, >28g/day), physical activity (sedentary yes/no), regular use of aspirin (yes/no), regular use of other NSAIDs (yes/no), regular use of PMH in women (yes/no), sex- and study-specific quartiles of dietary factors (red meat, processed meat, fruits, vegetables, fiber, folate, calcium), and history of diabetes (yes/no).
[b] Adjusted for age, study, total energy consumption, history of screening and education.

B) 30-year absolute risk for a 50-year old individual by E score quartiles

		Environmental risk score[a,b]							
		Q1		Q2		Q3		Q4	
	Average 30-year AR	AR	95% CI	AR	95% CI	AR	95% CI	AR	95% CI
Overall	3.64	2.29	(2.19, 2.42)	3.01	(2.96, 3.08)	3.94	(3.90, 3.98)	5.16	(4.91, 5.33)
Women	3.20	2.07	(1.91, 2.22)	2.69	(2.62, 2.76)	3.49	(3.45, 5.53)	4.52	(4.31, 4.76)
Men	4.10	2.49	(2.28, 2.67)	3.33	(3.21, 3.44)	4.45	(4.39, 4.51)	5.93	(5.50, 6.33)

AR: Absolute risk; 95% CI: 95% confidence interval
[a] Environmental risk score included BMI (kg/m^2), height (cm), smoking (ever/never, pack-years), alcohol consumption (non-drinkers, 1-28g/day, >28g/day), physical activity (sedentary yes/no), regular use of aspirin (yes/no), regular use of other NSAIDs (yes/no), regular use of PMH in women (yes/no), sex- and study-specific quartiles of dietary factors (red meat, processed meat, fruits, vegetables, fiber, folate, calcium), and history of diabetes (yes/no).
[b] Adjusted for age, study, total energy consumption, history of screening and education.

C) 10-year absolute risk for a 50-year old individual with low, medium and high E scores

		Environmental risk score[a,b]					
		Low (<10%)		Medium (45-55%)		High (>90%)	
	Average 10-year AR	AR	95% CI	AR	95% CI	AR	95% CI
Overall	0.59	0.34	(0.31, 0.35)	0.55	(0.55, 0.56)	0.90	(0.85, 0.87)
Women	0.49	0.29	(0.26, 0.34)	0.46	(0.46, 0.47)	0.74	(0.69, 0.79)
Men	0.68	0.36	(0.33, 0.40)	0.63	(0.62, 0.64)	1.09	(1.01, 1.18)

AR: Absolute risk; 95% CI: 95% confidence interval
[a] Environmental risk score included BMI (kg/m^2), height (cm), smoking (ever/never, pack-years), alcohol consumption (non-drinkers, 1-28g/day, >28g/day), physical activity (sedentary yes/no), regular use of aspirin (yes/no), regular use of other NSAIDs (yes/no), regular use of PMH in women (yes/no), sex- and study-specific quartiles of dietary factors (red meat, processed meat, fruits, vegetables, fiber, folate, calcium), and history of diabetes (yes/no).
[b] Adjusted for age, study, total energy consumption, history of screening and education.

D) 30-year absolute risk for a 50-year old individual with low, medium and high E scores

		Environmental risk score[a,b]					
		Low (<10%)		Medium (45-55%)		High (>90%)	
	Average 30-year AR	AR	95% CI	AR	95% CI	AR	95% CI

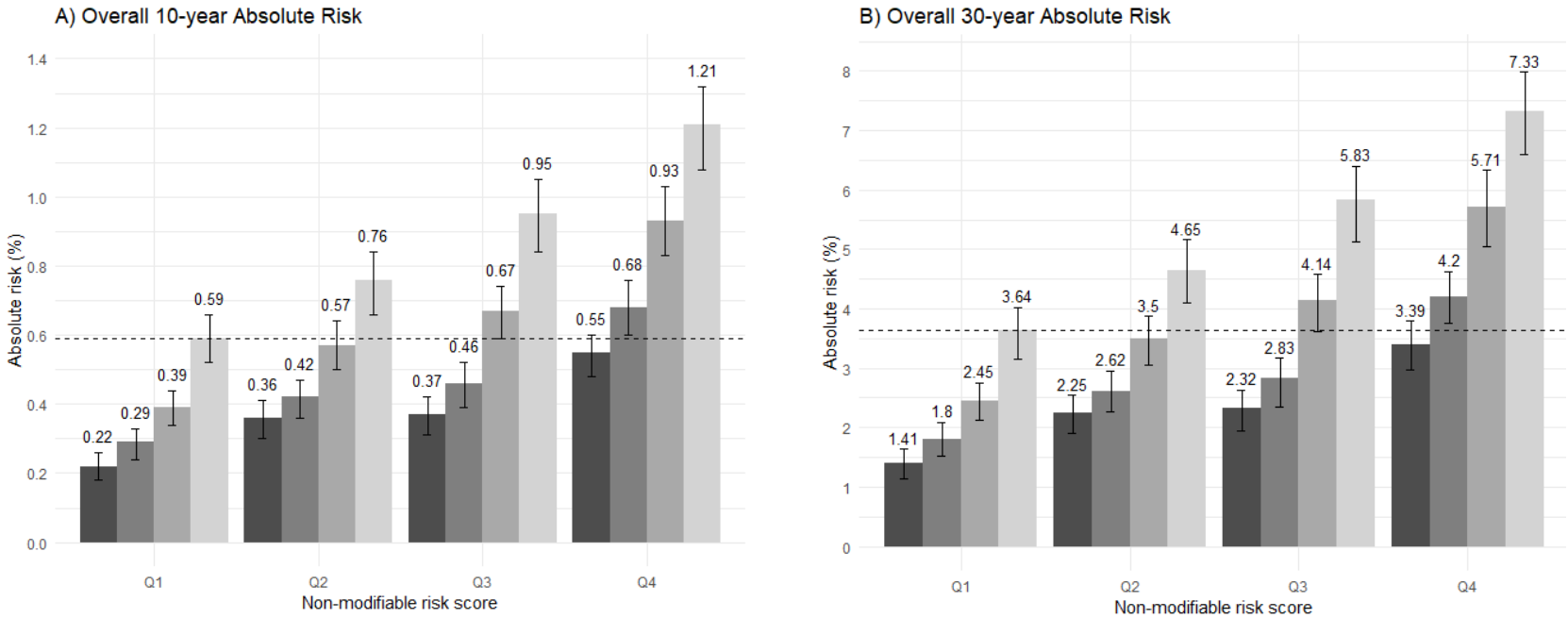
Overall	3.64	2.09	(1.94, 2.21)	3.40	(3.38, 3.44)	5.51	(5.31, 5.72)
Women	3.20	1.91	(1.76, 2.10)	3.03	(2.99, 3.07)	4.77	(4.52, 5.02)
Men	4.10	2.21	(2.00, 2.40)	3.80	(3.75, 3.86)	6.49	(5.97, 6.96)

AR: Absolute risk; 95% CI: 95% confidence interval

[a] Environmental risk score included BMI (kg/m^2), height (cm), smoking (ever/never, pack-years), alcohol consumption (non-drinkers, 1-28g/day, >28g/day), physical activity (sedentary yes/no), regular use of aspirin (yes/no), regular use of other NSAIDs (yes/no), regular use of PMH in women (yes/no), sex- and study-specific quartiles of dietary factors (red meat, processed meat, fruits, vegetables, fiber, folate, calcium), and history of diabetes (yes/no).

[b] Adjusted for age, study, total energy consumption, history of screening and education.

eFigure 2. Distribution of absolute risk associated with modifiable risk score[a] stratified by non-modifiable risk score quartiles[b] in the United States



Modifiable risk score	Q1	Q2	Q3	Q4
Q1	0.22 (0.18, 0.26)	0.36 (0.30, 0.41)	0.37 (0.31, 0.42)	0.55 (0.48, 0.60)
Q2	0.29 (0.24, 0.33)	0.42 (0.36, 0.47)	0.46 (0.39, 0.52)	0.68 (0.60, 0.76)
Q3	0.39 (0.34, 0.44)	0.57 (0.50, 0.64)	0.67 (0.59, 0.74)	0.93 (0.83, 1.03)
Q4	0.59 (0.52, 0.66)	0.76 (0.66, 0.84)	0.95 (0.84, 1.05)	1.21 (1.08, 1.32)

Modifiable risk score	Q1	Q2	Q3	Q4
Q1	1.41 (1.15, 1.64)	2.25 (1.90, 2.55)	2.32 (1.95, 2.64)	3.39 (2.98, 3.80)
Q2	1.80 (1.53, 2.09)	2.62 (2.26, 2.96)	2.83 (2.34, 3.17)	4.20 (3.75, 4.63)
Q3	2.45 (2.12, 2.76)	3.50 (3.05, 4.58)	4.14 (3.62, 4.58)	5.71 (5.04, 6.33)
Q4	3.64 (3.16, 4.03)	4.65 (4.10, 5.16)	5.83 (5.12, 6.40)	7.33 (6.60, 7.98)

* Dashed lines indicate the average absolute risks of CRC for a 50-year-old person: 0.59% for 10-year absolute risk, and 3.64% for 30-year absolute risk.
[a] Modifiable risk score included BMI, sedentary, smoking, pack-years of smoking, intakes of alcohol, fiber, calcium, folate, processed meat, red meat, fruit and vegetables, use of aspirin and non-aspirin NSAIDs, PMH use among women and diabetes.
[b] Non-modifiable risk score included age, sex, height, family history of CRC, and common genetic predisposition based on 63 GWAS-identified SNPs.

eTable 3. 10-year and 30-year absolute risk of colorectal cancer for a 50-year old individual by environmental risk scores[a,b] and history of screening

A) 10-year absolute risk for a 50-year old individual by E score quartiles

	Environmental risk score[a,b]							
	Q1		Q2		Q3		Q4	
	Yes[c]	No[d]	Yes[c]	No[d]	Yes[c]	No[d]	Yes[c]	No[d]
Overall	0.39	0.32	0.50	0.46	0.65	0.64	0.84	0.90
Women	0.34	0.28	0.43	0.39	0.54	0.53	0.69	0.73
Men	0.42	0.35	0.56	0.51	0.75	0.75	1.00	1.08

AR: Absolute risk; 95% CI: 95% confidence interval
[a] Environmental risk score included BMI (kg/m^2), height (cm), smoking (ever/never, pack-years), alcohol consumption (non-drinkers, 1-28g/day, >28g/day), physical activity (sedentary yes/no), regular use of aspirin (yes/no), regular use of other NSAIDs (yes/no), regular use of PMH in women (yes/no), sex- and study-specific quartiles of dietary factors (red meat, processed meat, fruits, vegetables, fiber, folate, calcium), and history of diabetes (yes/no).
[b] Adjusted for age, study, total energy consumption, history of screening and education.
[c] Estimated attributable risk based on participants with history of screening endoscopy
[d] Estimated attributable risk based on participants with no history of screening endoscopy

B) 30-year absolute risk for a 50-year old individual by E score quartiles

	Environmental risk score[a,b]							
	Q1		Q2		Q3		Q4	
	Yes[c]	No[d]	Yes[c]	No[d]	Yes[c]	No[d]	Yes[c]	No[d]
Overall	2.42	2.02	3.11	2.83	3.99	3.95	5.12	5.50
Women	2.24	1.87	2.81	2.55	3.54	3.48	4.44	4.73
Men	2.51	2.15	3.35	3.10	4.47	4.73	5.94	6.42

AR: Absolute risk; 95% CI: 95% confidence interval
[a] Environmental risk score included BMI (kg/m^2), height (cm), smoking (ever/never, pack-years), alcohol consumption (non-drinkers, 1-28g/day, >28g/day), physical activity (sedentary yes/no), regular use of aspirin (yes/no), regular use of other NSAIDs (yes/no), regular use of PMH in women (yes/no), sex- and study-specific quartiles of dietary factors (red meat, processed meat, fruits, vegetables, fiber, folate, calcium), and history of diabetes (yes/no).
[b] Adjusted for age, study, total energy consumption, history of screening and education.
[c] Estimated attributable risk based on participants with history of screening endoscopy
[d] Estimated attributable risk based on participants with no history of screening endoscopy

C) 10-year absolute risk for a 50-year old individual with low, medium and high E scores

	Environmental risk score[a,b]					
	Low (<10%)		Medium (45-55%)		High (>90%)	
	Yes[c]	No[d]	Yes[c]	No[d]	Yes[c]	No[d]
Overall	0.35	0.28	0.56	0.51	0.89	0.94
Women	0.32	0.26	0.48	0.44	0.72	0.76
Men	0.34	0.29	0.61	0.76	1.09	1.14

AR: Absolute risk; 95% CI: 95% confidence interval
[a] Environmental risk score included BMI (kg/m^2), height (cm), smoking (ever/never, pack-years), alcohol consumption (non-drinkers, 1-28g/day, >28g/day), physical activity (sedentary yes/no), regular use of aspirin (yes/no), regular use of other NSAIDs (yes/no), regular use of PMH in women (yes/no), sex- and study-specific quartiles of dietary factors (red meat, processed meat, fruits, vegetables, fiber, folate, calcium), and history of diabetes (yes/no).
[b] Adjusted for age, study, total energy consumption, history of screening and education.
[c] Estimated attributable risk based on participants with history of screening endoscopy

[d] Estimated attributable risk based on participants with no history of screening endoscopy

D) 30-year absolute risk for a 50-year old individual with low, medium and high E scores

	Environmental risk score[a,b]					
	Low (<10%)		Medium (45-55%)		High (>90%)	
	Yes[c]	No[d]	Yes[c]	No[d]	Yes[c]	No[d]
Overall	2.20	1.75	3.46	3.18	5.44	5.75
Women	2.11	1.68	3.14	2.88	4.66	4.93
Men	2.08	1.76	3.67	3.46	6.45	6.75

AR: Absolute risk (%); 95% CI: 95% confidence interval

[a] Environmental risk score included BMI (kg/m^2), height (cm), smoking (ever/never, pack-years), alcohol consumption (non-drinkers, 1-28g/day, >28g/day), physical activity (sedentary yes/no), regular use of aspirin (yes/no), regular use of other NSAIDs (yes/no), regular use of PMH in women (yes/no), sex- and study-specific quartiles of dietary factors (red meat, processed meat, fruits, vegetables, fiber, folate, calcium), and history of diabetes (yes/no).

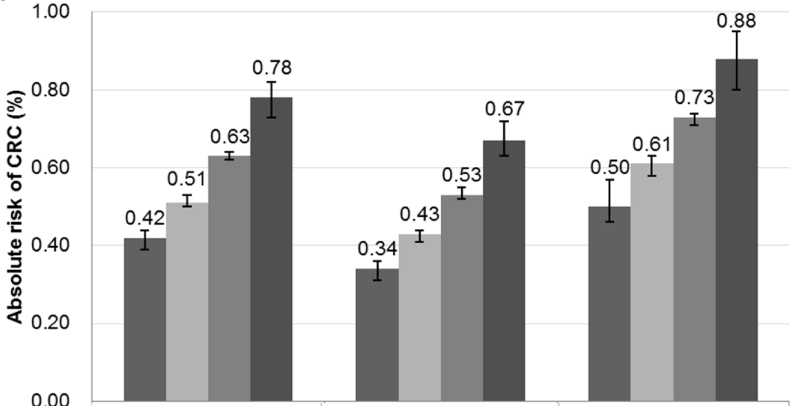
[b] Adjusted for age, study, total energy consumption, history of screening and education.

[c] Estimated attributable risk based on participants with history of screening endoscopy

[d] Estimated attributable risk based on participants with no history of screening endoscopy

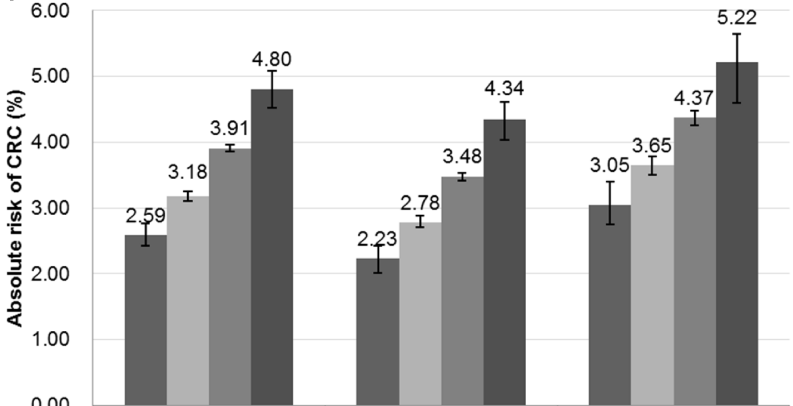
eFigure 3. 10-year and 30-year absolute risk of colorectal cancer for a 50-year old individual by environmental risk scores[a,b] by study design

A) 10-year absolute risk of colorectal cancer by environmental risk quartiles in cohort studies



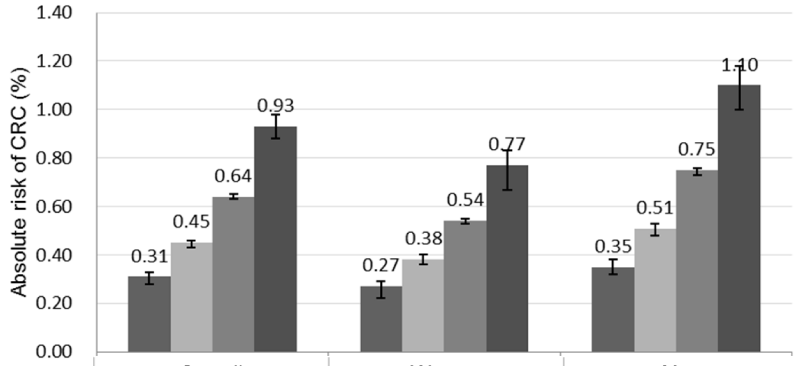
	Overall	Women	Men
Q1	0.42 (0.39, 0.44)	0.34 (0.31, 0.36)	0.50 (0.46, 0.57)
Q2	0.51 (0.50, 0.53)	0.43 (0.41, 0.44)	0.61 (0.58, 0.63)
Q3	0.63 (0.62, 0.64)	0.53 (0.52, 0.55)	0.73 (0.71, 0.74)
Q4	0.78 (0.73, 0.82)	0.67 (0.63, 0.72)	0.88 (0.80, 0.95)

B) 30-year absolute risk of colorectal cancer by environmental risk quartiles in cohort studies



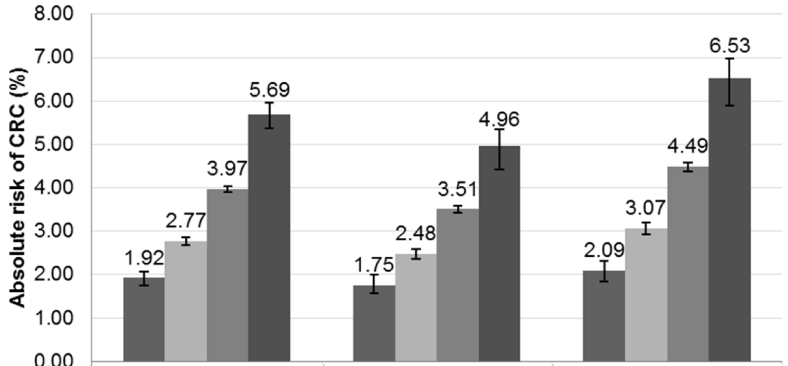
	Overall	Women	Men
Q1	2.59 (2.42, 2.76)	2.23 (2.02, 2.43)	3.05 (2.75, 3.40)
Q2	3.18 (3.11, 3.26)	2.78 (2.70, 2.89)	3.65 (3.51, 3.78)
Q3	3.91 (3.86, 3.96)	3.48 (3.41, 3.53)	4.37 (4.26, 4.48)
Q4	4.80 (4.53, 5.08)	4.34 (4.04, 4.61)	5.22 (4.59, 5.65)

C) 10-year absolute risk of colorectal cancer by environmental risk quartiles in case-control studies



	Overall	Women	Men
Q1	0.31 (0.28, 0.33)	0.27 (0.22, 0.29)	0.35 (0.32, 0.38)
Q2	0.45 (0.43, 0.46)	0.38 (0.36, 0.40)	0.51 (0.48, 0.53)
Q3	0.64 (0.63, 0.65)	0.54 (0.53, 0.55)	0.75 (0.73, 0.76)
Q4	0.93 (0.88, 0.98)	0.77 (0.67, 0.83)	1.10 (1.00, 1.18)

D) 30-year absolute risk of colorectal cancer by environmental risk quartiles in case-control studies



	Overall	Women	Men
Q1	1.92 (1.76, 2.07)	1.75 (1.56, 1.99)	2.09 (1.85, 2.32)
Q2	2.77 (2.67, 2.86)	2.48 (2.37, 2.58)	3.07 (2.92, 3.19)
Q3	3.97 (3.91, 4.03)	3.51 (3.43, 3.59)	4.49 (4.37, 4.59)
Q4	5.69 (5.37, 5.96)	4.96 (4.43, 5.34)	6.53 (5.89, 6.97)

[a] Environmental risk score included BMI (kg/m^2), height (cm), smoking (ever/never, pack-years), alcohol consumption (non-drinkers, 1-28g/day, >28g/day), physical activity (sedentary yes/no), regular use of aspirin (yes/no), regular use of other NSAIDs (yes/no), regular use of PMH in women (yes/no), sex- and study-specific quartiles of dietary factors (red meat, processed meat, fruits, vegetables, fiber, folate, calcium), and history of type 2 diabetes (yes/no)
[b] Adjusted for age, study, total energy consumption, history of screening and education.

Reference

1 Hutter CM, Chang-Claude J, Slattery ML, Pflugeisen BM, Lin Y, Duggan D*, et al.* Characterization of gene-environment interactions for colorectal cancer susceptibility loci. Cancer Res 2012;**72**:2036-44.
2 Thrift AP, Gong J, Peters U, Chang-Claude J, Rudolph A, Slattery ML*, et al.* Mendelian randomization study of height and risk of colorectal cancer. Int J Epidemiol 2015;**44**:662-72.
3 Kantor ED, Hutter CM, Minnier J, Berndt SI, Brenner H, Caan BJ*, et al.* Gene-environment interaction involving recently identified colorectal cancer susceptibility Loci. Cancer Epidemiol Biomarkers Prev 2014;**23**:1824-33.
4 Moghaddam AA, Woodward M, Huxley R. Obesity and risk of colorectal cancer: a meta-analysis of 31 studies with 70,000 events. Cancer Epidemiol Biomarkers Prev 2007;**16**:2533-47.
5 Thrift AP, Gong J, Peters U, Chang-Claude J, Rudolph A, Slattery ML*, et al.* Mendelian Randomization Study of Body Mass Index and Colorectal Cancer Risk. Cancer Epidemiol Biomarkers Prev 2015;**24**:1024-31.
6 Slattery ML. Physical activity and colorectal cancer. Sports Med 2004;**34**:239-52.
7 Botteri E, Iodice S, Bagnardi V, Raimondi S, Lowenfels AB, Maisonneuve P. Smoking and colorectal cancer: a meta-analysis. JAMA 2008;**300**:2765-78.
8 Gong J, Hutter CM, Newcomb PA, Ulrich CM, Bien SA, Campbell PT*, et al.* Genome-Wide Interaction Analyses between Genetic Variants and Alcohol Consumption and Smoking for Risk of Colorectal Cancer. PLoS Genet 2016;**12**:e1006296.
9 Liang PS, Chen TY, Giovannucci E. Cigarette smoking and colorectal cancer incidence and mortality: systematic review and meta-analysis. Int J Cancer 2009;**124**:2406-15.
10 Gong J, Hutter C, Baron JA, Berndt S, Caan B, Campbell PT*, et al.* A pooled analysis of smoking and colorectal cancer: timing of exposure and interactions with environmental factors. Cancer Epidemiol Biomarkers Prev 2012;**21**:1974-85.
11 Cho E, Smith-Warner SA, Ritz J, van den Brandt PA, Colditz GA, Folsom AR*, et al.* Alcohol intake and colorectal cancer: a pooled analysis of 8 cohort studies. Ann Intern Med 2004;**140**:603-13.
12 Chubak J, Whitlock EP, Williams SB, Kamineni A, Burda BU, Buist DS*, et al.* Aspirin for the Prevention of Cancer Incidence and Mortality: Systematic Evidence Reviews for the U.S. Preventive Services Task Force. Ann Intern Med 2016;**164**:814-25.
13 Nan H, Hutter CM, Lin Y, Jacobs EJ, Ulrich CM, White E*, et al.* Association of aspirin and NSAID use with risk of colorectal cancer according to genetic variants. JAMA 2015;**313**:1133-42.
14 Garcia-Albeniz X, Rudolph A, Hutter C, White E, Lin Y, Rosse SA*, et al.* CYP24A1 variant modifies the association between use of oestrogen plus progestogen therapy and colorectal cancer risk. Br J Cancer 2016;**114**:221-9.
15 Grodstein F, Newcomb PA, Stampfer MJ. Postmenopausal hormone therapy and the risk of colorectal cancer: a review and meta-analysis. Am J Med 1999;**106**:574-82.
16 Cho E, Smith-Warner SA, Spiegelman D, Beeson WL, van den Brandt PA, Colditz GA*, et al.* Dairy foods, calcium, and colorectal cancer: a pooled analysis of 10 cohort studies. J Natl Cancer Inst 2004;**96**:1015-22.
17 Giovannucci E, Stampfer MJ, Colditz GA, Hunter DJ, Fuchs C, Rosner BA*, et al.* Multivitamin use, folate, and colon cancer in women in the Nurses' Health Study. Ann Intern Med 1998;**129**:517-24.
18 Park Y, Hunter DJ, Spiegelman D, Bergkvist L, Berrino F, van den Brandt PA*, et al.* Dietary fiber intake and risk of colorectal cancer: a pooled analysis of prospective cohort studies. JAMA 2005;**294**:2849-57.
19 Suitor CW, Bailey LB. Dietary folate equivalents: interpretation and application. J Am Diet Assoc 2000;**100**:88-94.
20 Ananthakrishnan AN, Du M, Berndt SI, Brenner H, Caan BJ, Casey G*, et al.* Red meat intake, NAT2, and risk of colorectal cancer: a pooled analysis of 11 studies. Cancer Epidemiol Biomarkers Prev 2015;**24**:198-205.
21 Chao A, Thun MJ, Connell CJ, McCullough ML, Jacobs EJ, Flanders WD*, et al.* Meat consumption and risk of colorectal cancer. JAMA 2005;**293**:172-82.
22 Du M, Zhang X, Hoffmeister M, Schoen RE, Baron JA, Berndt SI*, et al.* No evidence of gene-calcium interactions from genome-wide analysis of colorectal cancer risk. Cancer Epidemiol Biomarkers Prev 2014;**23**:2971-6.
23 Figueiredo JC, Hsu L, Hutter CM, Lin Y, Campbell PT, Baron JA*, et al.* Genome-wide diet-gene interaction analyses for risk of colorectal cancer. PLoS Genet 2014;**10**:e1004228.
24 Kim DH, Smith-Warner SA, Spiegelman D, Yaun SS, Colditz GA, Freudenheim JL*, et al.* Pooled analyses of 13 prospective cohort studies on folate intake and colon cancer. Cancer Causes Control 2010;**21**:1919-30.
25 Koushik A, Hunter DJ, Spiegelman D, Beeson WL, van den Brandt PA, Buring JE*, et al.* Fruits, vegetables, and colon cancer risk in a pooled analysis of 14 cohort studies. J Natl Cancer Inst 2007;**99**:1471-83.

26 Hsu L, Jeon J, Brenner H, Gruber SB, Schoen RE, Berndt SI*, et al.* A model to determine colorectal cancer risk using common genetic susceptibility loci. Gastroenterology 2015;**148**:1330-9 e14.
27 SEER*Explorer: An interactive website for SEER cancer statistics. Surveillance Research Program, National Cancer Institute.
28 Gail MH, Brinton LA, Byar DP, Corle DK, Green SB, Schairer C*, et al.* Projecting individualized probabilities of developing breast cancer for white females who are being examined annually. J Natl Cancer Inst 1989;**81**:1879-86.