
F!GHT
COLORECTAL CANCER

LEARNING SERIES

FIGHT COLORECTAL CANCER

The Role of Gene-Environment Interactions on Early-Age Onset Colorectal Cancer

Tuesday, January 12 12:00 PM Eastern

RICHARD B. HAYES DDS, PHD, MPH

Professor of Epidemiology

NYU School of Medicine

PETER T. CAMPBELL PHD, MSC

Scientific Director

American Cancer Society

NEIL MURPHY PHD, MSC

Scientist,
Nutrition and Metabolism Section

International Agency for Research on Cancer

Early-Age Onset Workgroup Research Learning Session #4 Agenda

12:00-12:10p ET	Welcome and Introductions: Elsa Weltzien and Andrea (Andi) Dwyer
12:10- 12:45p ET	Dr. Richard Hayes: Role of gene-environment interactions on EAO CRC
12:45-12:55p ET	Discussion with Drs Peter Campbell and Neil Murphy: implications and opportunities for future work
1:05-1:50p ET	Discussion
1:50-2:00p ET	Close out and next steps: Andi Dwyer

- **Next EAO Workgroup webinar:**

- March 4, 2021 (Tuesday, 12pm ET)**.** Registration coming soon!

- **3rd Annual EAO CRC International Symposium**

- **Date:** June 24 & 25, 2021**.** Registration launching March 2021
- **Location:** Virtual
- **Goal:** During the 2021 symposium, the EAO workgroup and advocacy and clinical partners worldwide will continue multi-disciplinary, action-based discussions in order to advance research on the causes of EAO CRC and practice-based strategies for clinical public health.

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NYU Langone Health

RISK FACTORS AND EARLY-ONSET COLORECTAL CANCER (CRC)

NYU Langone Health, NYC

Alexi N. Archambault, MPH

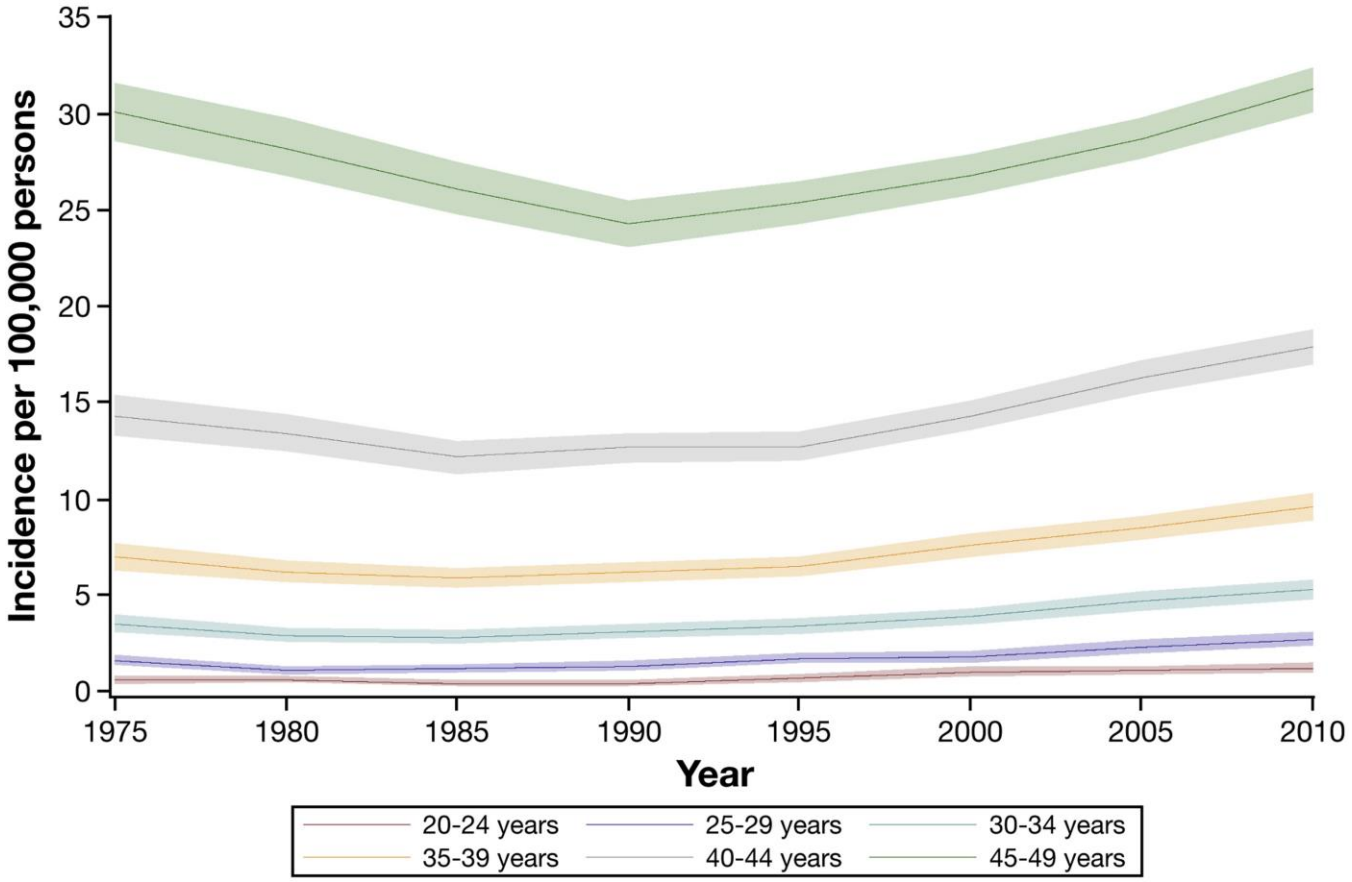
Richard B. Hayes, DDS, MPH, PhD

Fred Hutchinson Cancer Center, Seattle

Ulrike Peters, PhD, MPH

Background

- Early-onset CRC projected to account for 10% to 25% of newly-diagnosed CRC in the U.S. by 2030
- Presents with:
  - Higher pathologic grade
  - Distant disease
  - Greater incidence of recurrence and metastatic disease



Murphy CC, Singal AG, Baron JA, Sandler RS. Decrease in Incidence of Young-Onset Colorectal Cancer Before Recent Increase. *Gastroenterology*. 2018;155(6):1716–1719.e4.

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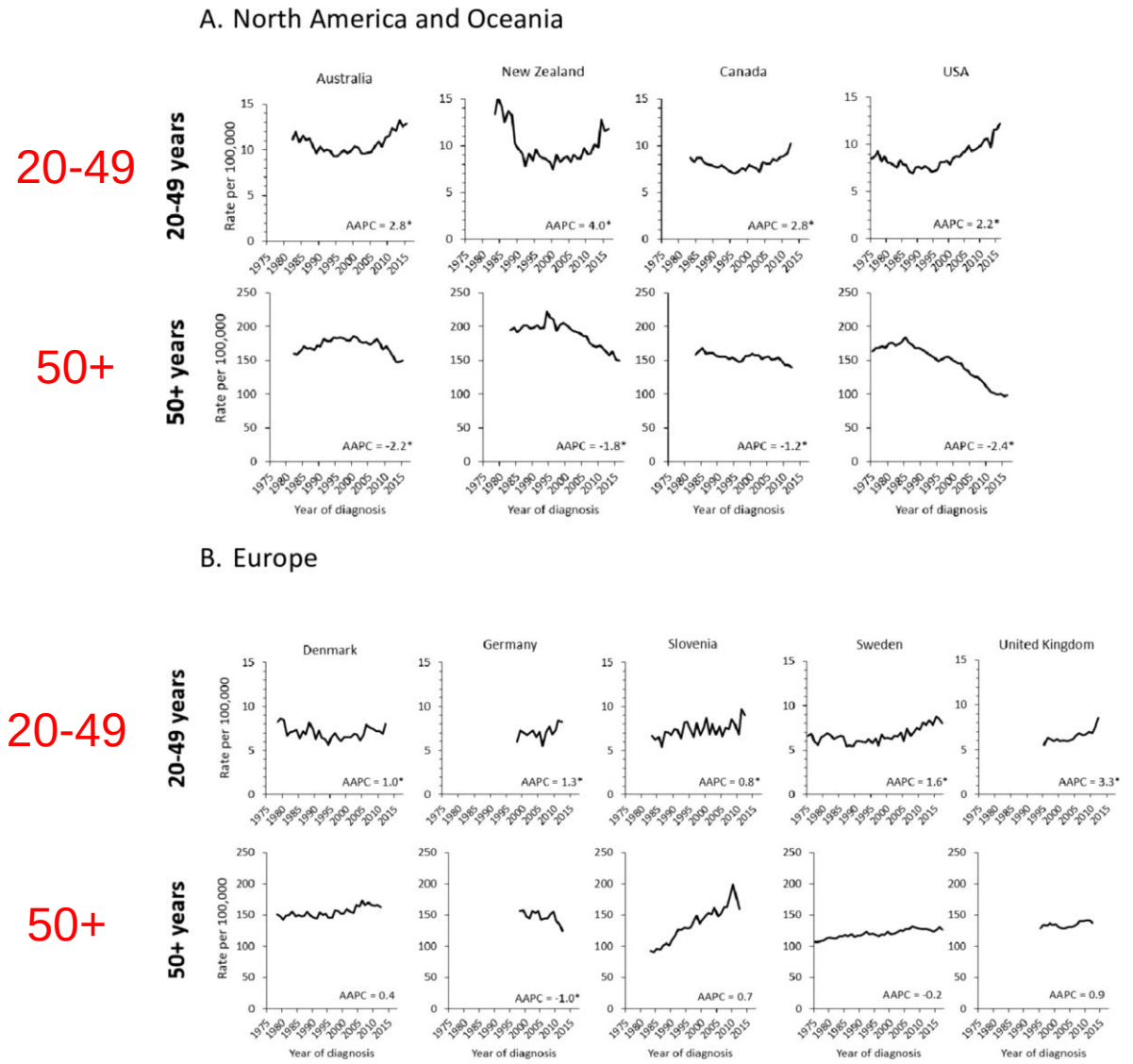
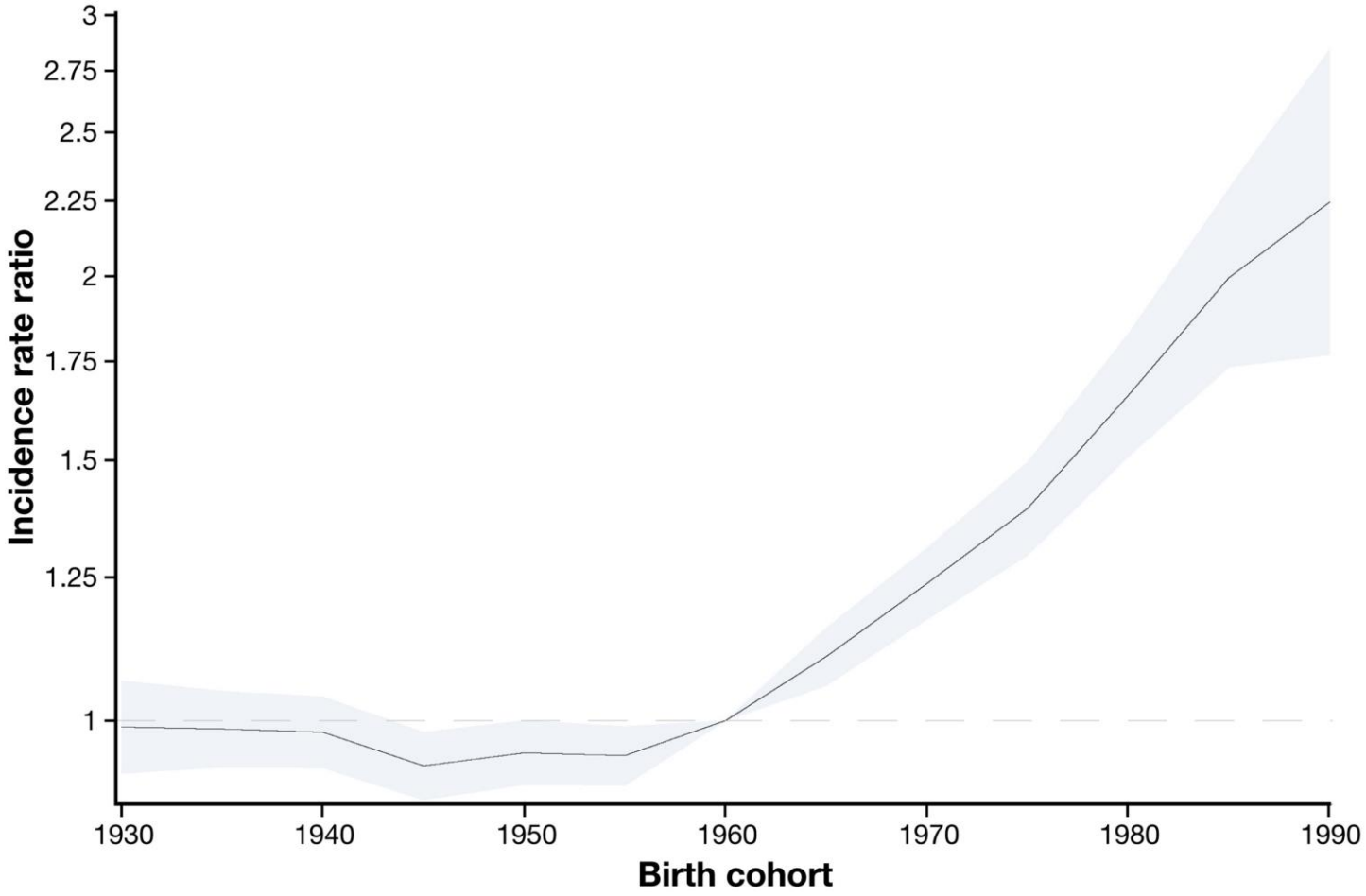
CRC incidence increases in young adults in nine high-income countries spanning three continents



Rebecca L Siegel et al. Gut 2019

Birth cohort effects



- Incidence increasing by birth cohort
- Beginning with the 1960 birth cohort

Murphy CC, Singal AG, Baron JA, Sandler RS. Decrease in Incidence of Young-Onset Colorectal Cancer Before Recent Increase. *Gastroenterology*. 2018;155(6):1716–1719.e4.

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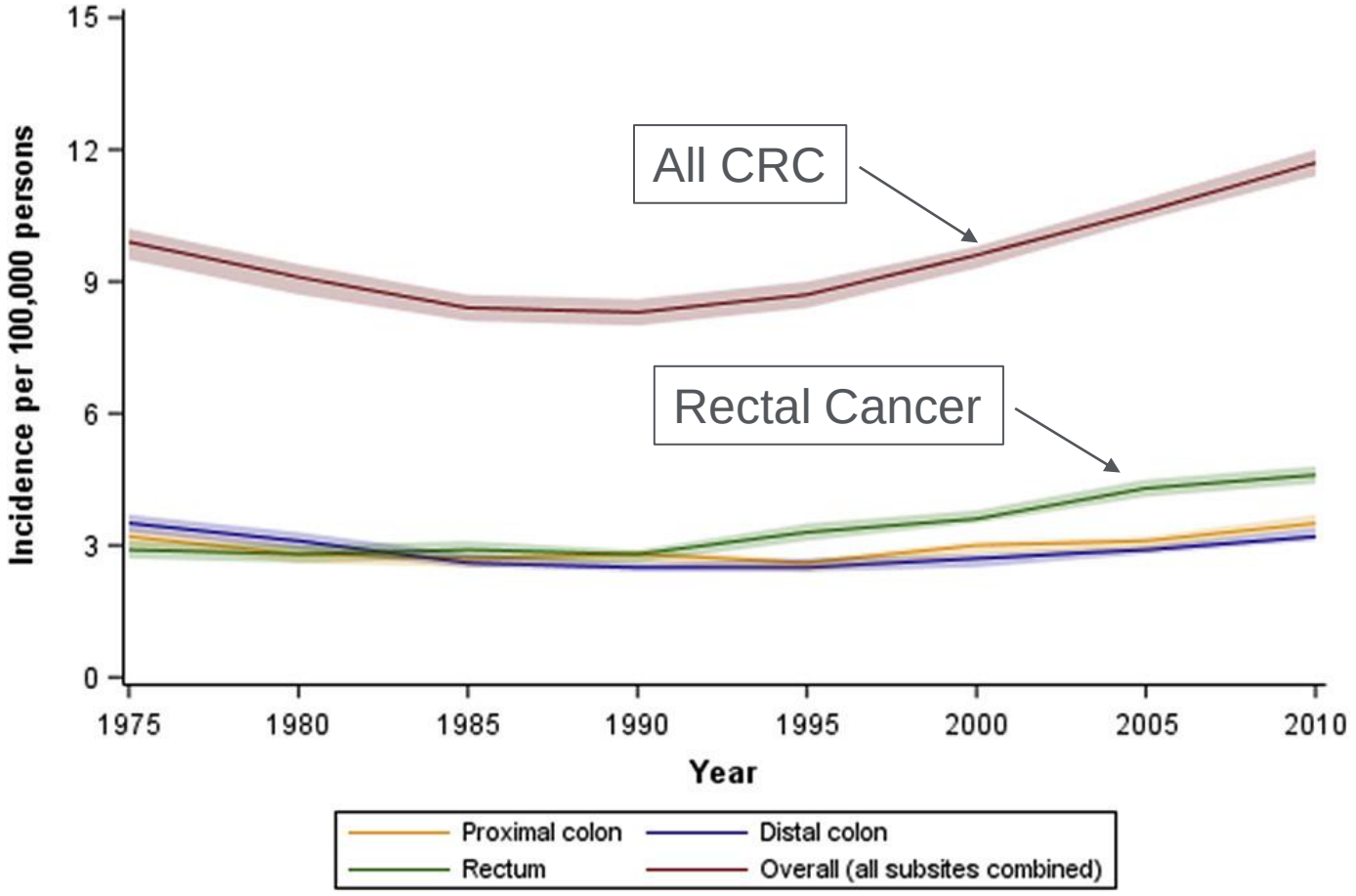
Greater proportion of rectal cancer

- Since 1990, increases in incidence have been driven primarily by higher rates of rectal cancer



Murphy CC, Singal AG, Baron JA, Sandler RS. Decrease in Incidence of Young-Onset Colorectal Cancer Before Recent Increase. *Gastroenterology*. 2018;155(6):1716–1719.e4.

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Objectives

- Investigate early-onset CRC risks associated with a 95 SNP polygenic risk score (PRS)
- Investigate early-onset CRC risks associated with lifestyle and environmental risk factors (E-score)
- Investigate prediction of CRC using a genetic score (PRS) and lifestyle/environmental score (E-score)

Study Participants

Discovery Dataset

- 108,062 participants, including 50,023 CRC cases and 58,039 controls
- From three large consortia: the Colon Cancer Family Registry (CCFR), the Colorectal Transdisciplinary (CORECT) Study, and the Genetics and Epidemiology of Colorectal Cancer Consortium (GECCO)
- European descent
- PRS in unconditional logistic regression

Replication Dataset

- 72,573 participants (25 cases <50 years at diagnosis)
- Research Program on Genes, Environment and Health (RPGEH), a cohort comprised of Kaiser Permanente Northern California (KPNC) health plan members
- European descent
- PRS in Cox regression

Replication Excluding Cases with Lynch Syndrome

- 518 non-Lynch cases and 979 controls, <50 years of age
- Ohio State University Medical Center (OSUMC) & CCFR
- European descent
- PRS in unconditional logistic regression

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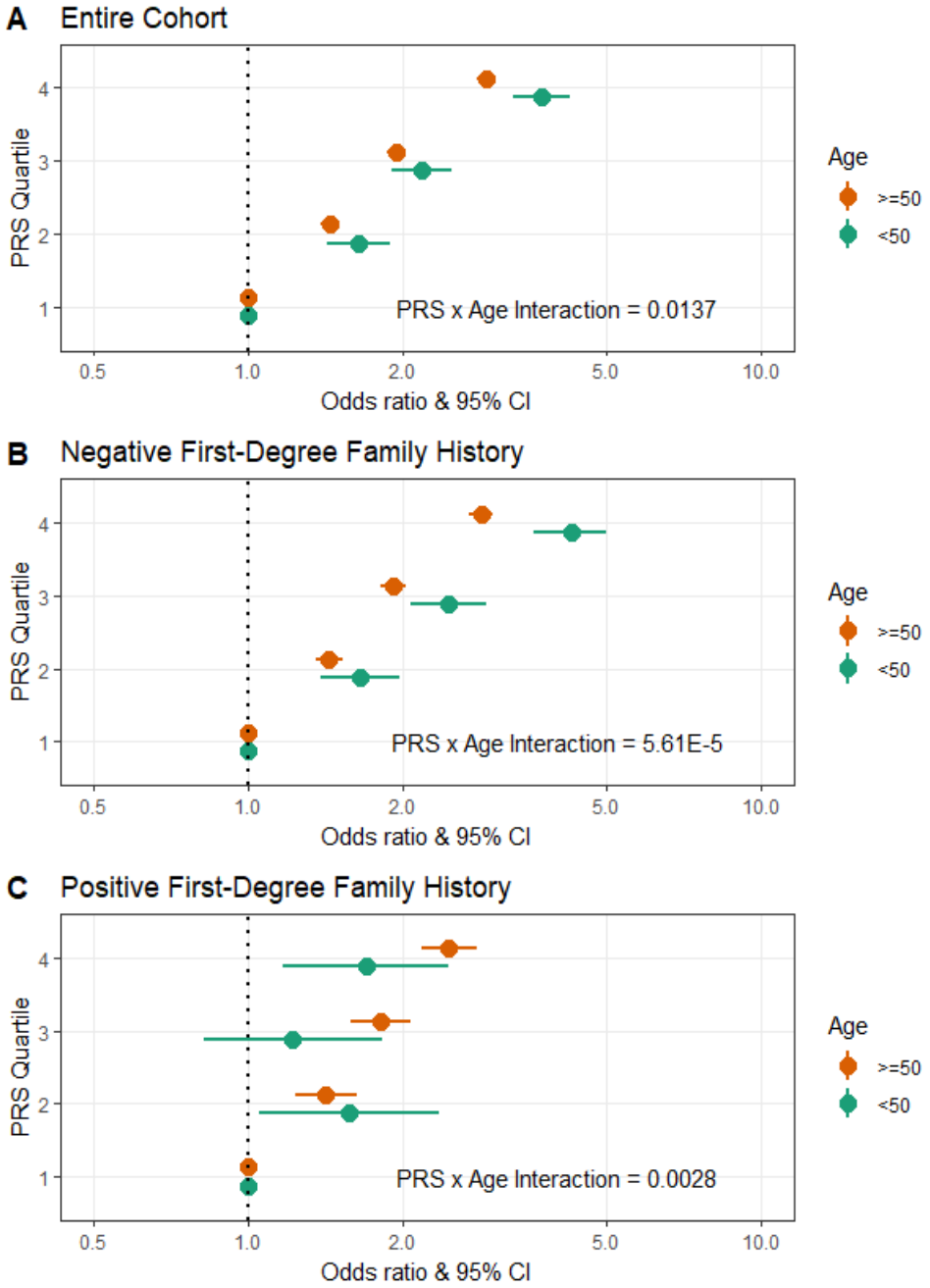
Weighted PRS Development

- Prior discovery of 95 SNPs associated with CRC
  - 55 from prior initiatives
  - 40 novel SNPs from this consortium
- Computed log-odds ratios for CRC with the following independent variables: 95 SNPs, sex, age, principal components, and genotype platform
  - For 40 SNPs first discovered in this dataset, we implemented a winner's curse adjustment (Zhong and Prentice, 2008)
- PRS was weighted by multiplying the number of risk alleles for each SNP by their adjusted log-odds ratios
- Modelled as a continuous variable per 1 standard deviation (SD), transformed to the standard normal distribution, and in quartiles

Relative Risk of CRC, by age and First-degree family history of CRC



(A) All participants

(B) Negative for a family history of CRC

(C) Positive for a family history of CRC

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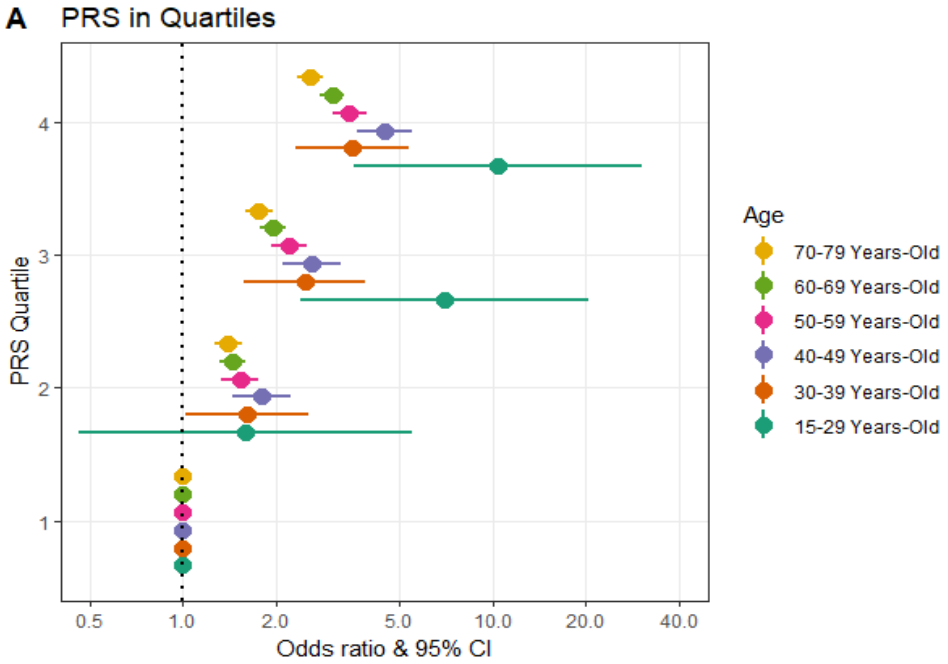
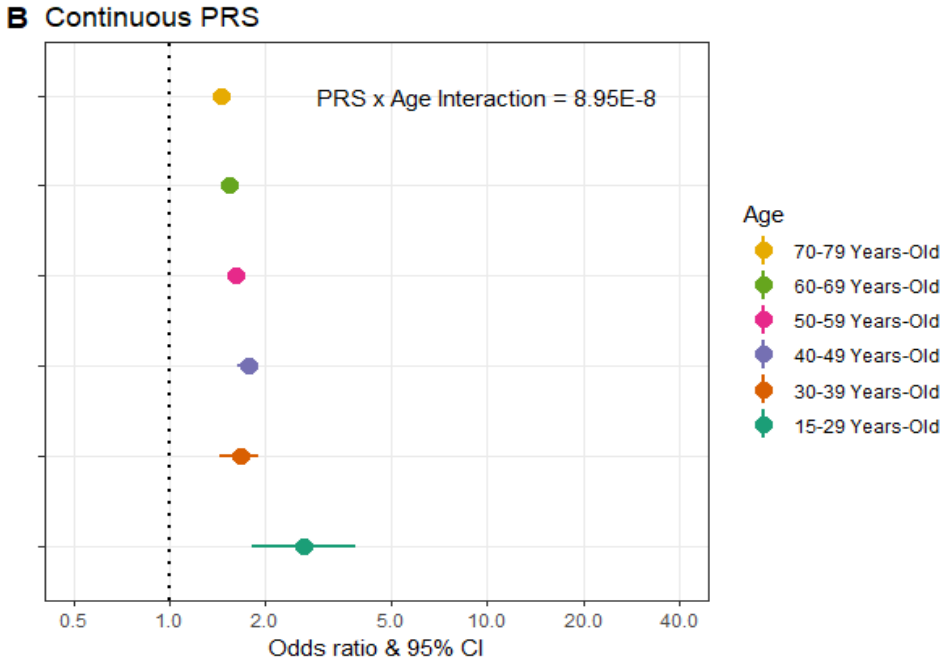
Relative Risk of CRC, by age among participants without a first-degree family history of CRC



(A) Model incorporates the PRS in quartiles



(B) Model incorporates the continuous PRS.

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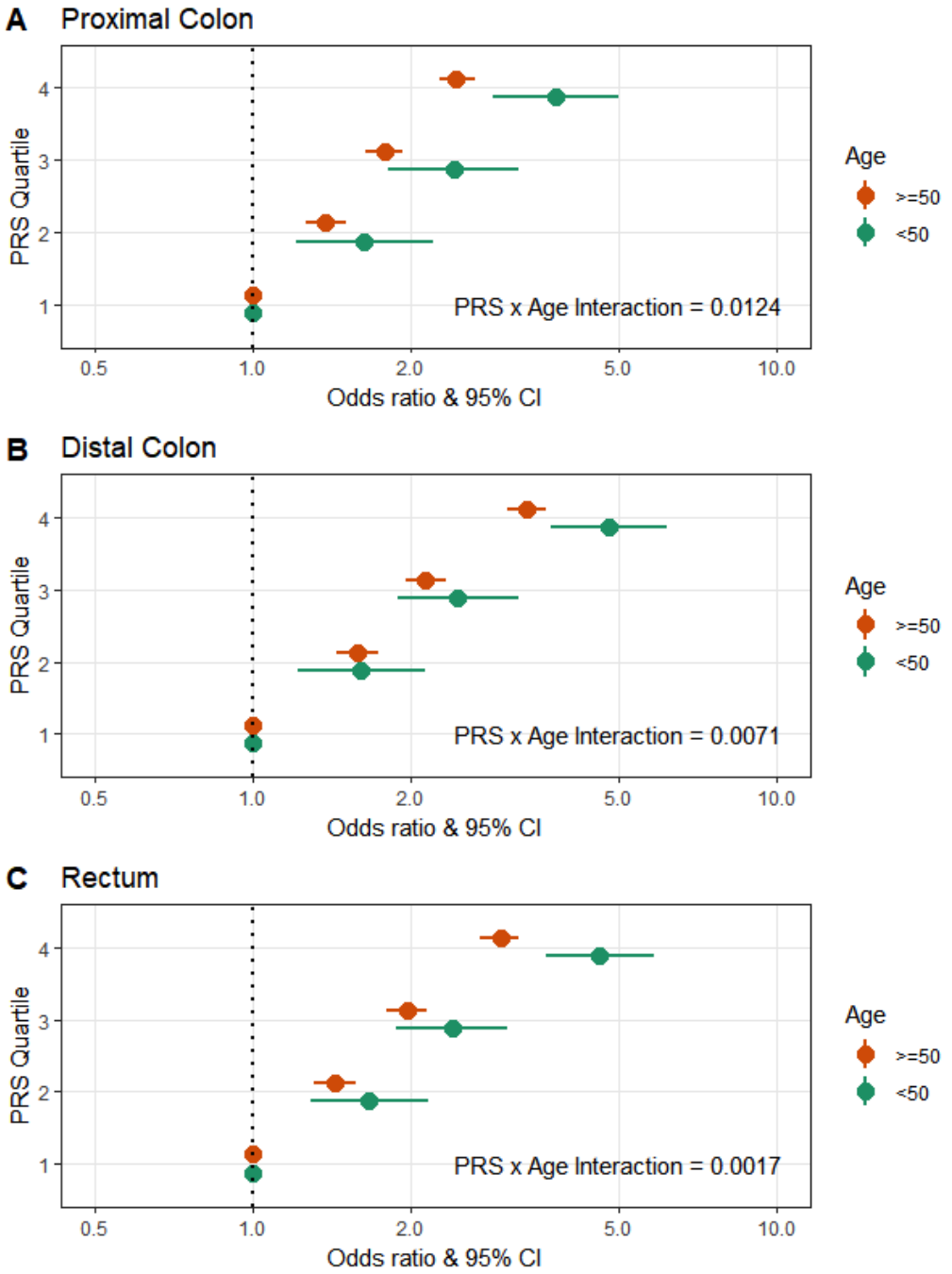

Family History Negative Subjects

Relative Risk of CRC, by Disease Site

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Lynch carriers: Association between the PRS and colorectal cancer risk

Category	N carriers	PRS using the per-allele odds ratio		PRS using the risk allele count	
		HR per SD	95% CI	HR per SD	95% CI
All genes, all carriers	826	0.97	0.88 to 1.06	0.99	0.90 to 1.10
MLH1	293	0.98	0.86 to 1.12	0.97	0.83 to 1.14
MSH2	314	1.02	0.86 to 1.22	1.02	0.88 to 1.17
MSH6	126	0.94	0.76 to 1.16	1.02	0.80 to 1.30
PMS2	71	0.90	0.63 to 1.28	0.99	0.76 to 1.31
EPCAM	22	1.40	0.92 to 2.14	1.95	0.94 to 4.04
Males	387	1.01	0.89 to 1.15	1.01	0.90 to 1.14
Females	439	0.94	0.83 to 1.07	0.98	0.86 to 1.13

Jenkins M et al., JNCI Spectrum, in press

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Independent replication of PRS (per 1 SD) and CRC
Kaiser RPGH Cohort

Study Group	N in cohort	Cases	HR (95% CI)	*P* value
Negative Family History				
<50 Years-Old				
	24,472	18	**1.76** (1.11, 2.78)	0.0161
≥50 Years-Old				
	61,129	871	**1.42** (1.33, 1.52)	2.85E-25
Positive Family History				
<50 Years-Old				
	2,511	7	**1.56** (0.75, 3.26)	0.2334
≥50 Years-Old				
	6,668	202	**1.34** (1.17, 1.54)	2.87E-05

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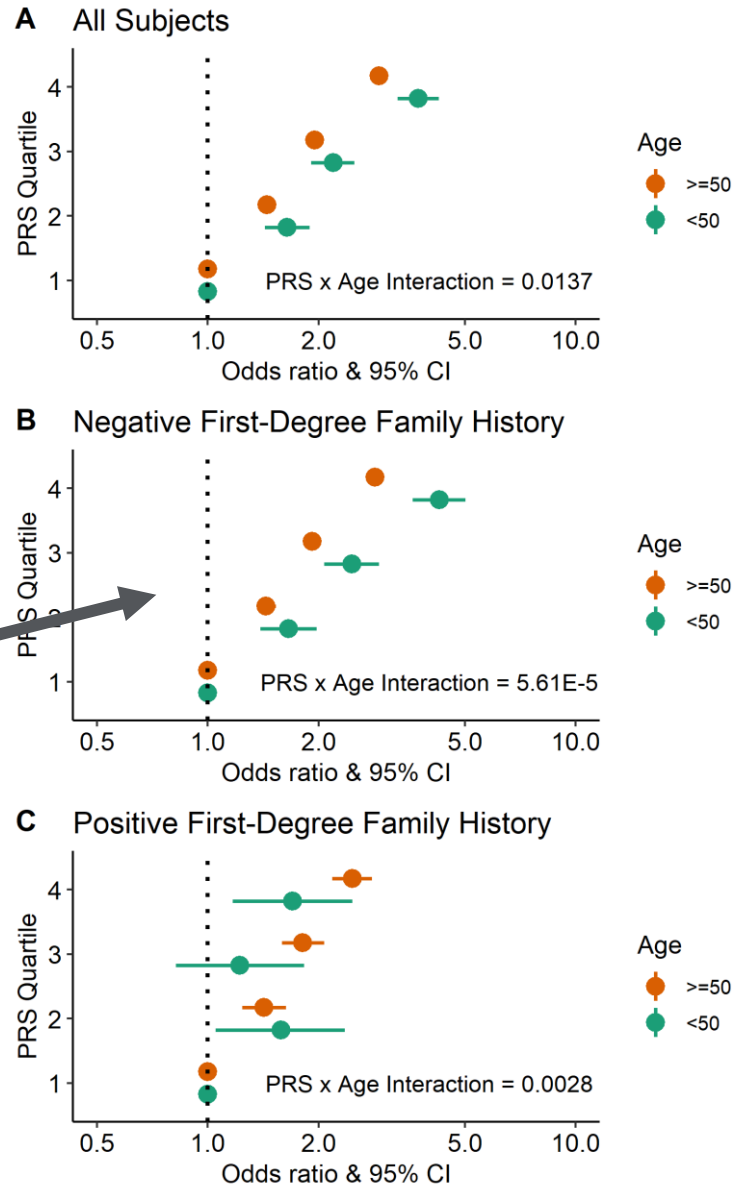
Summary: Genetics and Early-onset CRC

- PRS was more strongly associated with early-onset cancer, particularly for those without a family history.
- PRS tended to predict more strongly for rectal cancer.
- There is a continuous relationship between age and PRS-related risk.
- PRS is not predictive in Lynch carriers in CCFR



Archambault A. et al., *Gastroenterology*. 2020.

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Environment and Early-onset CRC

- Three large, international consortia:
  - The Colon Cancer Family Registry (CCFR)
  - The Colorectal Transdisciplinary (CORECT) Study
  - The Genetics and Epidemiology of Colorectal Cancer Consortium (GECCO)
- 13 studies, with 3,767 CRC cases and 4,049 controls, <50 years. of age
- *Countries represented*: United States, Canada, France, Germany, Greece, Italy, Netherlands, Spain, Sweden, United Kingdom, Australia, and Israel
- Both nested case-control and case-control designs

Escore Variables (N = 18)

Factor	Description, modeling
Anthropometric	
Height	Height per 10 cm, continuous
BMI	Bmi per 5 kg/m2, continuous
Education	Highest education level completed (REF = college graduate + graduate degree)
Dietary intake	
Fiber	Total fiber intake (g/day), study- and sex-specific quartiles, ordinal (REF value “0” = Q4)
Calcium	Total calcium intake (mg/day), study- and sex-specific quartiles, ordinal (REF value “0” = Q4)
Folate	Total folate intake (mcg/day), study- and sex-specific quartiles, ordinal (REF value “0” = Q4)
Processed meat	Processed meat intake (servings/day), study- and sex-specific quartiles, ordinal (REF value “0” = Q1)
Red meat	Red meat intake (servings/day), study- and sex-specific quartiles, ordinal (REF value “0” = Q1)
Fruit	Fruit intake (servings/day), study- and sex-specific quartiles, ordinal (REF value “0” = Q4)
Vegetable	Vegetable intake (servings/day), study- and sex-specific quartiles, ordinal (REF value “0” = Q4)
Total energy consumption	Total energy scaled by standard error, continuous
Lifestyle	
Sedentary	Sedentary lifestyle (y/n; yes = vigorous + moderate PA hrs/wk and leisure + undifferented <1hr/wk) (REF = no)
Ever smoked	Ever smoked cigarettes (y/n) (REF = no)
Pack-years	Pack-years of smoking, study- and sex-specific quartiles, ordinal (REF value “0” = never smoker/Q1)
Alcohol	Alcohol use (g/d; NONDRINKER = ≤1g/day) (REF = nondrinker)
Pharmacological	
Aspirin	Aspirin use at referent time period (y/n) (REF = yes)
NSAIDs	Non-aspirin NSAIDs use at referent time period (y/n) (REF = yes)
Clinical	
Diabetes	Ever diagnosed with diabetes by a doctor (y/n) (REF = no)

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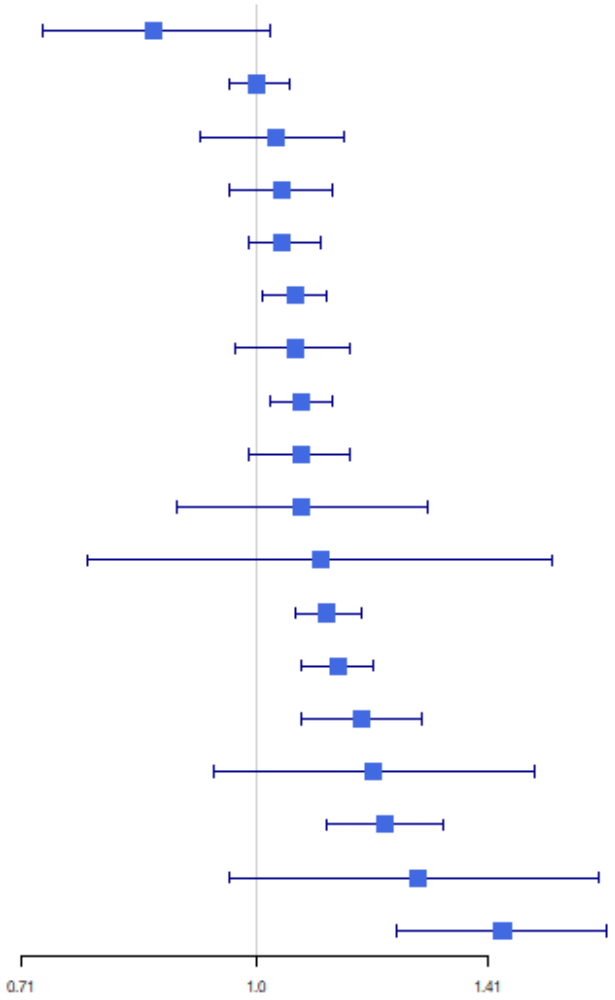
Minimally-Adjusted Associations of Environmental Risk Factors with Early-Onset CRC

Escore Variable	Cases	Controls	Odds Ratio (95% CI)
Alcohol use (1-28g/d)	1678	2967	0.86 (0.73, 1.02)
Pack-years of smoking	3290	3681	1.00 (0.96, 1.05)
Ever smoked cigarettes	3685	4305	1.03 (0.92, 1.14)
Height	3746	4357	1.04 (0.96, 1.12)
Vegetable (servings/day)	3669	4127	1.04 (0.99, 1.10)
BMI	3574	4244	1.06 (1.01, 1.11)
Total folate intake (mcg/day)	2044	3361	1.06 (0.97, 1.15)
Fruit (servings/day)	3633	4109	1.07 (1.02, 1.12)
Processed meat (servings/day)	2094	3344	1.07 (0.99, 1.15)
No aspirin use	3527	4170	1.07 (0.89, 1.29)
Alcohol use (>28g/d)	1678	2967	1.10 (0.78, 1.55)
Red meat (servings/day)	3632	4270	1.11 (1.06, 1.17)
Education, highest level completed	3596	4164	1.13 (1.07, 1.19)
Total fiber (g/day)	1454	1124	1.17 (1.07, 1.28)
Sedentary lifestyle	993	2245	1.19 (0.94, 1.51)
Total calcium intake (mg/day)	3098	3991	1.21 (1.11, 1.32)
Diabetes diagnosis	3726	4258	1.27 (0.96, 1.66)
No NSAIDS use	3498	4152	1.44 (1.23, 1.68)



- Unconditional logistic regression
- Assess independent associations between individual lifestyle/environmental risk factors and early-onset CRC, adjusting for age, sex, and study
- Dietary factors were also adjusted for scaled total energy consumption

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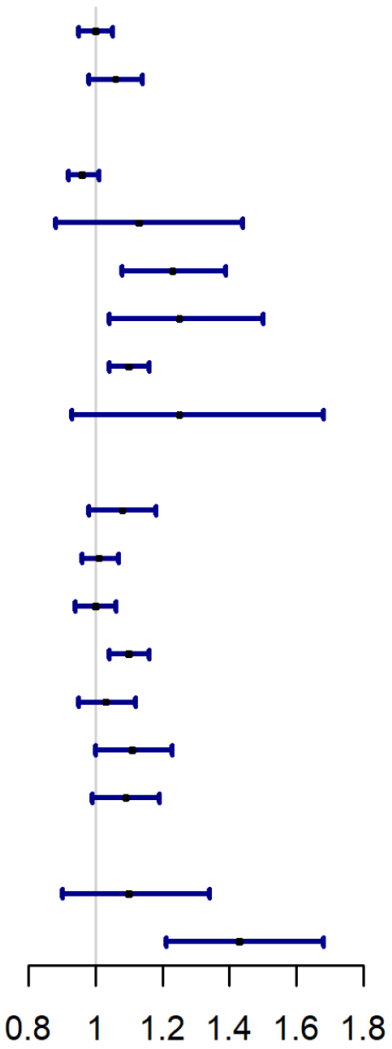
Risk factors and early-onset CRC

Risk Factor	OR (95% CI)	p-value
Anthropometric		
BMI (per 5 kg/m2)	1.00 (0.95, 1.05)	0.950
Height (per 10 cm)	1.06 (0.98, 1.14)	0.160
Lifestyle		
Pack-years of smoking	0.96 (0.92, 1.01)	0.116
Sedentary lifestyle	1.13 (0.88, 1.44)	0.338
Alcohol use (0 g/day)	1.23 (1.08, 1.39)	0.001
Alcohol use (>28 g/day)	1.25 (1.04, 1.50)	0.016
Lower educational attainment, highest level completed	1.10 (1.04, 1.16)	8.92E-04
Diabetes diagnosis	1.25 (0.93, 1.68)	0.142
Dietary		
Lower total folate intake (mcg/day)	1.08 (0.98, 1.18)	0.113
Lower fruit intake (servings/day)	1.01 (0.96, 1.07)	0.691
Lower vegetable intake (servings/day)	1.00 (0.94, 1.06)	0.981
Greater red meat intake (servings/day)	1.10 (1.04, 1.16)	3.53E-04
Greater processed meat intake (servings/day)	1.03 (0.95, 1.12)	0.430
Lower total fiber intake (g/day)	1.11 (1.00, 1.23)	0.058
Lower total calcium intake (mg/day)	1.09 (0.99, 1.19)	0.080
Pharmacological		
No aspirin use	1.10 (0.90, 1.34)	0.359
No NSAIDs use	1.43 (1.21, 1.68)	2.36E-05



- Incorporated all 16 risk factors (i.e., fully-adjusted model)
  - Adjusted for age, sex, study, family history, and total energy consumption
  - 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 marginally. These variables were treated as continuous variables in the analysis.

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Distribution of risk factors comparing rectal to colon cancer in early-onset CRC (referent = colon cancer)

	OR (95% CI)	*p* -value
Anthropometric		
BMI (per 5 kg/m^2)[1]	0.96 (0.90, 1.02)	0.162
Height (per 10 cm)[1]	1.00 (0.91, 1.10)	0.986
Lifestyle		
Pack-years of smoking[1]	1.00 (0.95, 1.06)	0.909
Sedentary lifestyle[1]	0.90 (0.61, 1.34)	0.600
Alcohol use (0 g/d)[1]	1.02 (0.86, 1.20)	0.826
Alcohol use (>28 g/d)[1]	1.05 (0.83, 1.33)	0.671
Lower educational attainment, highest level completed[1]	1.03 (0.96, 1.10)	0.462
Diabetes diagnosis[1]	1.09 (0.78, 1.52)	0.620
Dietary		
Lower total folate intake (mcg/day)[2,§]	1.09 (0.98, 1.21)	0.110
Lower fruit intake (servings/day)[2,§]	1.05 (0.99, 1.12)	0.116
Lower vegetable intake (servings/day)[2,§]	1.06 (0.98, 1.14)	0.132
Greater red meat intake (servings/day)[2,§]	1.01 (0.94, 1.07)	0.831
Greater processed meat intake (servings/day)[2,§]	1.05 (0.94, 1.18)	0.358
Lower total fiber intake (g/day)[2,§]	**1.14 (1.00, 1.30)**	**0.044**
Lower total calcium intake (mg/day)[2,§]	1.10 (0.97, 1.23)	0.131
Pharmacological		
No aspirin use[1]	0.98 (0.75, 1.28)	0.884
No NSAID use[1]	1.22 (0.95, 1.57)	0.121

[1]Adjusted for age, sex, study, and family history

[2]Adjusted for age, sex, study, family history, and total energy consumption

[§]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 marginally. These variables were treated as continuous variables in the analysis.

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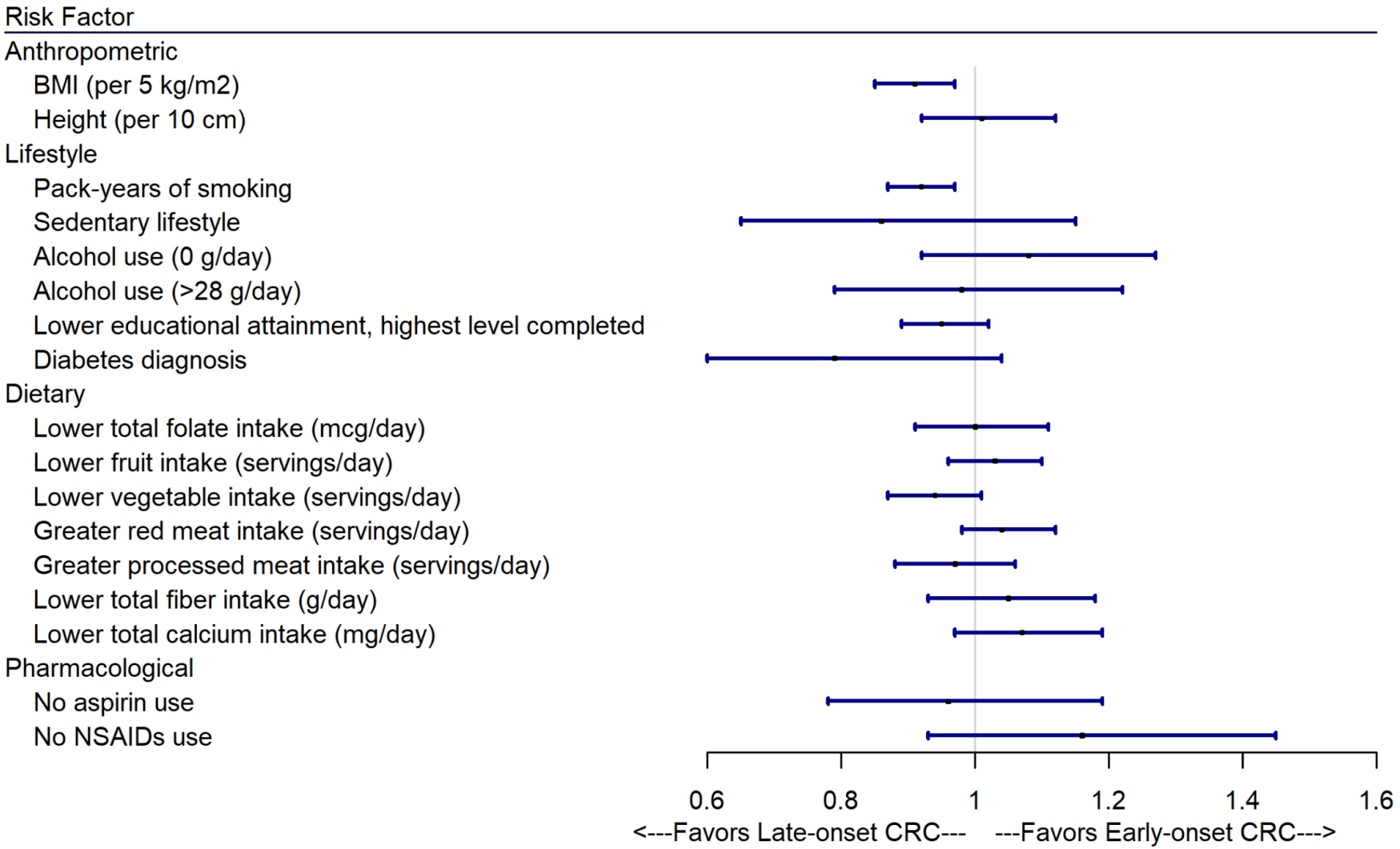
Early-onset vs. late-onset CRC



- Incorporated all 16 risk factors (i.e., fully-adjusted model)
- Case-only analysis
- Binary outcome was early- vs. late-onset CRC

Adjusted for age, sex, study, family history, and total energy consumption.
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 marginally. These variables were treated as continuous variables in the analysis.

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Summary: Environment and Early-onset CRC

- Many known CRC risk factors are also linked with early-onset disease
- No prominent differentials between early and late-onset factors
- Few differentials for rectal cancer: Low fiber intake

Next Steps

- Combine these risk factors into a cumulative risk score (Escore), and determine discriminatory capabilities for early-onset CRC
- Additionally factor in genetic risks using the PRS and individual risk factors

Thank You!

NYU Langone Health:
Alexi Archambault

Fred Hutchinson Cancer Research Center:
Ulrike Peters
Yu-Ru Su
Minta Thomas
Yi Lin
Li Su
Jeroen R Huyghe

Kaiser Permanente Northern California:
Douglas A Corley
Lori C. Sakoda

University of Michigan:
Jihyoun Jeon

And all the participating studies…

Research Program on Genes, Environment and Health (RPGEH), Kaiser Permanente Northern California (KPNC)
The french Association STudy Evaluating RISK for sporadic colorectal cancer (ASTERISK)
Alpha-Tocopherol, Beta Carotene Cancer Prevention Study (ATBC)
Colon Cancer Family Registry (CCFR)
Hawai'i Colorectal Cancer Studies 2 & 3 (Colo2&3)
ColoCare Consortium (ColoCare)
Colorectal Cancer: Longitudinal Observational study on Nutritional and lifestyle factors that influence colorectal tumor recurrence, survival and quality of life (COLON)
Colorectal Cancer Study of Austria (CORSA)
American Cancer Society Cancer Prevention Study II nested case-control study (CPS-II)
Czech Republic Colorectal Cancer Study (Czech Republic CCS)
Darmkrebs: Chancen der Verhütung durch Screening (DACHS)
Diet, Activity, and Lifestyle Study (DALS3)
Early Detection Research Network (EDRN)
European Prospective Investigation into Cancer and Nutrition (EPIC)
The EPICOLON Consortium (EPICOLON)
Epidemiologische Studie zu Chancen der Verhütung, Früherkennung und optimierten Therapie chronischer Erkrankungen in der älteren Bevölkerung, Verlauf der diagnotischen Abklärung bei Krebspatienten (ESTHER-VERDI)
Columbus-area HNPCC study, Ohio Colorectal Cancer Prevention Initiative, and Ohio State University Medical Center (HNPCC, OCCPI, and OSUMC)
Health Professionals Follow-up Study (HPFS)
Kentucky Case-Control Study (Kentucky)
PopGen Biobank (Kiel)
Leeds Colorectal Cancer Study (LCCS)
Melbourne Collaborative Cohort Study (MCCS)
Multiethnic Cohort study (MEC)
Molecular Epidemiology of Colorectal Cancer Study (MECC)
Memorial Sloan Kettering Cancer Center Cohort (MSKCC)
North Carolina Colon Cancer Study-I (NCCCS I)
North Carolina Colon Cancer Study-II (NCCCS II)
Newfoundland Case-Control Study (NFCCR)
Nurses' Health Study (NHS)
Nurses' Health Study (NHS II)
The Northern Sweden Health and Disease Study (NSHDS)
Ontario Familial Colorectal Cancer Registry (OFCCR)
Physicians' Health Study (PHS)
Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO)
Postmenopausal Hormones Supplementary Study to the CCFR (PMH-CCFR)
Studies of Epidemiology and Risk Factors in Cancer Heredity (SEARCH)
Swedish Low-Risk Colorectal Cancer Study (SLRCCS)
Swedish Mammography Cohort and Cohort of Swedish Men (SMC and COSM)
The Spanish study (University Hospital of Bellvitge, Hospital of Leon) (Spain)
United Kingdom Biobank (UK Biobank)
Los Angeles County Cancer Surveillance Program (USC-HRT-CRC)
VITamins And Lifestyle (VITAL)
Women's Health Initiative (WHI)

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THANK YOU

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THE ROLE OF GENE-ENVIRONMENT INTERACTIONS ON EARLY AGE ONSET COLORECTAL CANCER: DISCUSSANTS

Neil Murphy, PhD
IARC

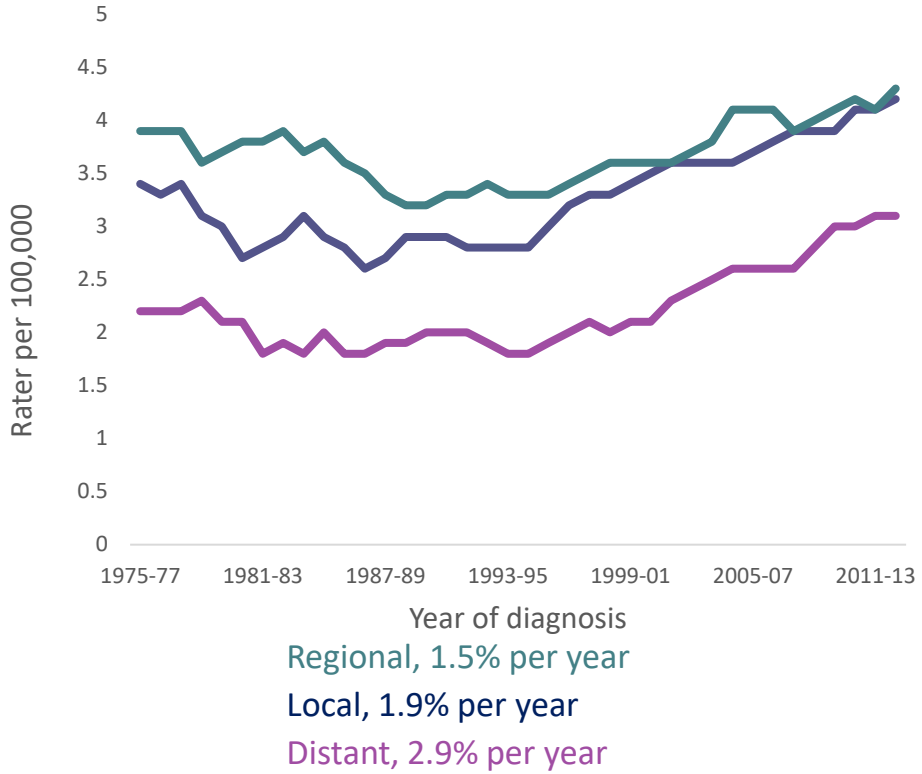
Peter Campbell, PhD
ACS

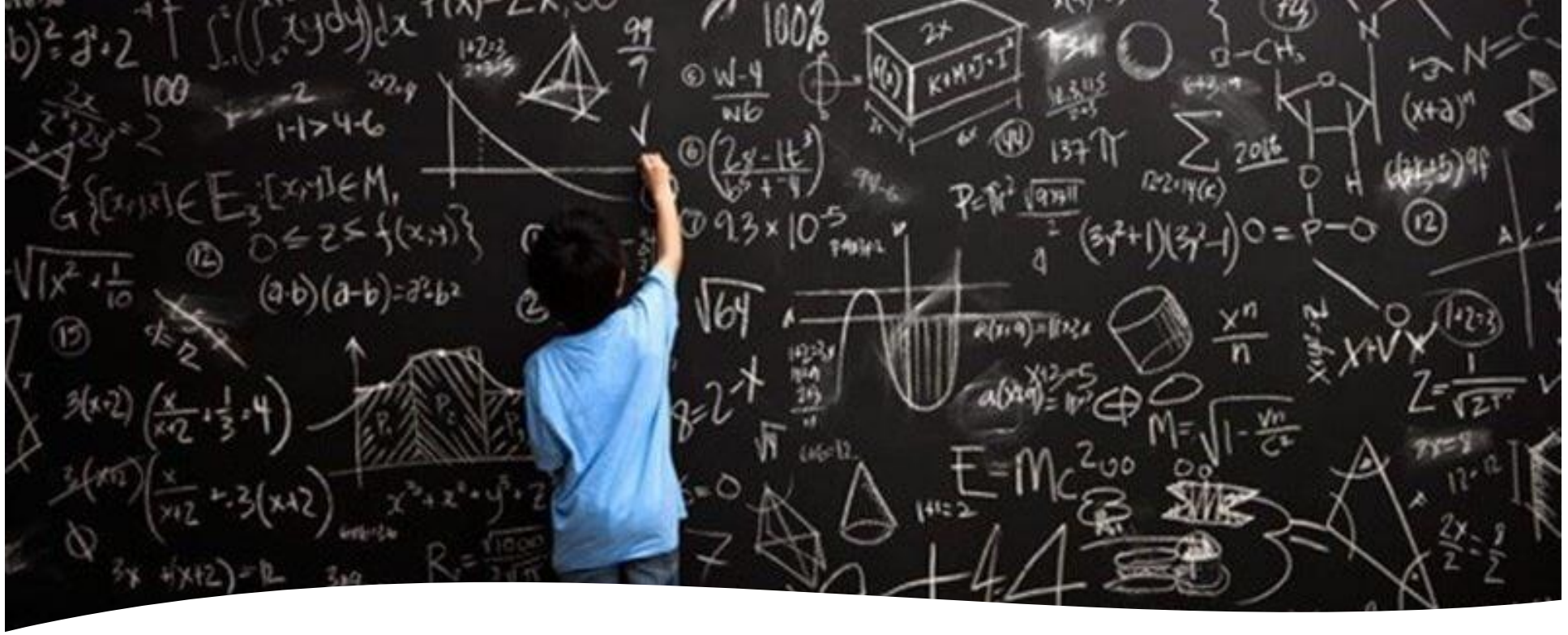
Discussion points:

- Points of emphasis from Dr Hayes' talk
- Considerations for future research
- Methods issues in G-, E-, and GxE for colorectal cancer
- Future work and resources development on early onset colorectal cancer

Points of emphasis

- Increase in CRC in young adults is real
- Enormous sample sizes are needed
- PRS results: surprising and will only get stronger
- Etiology in early-onset and later-onset CRC seems more similar than different



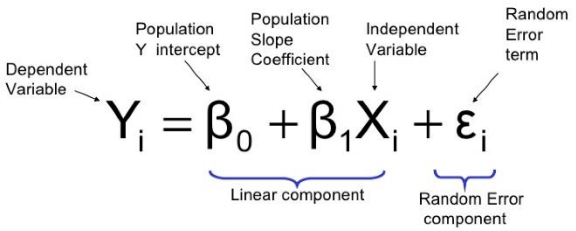


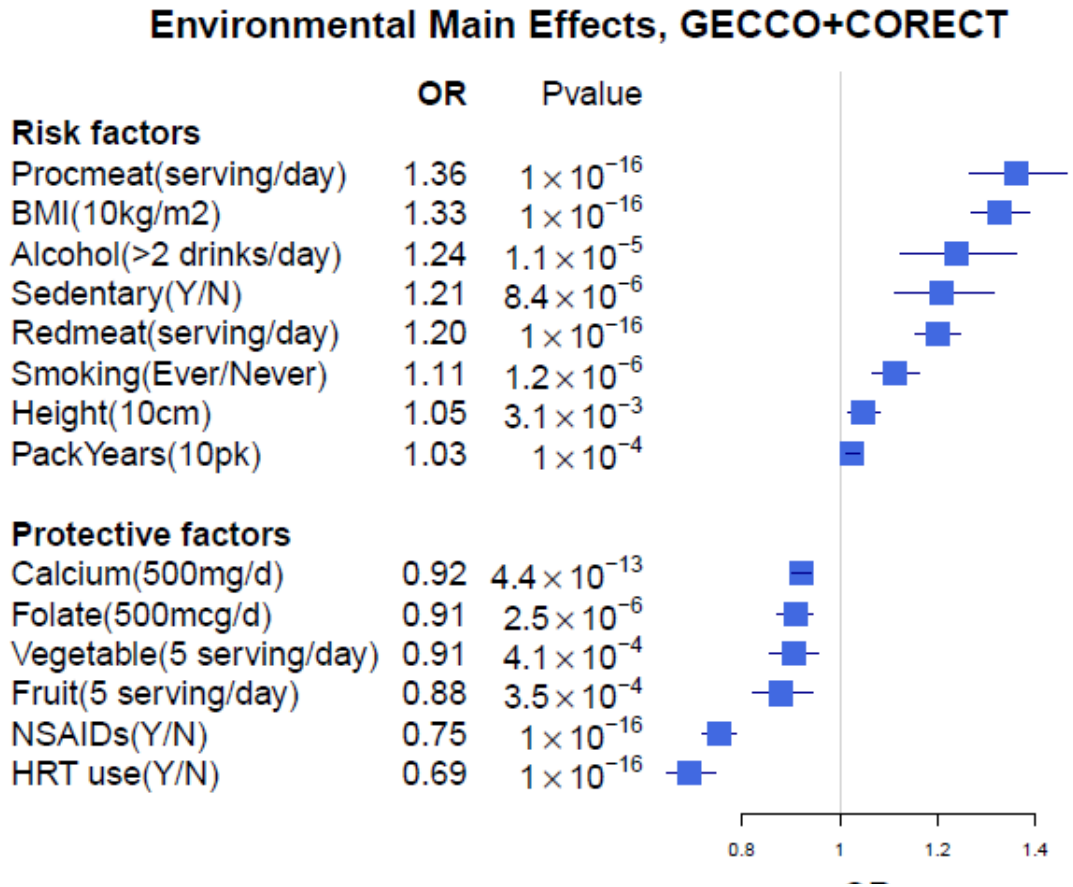
Important high-level considerations

- Study heterogeneity: case-control, nested case-control, case series, etc.
- Novel risk factors we're missing
- Pre-diagnostic blood biomarkers
- Tumor heterogeneity
- Non-White participants
- Implementation -> risk stratification

Main effects of ‘E’ and CRC risk in older populations

- Alcohol (↑)
- Red and processed meats (↑)
- Fruits and vegetables (↓)
- Garlic (from food) (↓)
- Milk (↓)
- Calcium (from food) (↓)
- Selenium (from food) (↓)
- Postmenopausal hormones (↓)
- Obesity (↑)
- Height (↑)
- Smoking (↑)
- Physical activity (↓)
- NSAIDs (↓)
- Type 2 DM (↑)



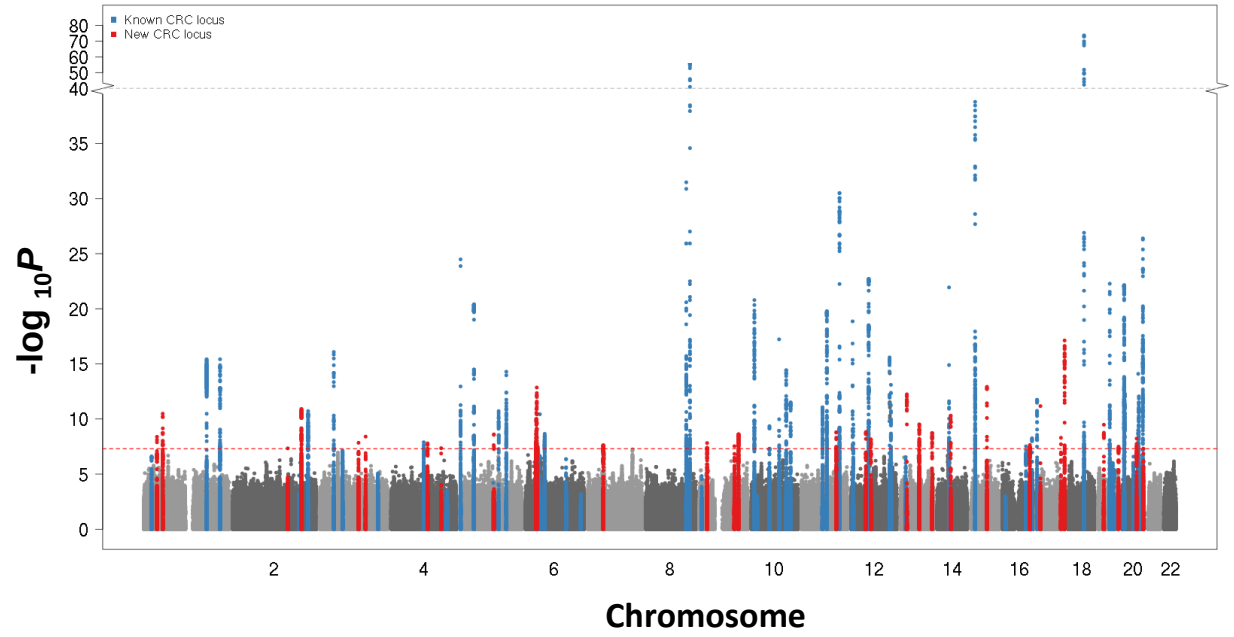


~18,000 cases and 18,000 controls

74 variables collected in 11 categories

Main effects of ‘G’ and CRC risk in older populations

Total # of genetic variants tested 16,900,000




Jeroen Huyghe


Stephanie Bien


Tabitha Harrison

20k

- **Discovery GWAS +Seq**
- 64,000 mainly Europeans

40 loci

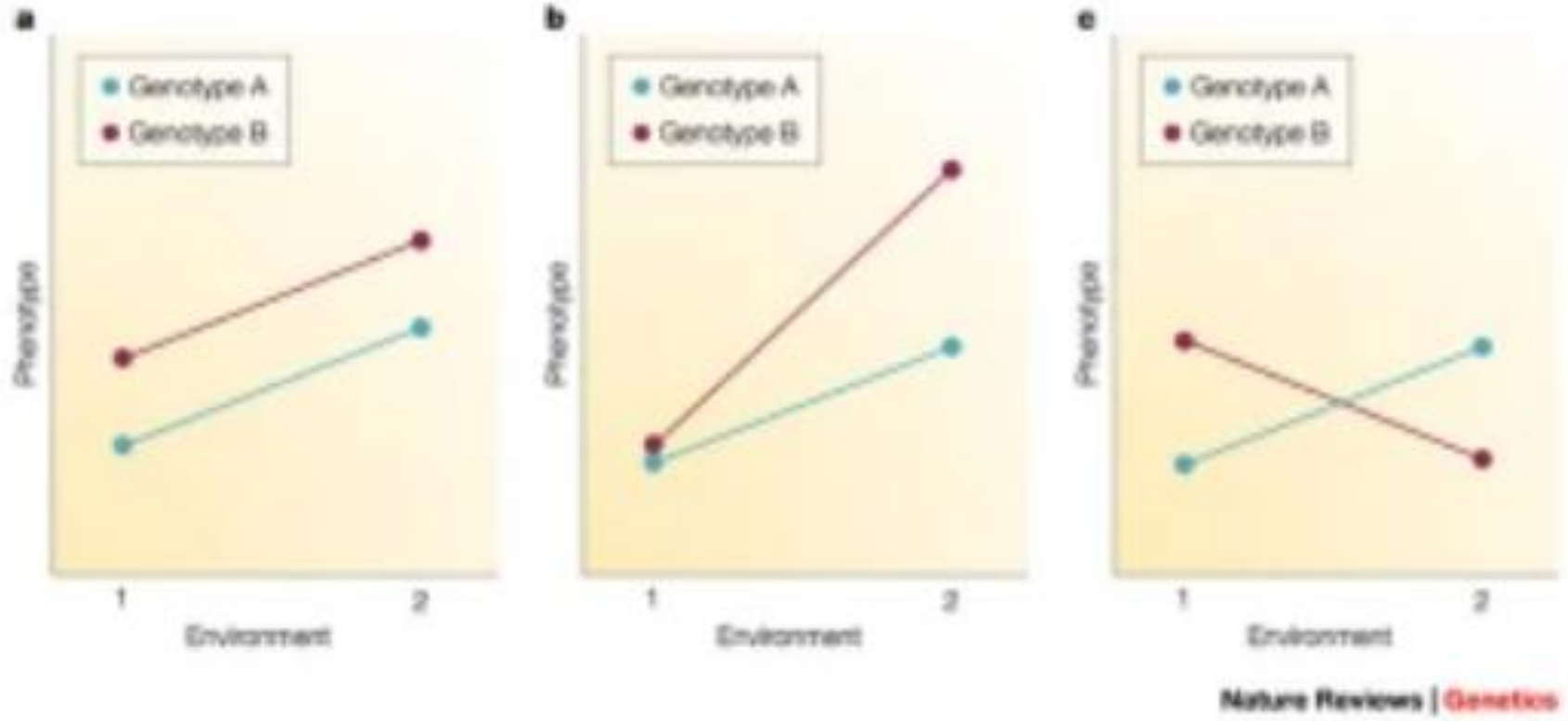
- **Replication GWAS**
- 61,000 Europeans

Summary:

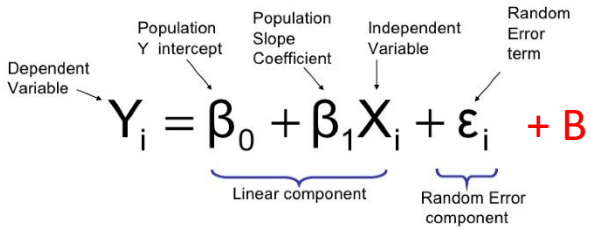
- Replicate **51** previously reported signals
- Discover **30** new loci with *P* < 5×10-8 and >500kb away from previously reported loci
- Discover **10** additional new conditionally independent signals with *P* < 5×10-8 and <500kb from known and new loci

Huyghe, Bien, Harrison et al. Nat Genet, 2019

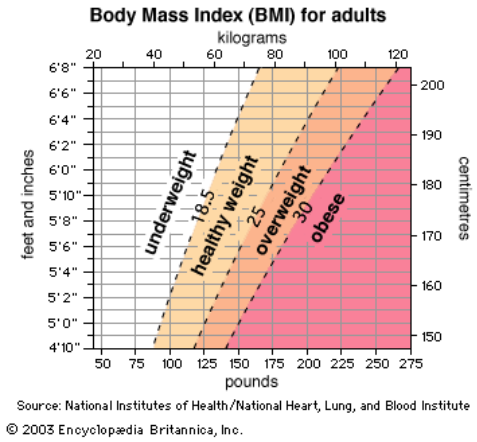
G x E interaction: an example



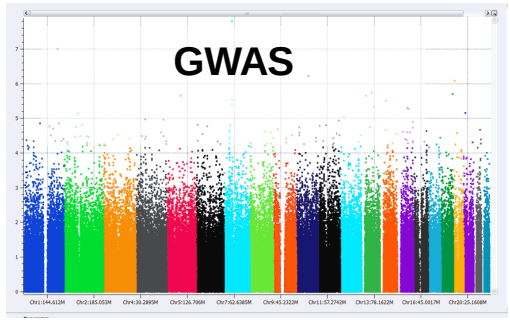
GENE-OBESITY INTERACTIONS FOR COLORECTAL CANCER



+ B2 + e2 + B1 x B2 + e3



X



Modular framework for GxE methods

Module A: Screening	Module C: Testing	Module B: Multiple Comparisons
• No Screening • **Marginal G-D association** • **Correlation G-E** • Hybrid approaches	• **Case-control** • Case-only • Empirical Bayes (EB) • Bayesian Model Averaging	• Bonferroni testing • Permutations • **Weighted hypothesis testing**

Kooperberg & LeBlanc (2008, Genetic Epi); Murcray et al. (2009, AJE); Gauderman et al. (2013, Genetic Epi); Murcray et al.(2011, Genetic Epi); Mukherjee and Chatterjee(2008, Biometrics); Li and Conti (2009, AJE); Dai et al. (2012, Biometrika); Dai et al. (2012, AJE), Kraft et al. (2007); Jiao (Genet Epi 2013); Hsu et al. (2012, Genetic Epi)

BMI by *SMAD7* genotype and CRC risk

		rs4939827 genotype						
		TT		CT		CC		OR (95% CI) per C allele within strata of BMI categories
	BMI	N Cases/Controls	OR (95% CI)	N Cases/Controls	OR (95% CI)	N Cases/Controls	OR (95% CI)	
ORs (95% CI) for BMI and genotype categories with a common reference group	Normal	925/931	1 (referent)	1460/1762	0.81 (0.72-0.92)	572/826	0.68 (0.59-0.78)	0.82 (0.76-0.88)
					P= 0.0007		P= 1.7E-07	P= 8.6e-08
	Overweight	814/703	1.16 (1.01-1.33)	1301/1352	0.96 (0.85-1.08)	539/614	0.87 (0.75-1.01)	0.86 (0.79-0.93)
			P= 0.04		P= 0.48		P= 0.07	P= 0.00025
	Obese	555/439	1.24 (1.05-1.45)	876/788	1.07 (0.93-1.23)	432/348	1.21 (1.02-1.45)	0.99 (0.89-1.09)

BMI5				**Female**	
SNP			**TT**	**CT**	**CC**
rs4939827	**Ca/Co**		1698.9/1561.5	2696.3/2925.2	1206.8/1346.3
	OR(95% CI)		**1.07 (1.01-1.14)**	**1.14 (1.09-1.19)**	**1.24 (1.16-1.32)**
	Pvalue		0.02	1.04E-08	2.6E-10

ORs (95% CI) for BMI categories within strata of genotype: Normal, Overweight, Obese

ORs (95% CI) for BMI per 5 kg/m^2 within strata of genotype: BMI continuous

Campbell et al, JNCI, 2021

NCI Colorectal Cancer Pooling Project (C2P2): Overall goals

"To understand the role of modifiable and non-modifiable risk factors for early-onset versus late-onset colorectal cancer and to create a resource for studies of blood-based biomarkers that include hypothesis-driven and discovery-based approaches."

PI's: P. Campbell, N. Murphy and M. Gunter
Co-I's: Y. Cao, A. Chan, T. Harrison, R. Hayes, P. Newcomb, U. Peters

Rationale for C2P2

- Early-onset CRC is relatively rare (currently ~10% of CRC)
- Individual prospective cohort studies have typically recruited participants beginning in middle age
- Even large cohorts have insufficient incident early-onset CRC cases to conduct robust epidemiological investigations

Progress to date

- Initiated Feb 2019.
- Approved by NCI leadership in May 2019.
- Cohorts invited in July 2019.
  - 51 cohorts invited to participate
- 26 cohorts have data from EOCRC cases, mostly with pre-dx bloods:
- ACS funding to harmonize data
- NCI ‘provocative question #1’ R01 submitted in Nov ‘20.

Cohorts included to date

Table 1. Prospective cohort studies included in the Colorectal Cancer Pooling Project (C2P2)

Study Name	Region	Year(s) of recruitment	N participants	% female	Cases <50 years	Cases 50-64 years	Cases >=65 years	Total cases
Agricultural Health Study (AHS)	US	1993-1997	89,655	40	403	634	279	1,316
Black Women's Health Study (BWHS)	US	1995-2007	59,000	100	152	351	199	702
Breakthrough Generations Study	UK	2003-2011	112,049	100	59	227	309	595
California Teachers Study (CTS)	US	1995-1996	133,479	100	99	522	1,449	2,070
The Canadian Partnership for Tomorrow Project (CanPath) - collaboration of 5 provinces (studies)	Canada	2008-2019	330,000	62	164	542	897	1,603
Canadian Study of Diet, Lifestyle, and Health	Canada	1995-1998	73,909	54	57	187	630	874
Cancer Prevention Study-3 (CPS-3)	US	2006-2013	304,000	77	67	164	37	268
European Prospective Investigation into Cancer and Nutrition (EPIC)	10 European countries	1992-1999	521,000	57	177	2,587	3,767	6,531
Golestan Cohort Study (GCS)	Iran	2004-2008	50,045	58	15	91	55	161
Janus Serum Bank	Norway	1972-2004	318,628	48	652	3,928	6,277	10,857
Japan Public Health Center-Based Prospective Study (JPHC)	Japan	1990-1992	140,420	54	82	1,175	2,353	3,610
Melbourne Collaborative Cohort Study	Australia	1990-1994	41,500	59	67	469	1,582	2,118
Northern Sweden Health and Disease Study (NSHDS)	Sweden	1985-1995	95,000	59	78	654	1,276	2,008
Nurses' Health Study I (NHSI)	US	1976	121,700	100	71	681	1,289	2,041
Nurses' Health Study II (NHSII)	US	1989	116,430	100	116	321	14	451
NYU Women's Health Study	US	1985-1991	14,274	100	12	119	376	507
RERF Life Span Study, Adult Health Study, and F1 Cohort (Hiroshima and Nagasaki)	Japan	1950-1960	120,000	58	19	258	880	1,157
Shanghai Men's Health Study (SMHS)	China	2002-2006	61,480	0	26	334	634	994
Shanghai Women's Health Study (SWHS)	China	1997-2000	75,000	100	46	405	762	1,213
Swedish National March Cohort	Sweden	1997	43,880	60	19	137	582	738
UK Biobank	UK	2006-2010	502,505	56	220	1,396	1,741	3,357
Total			**3,323,954**		**2,601**	**15,182**	**25,388**	**43,171**

Our underlying hypotheses…

- Increasing trends in early-onset CRC (EOCRC) are unexplained but may reflect secular changes that began in the 1970s to putative risk factors including early-life excess adiposity, Westernized diet patterns, antibiotic-use in early life, and increased physical inactivity; in turn, these secular changes to risk factors may cause increased gut permeability, sustained systemic inflammation, and increased metabolic dysregulation, all of which lead to a pro-carcinogenetic environment in the colon and rectum

'Causes' of EOCRC: a testable model

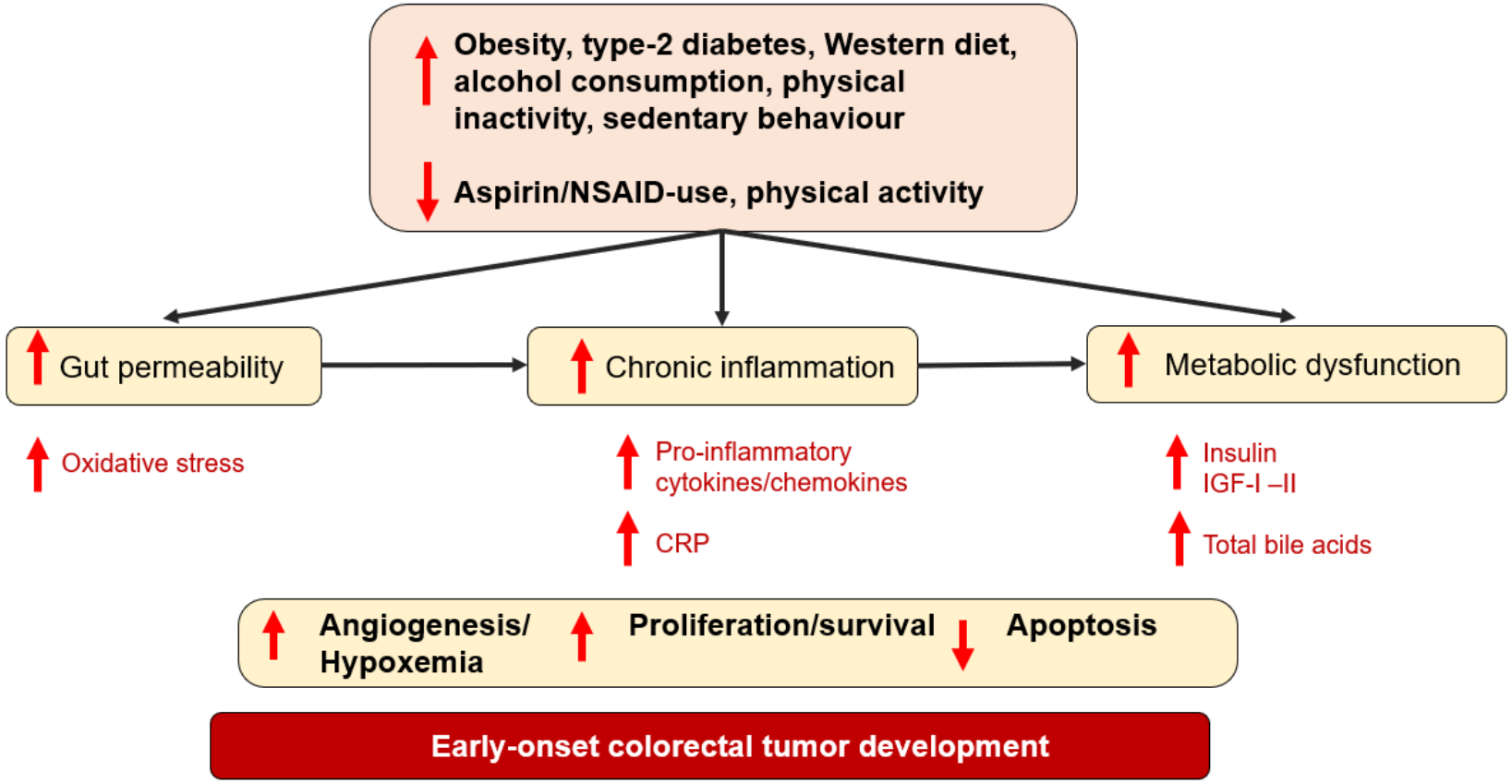


Figure 3: Early life and young adulthood exposures predispose the colon and rectum to early-onset cancer.

Case-control study of EOCRC: Rationale

- ‘Bespoke’ case-control study able to capture exposures not queried by broader cohort studies
- Family history and germline genetic risk factors could be evaluated in far greater detail
- Avoids data harmonization (‘lowest common denominator’) troubles in consortia
- Surgical and treatment data collection
- Consistent high standard collection of biospecimens (buccal, feces, urine, fresh-frozen CR tissues, etc.)

Contact information

- Neil Murphy: murphyn@iarc.fr
- Peter Campbell: peter.campbell@cancer.org

Discussion

- **Next EAO Workgroup webinar:**

- March 4, 2021 (Tuesday, 12pm ET)**.** Registration coming soon!

- **3rd Annual EAO CRC International Symposium**

- **Date:** June 24 & 25, 2021**.** Registration launching March 2021
- **Location:** Virtual
- **Goal:** During the 2021 symposium, the EAO workgroup and advocacy and clinical partners worldwide will continue multi-disciplinary, action-based discussions in order to advance research on the causes of EAO CRC and practice-based strategies for clinical public health.


F!GHT
COLORECTAL CANCER