
F!GHT
COLORECTAL CANCER

FIGHT COLORECTAL CANCER

Agenda

12:00-12:15p ET	Welcome and Introductions: Andrea Andi (Dwyer) and Dr. Jose Perea
12:15- 12:40p ET	Unraveling EAO CRC Disparities: Dr. Andreana Holowatyj
12:40-12:50p ET	Discussion with Jose: Addressing Questions
12:50-1:00p ET	Addressing Specific Questions Posed before Webinar
1:00-1:30p ET	Discussion
1:30-1:50p ET	Overview of research and papers, funding mechanisms: Jose and Andi
1:50-2:00p ET	Close out and next steps: Jose

FIGHT COLORECTAL CANCER

Objectives

- Understand the context of health disparities among patients with early-onset CRC;
- Summarize current literature on differences in health outcomes across early-onset CRC patient population subgroups; and
- Broaden knowledge in early-onset CRC and current research.

Unraveling early-onset colorectal cancer disparities worldwide

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Vanderbilt University School of Medicine
Vanderbilt-Ingram Cancer Center

VANDERBILT HEALTH

The New York Times

'Black Panther' Star Chadwick Boseman Dies of Cancer at 43

The actor also played groundbreaking figures like James Brown, Jackie Robinson and Thurgood Marshall.

What to Know About Colon Cancer

The cancer that killed Chadwick Boseman is the second-leading cause of cancer deaths in the United States, and rates are rising among younger people.

Outline

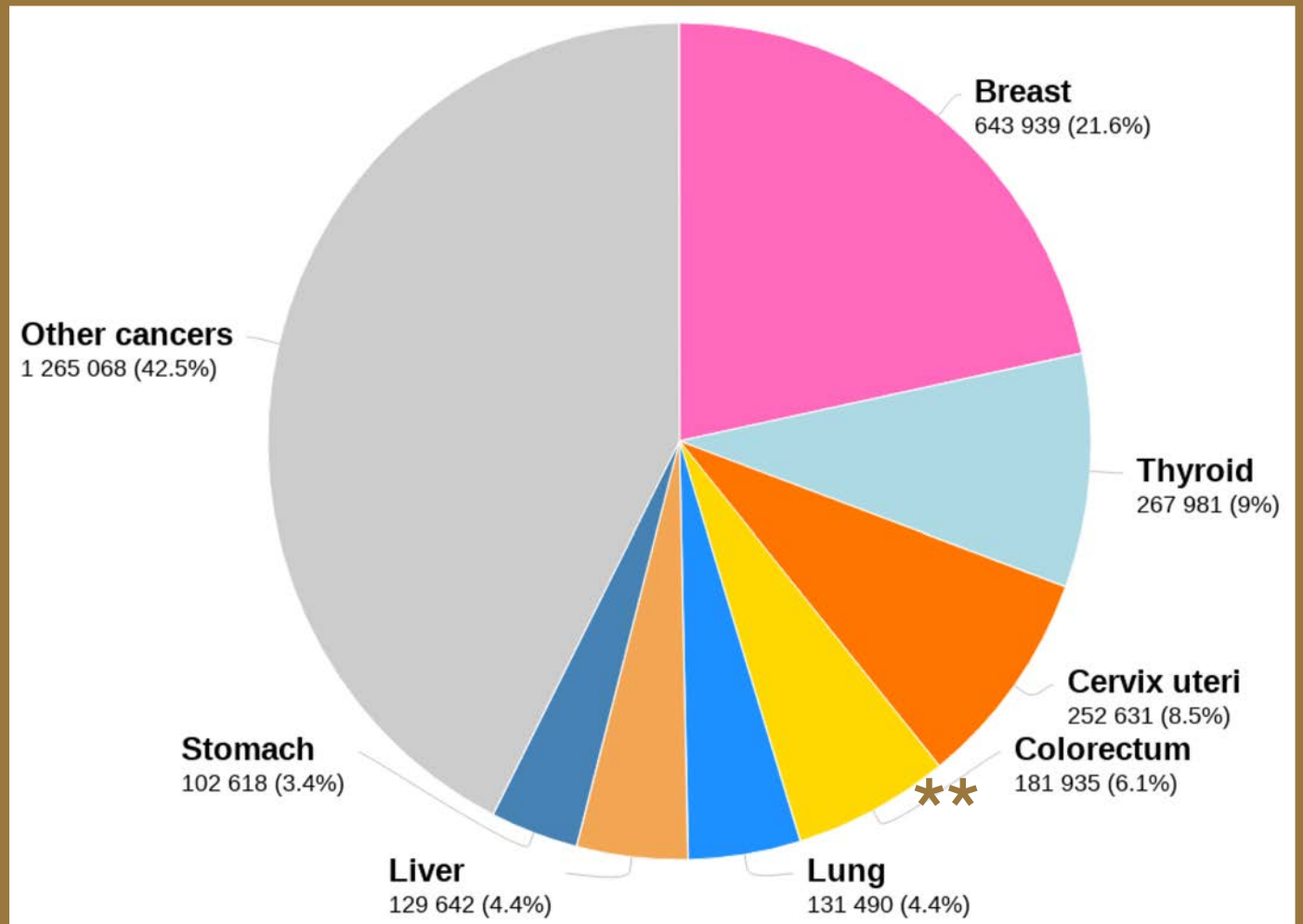
Background—Early-onset CRC

Disparities in early-onset CRC patterns & outcomes: a global look

- Race/ethnicity, sex and geography
- USA, Nigeria, Spain & Indonesia

Future early-onset CRC disparities research directions

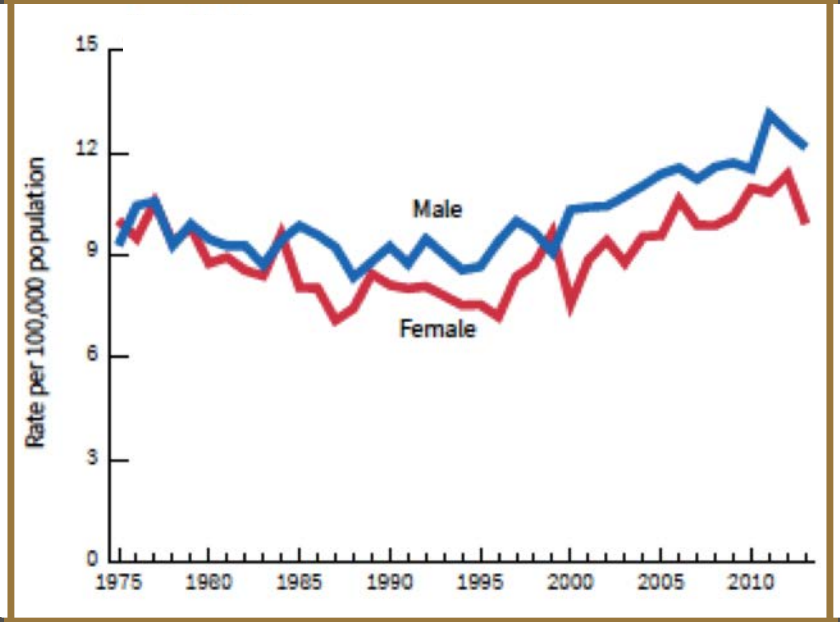
Colorectal cancer (CRC) is the fourth most commonly diagnosed cancer among young patients worldwide



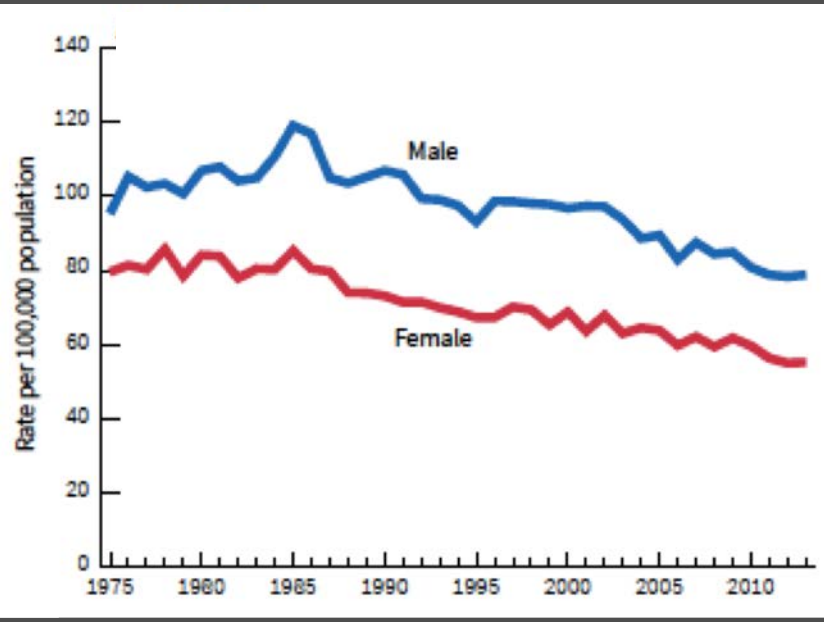
***Approximately 181,935 new cases of early-onset CRC (6.1%) diagnosed annually.*

GLOBOCAN. 2018.

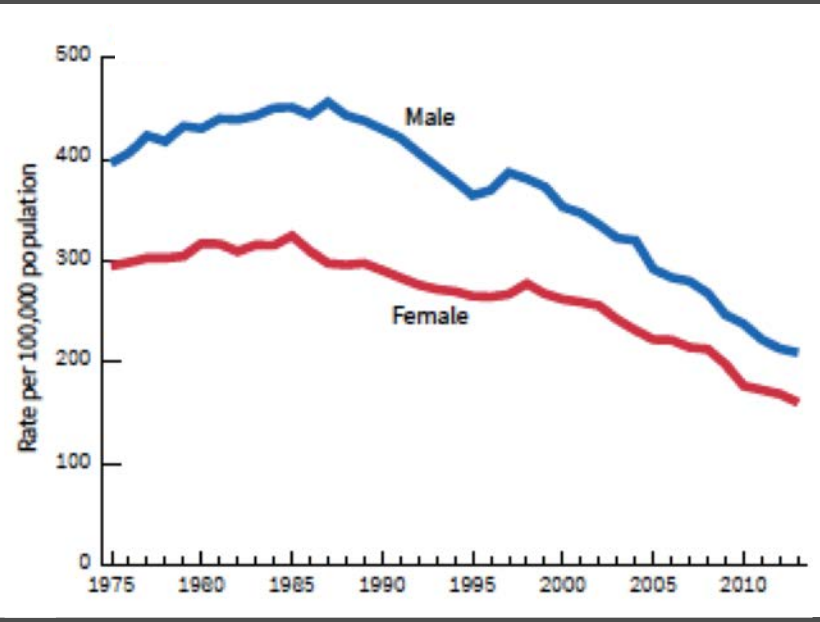
CRC incidence rates among young persons continue to rise annually since 1992



Ages 20-49



Ages 50-64

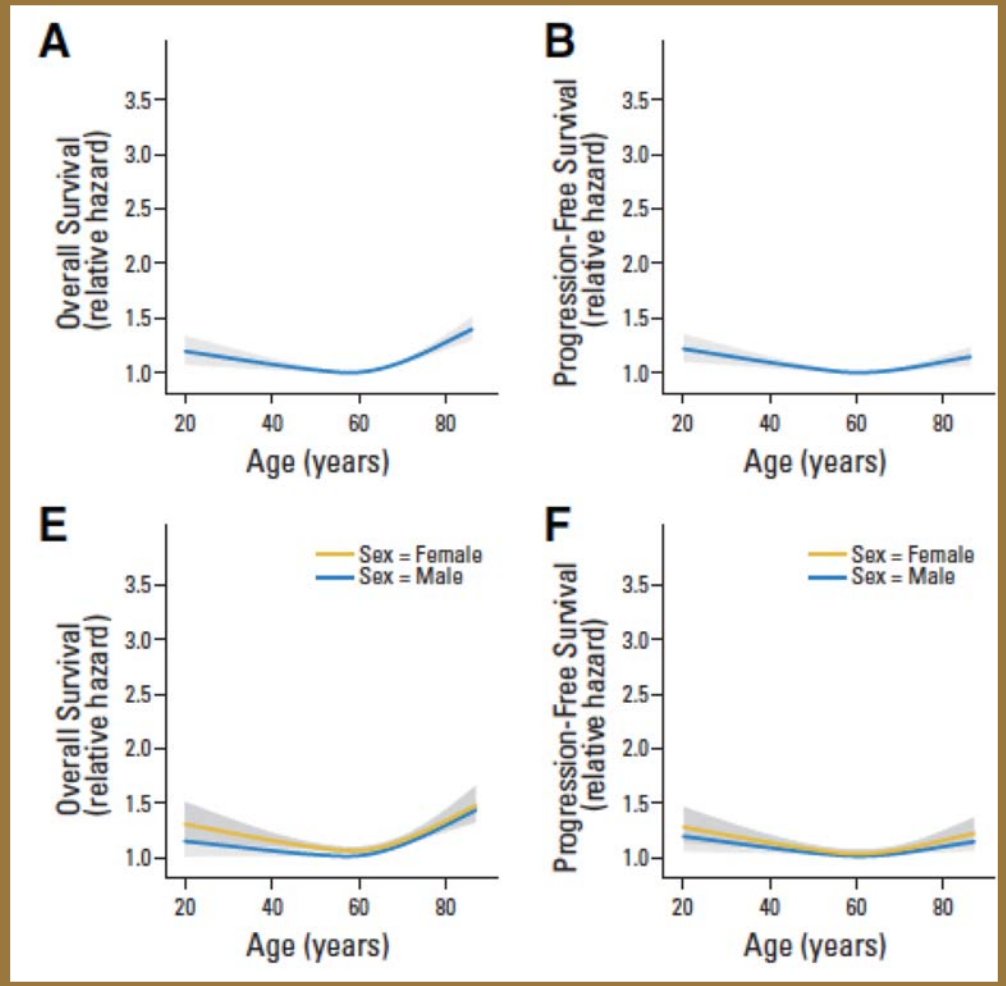


Ages 65+

- Trend is paralleled across many countries, including: Denmark, Taiwan, Korea, New Zealand, Australia, the UK, and China.

American Cancer Society. 2017; Sung et al. *AJG*. 2019; Araghi et al. *Lancet Gastroenterol Hepatol*. 2019.

CRCs behave more aggressively in young patients compared with late-onset (50+ yo) cases

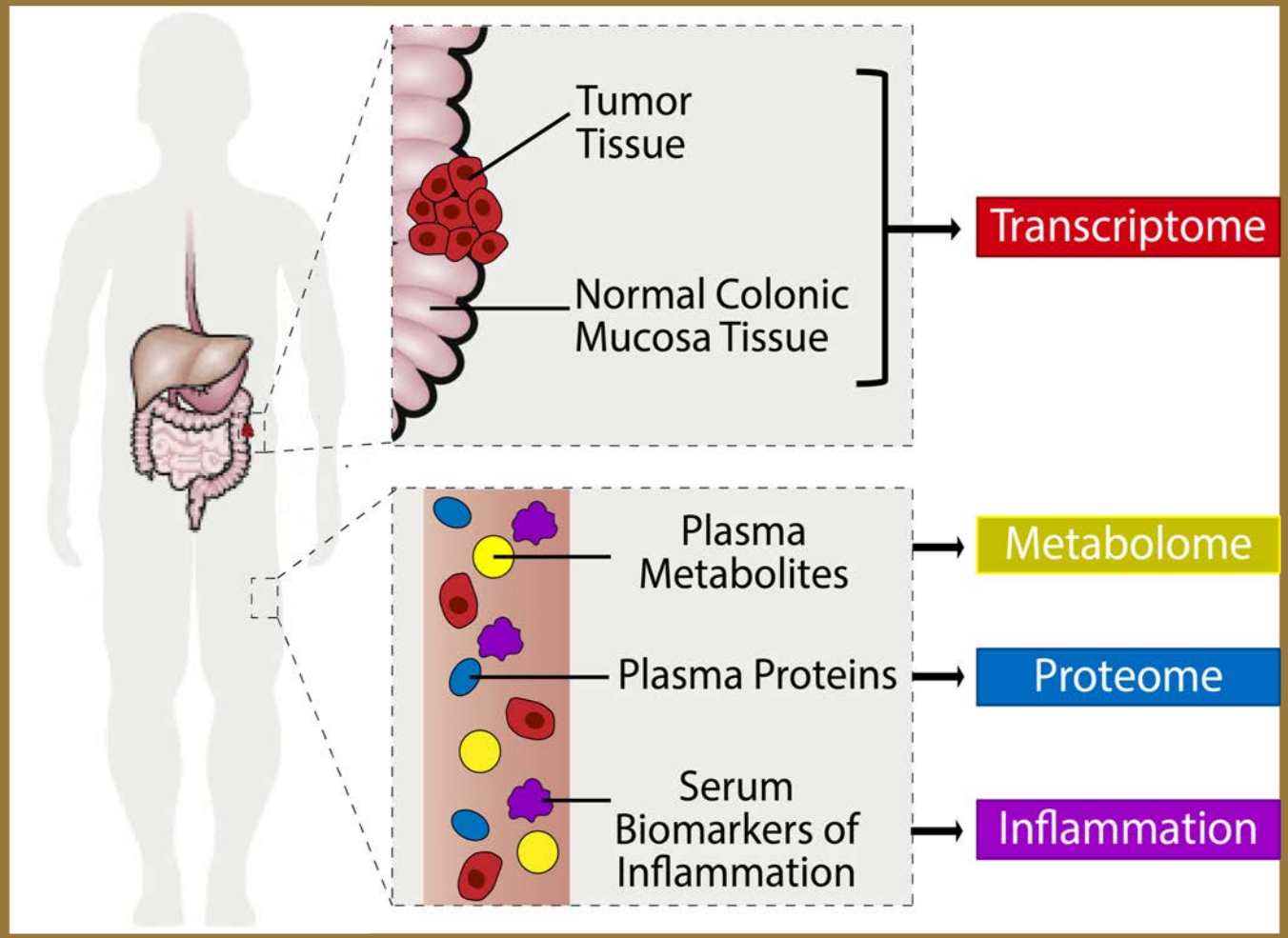


- Adverse CRC histological features more common among young patients
- Patients with early-onset CRC more likely to present with or develop metastatic disease vs late-onset cases

- Younger & older age associated with poorer OS/PFS among mCRC
- Disproportionate burden of CRC recurrence among young patients

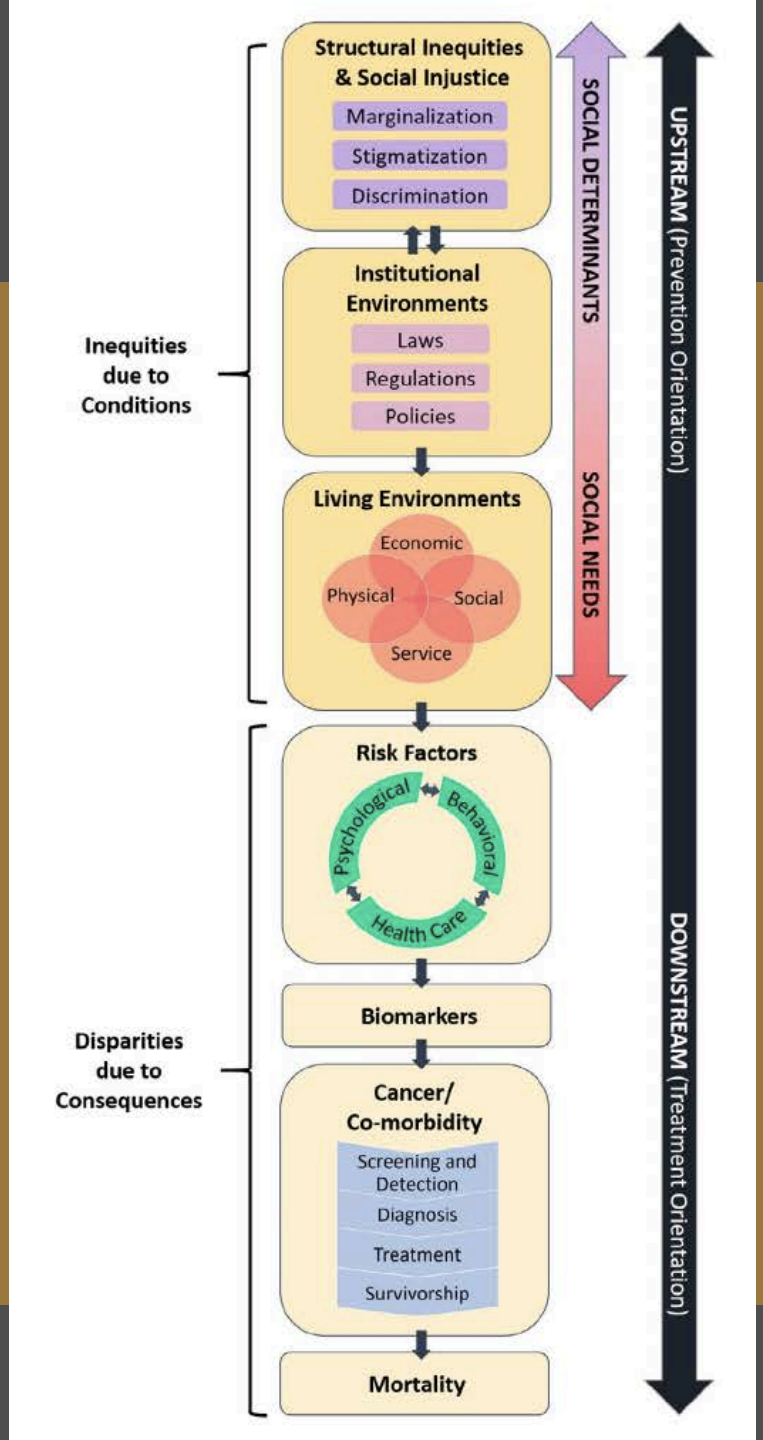
Chang et al. *Mod Pathol*. 2012; Fairley et al. *Cancer*. 2006; Willauer et al. *Cancer*. 2019; Lieu et al. *J Clin Oncol*. 2014.

Early-onset sporadic CRC is a biologically different disease from late-onset (50+ yo) sporadic CRC



- Imbalanced redox status is a distinct hallmark of early-onset sporadic CRC
- Obesity is a major factor in oxidative stress
- 233 **German** patients (14.6% with early-onset CRC)

Holowatyj et al. *Gastroenterology*. 2020.



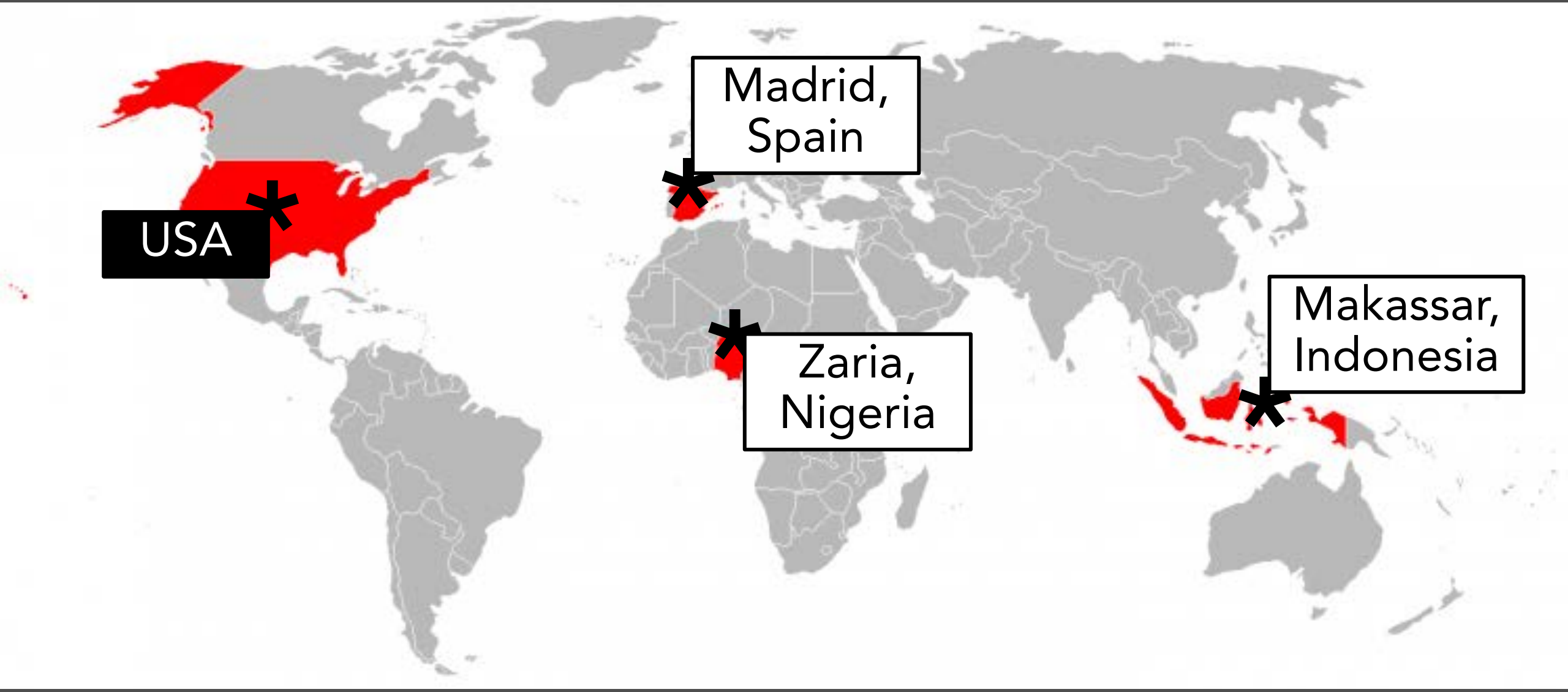
Addressing social determinants to advance cancer health equity

- *Determinants of individual cancer risk and survival: biological/genetic, environmental, behaviors, health care,* ***social***

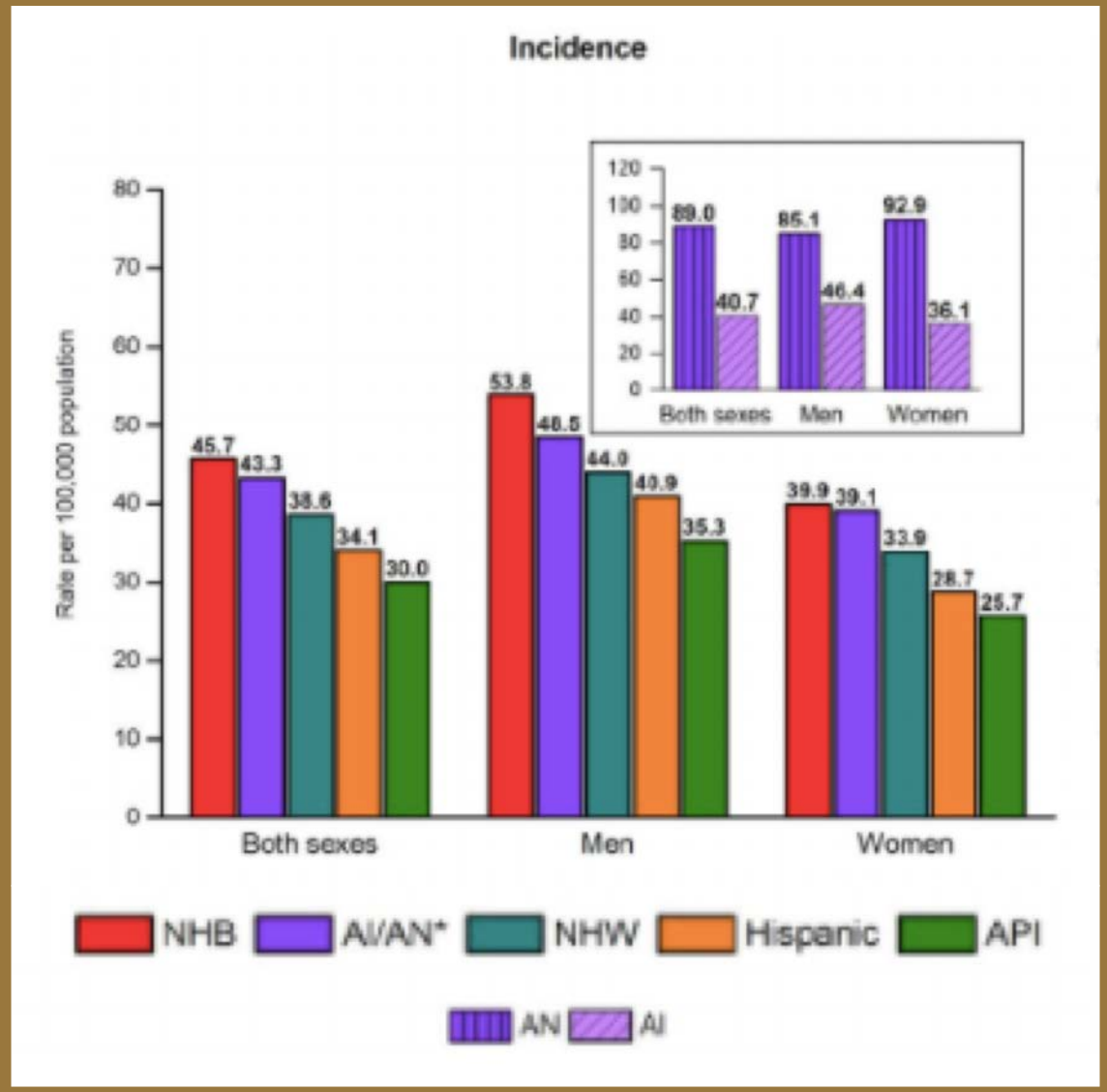
- *Social, economic, and geographic disparities cut across multiple other population characteristics, such as:*
  - *Race/ethnicity, age, disability status, sexual orientation or gender identity, or other characteristics historically linked to discrimination or exclusion*

Alcaraz KI et al. *Ca Cancer J Clin. 2020.*

Early-onset CRC is a global epidemic



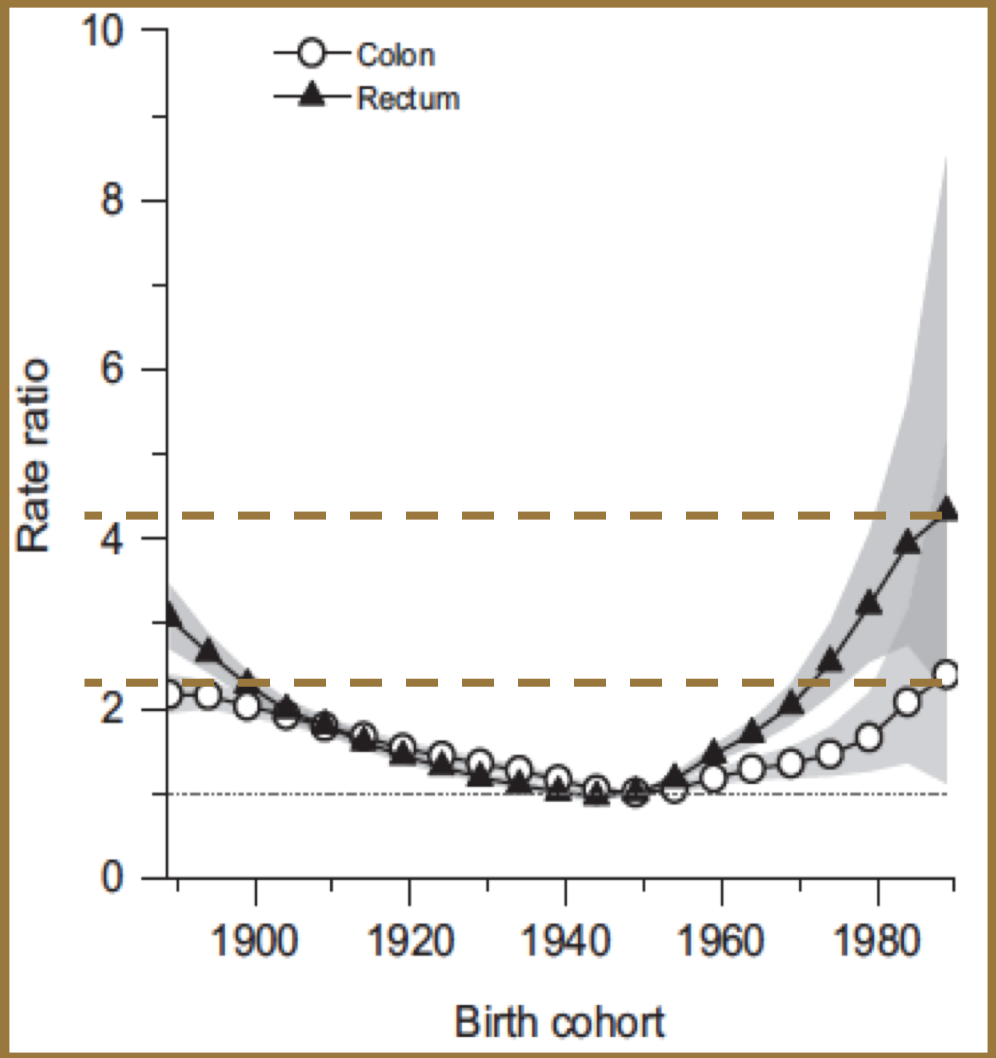
Proportion of CRCs occurring before age 50 is higher among non-white races/ethnicities



- CRC incidence rates are highest in non-Hispanic blacks followed closely by Alaska Natives
- The proportion of individuals with early-onset CRC is nearly two-fold higher among non-white races/ethnicities

Theuer et al. *Gastroenterology*. 2001;
Siegel at al. *Ca Cancer J Clin*. 2020.

Individuals born c.1990 have 2-fold colon & 4-fold rectal cancer risk vs individuals born c.1950



- Five out of every six early-onset CRC patients do not carry a germline mutation associated with cancer predisposition

Etiologies underlying this CRC epidemic, particularly sporadic CRC, among young individuals remain unexplained.

Siegel et al. *JNCI*. 2017; Pearlman et al. *JAMA Oncol*. 2017.

Proportion of Hispanic adolescents & young adults diagnosed with CRC increases with younger age

SEER18: 5,350 cases age 15-39 at CRC diagnosis, 2010-2015.

	AYA population											
	15–19 yr		20–24 yr		25–29 yr		30–34 yr		35–39 yr		*P*	
Characteristic	No.	%	No.	%	No.	%	No.	%	No.	%	Value	Trend
Total	60		250		706		1,539		2,795			
Race/ethnicity											0.36	
Non-Hispanic white	26	43.3	130	52.0	370	52.4	856	55.6	1,531	54.8		0.10
Non-Hispanic black	11	18.3	32	12.8	79	11.2	183	11.9	368	13.2		0.52
Hispanic	17	28.3	67	26.8	173	24.5	347	22.5	587	21.0		0.003
Asian or Pacific Islander	5	8.3	18	7.2	74	10.5	137	8.9	275	9.8		0.43
American Indian/Alaska Native	1	1.7	3	1.2	10	1.4	16	1.0	34	1.2		0.80

- Hispanic patients accounted for 21% of cases age 35-39 years up to 28.3% of 15-19 year old cases.

Holowatyj et al. *Clin Transl Gastroenterol*. 2019.

CRC disparities among Latino subpopulations defined by country of origin

California Cancer Registry: 1995-2011

	All Latinos N = 36,133		Mexican N = 9678		Puerto Rican N = 295		Cuban N = 558		Central/South American N = 2636		Other/NOS Latinos N = 22966		NH white N =174710	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Age at DX														
<50	5,839	16	1,900	20	27	9	24	4	515	20	3,373	15	12,238	7
50–65	12,496	35	3,464	36	90	31	118	21	970	37	7,854	34	44,899	67
>65	17,798	49	4,314	44	178	60	416	75	1,151	43	11,739	51	117,573	26

- CRC incidence rates in US Latinos are generally higher than those reported for most Latin American countries
- Proportion of early-onset CRC cases highest among Mexicans & Central/South Americans (20%) and lowest in Cubans (4%) vs NHWs (7%)

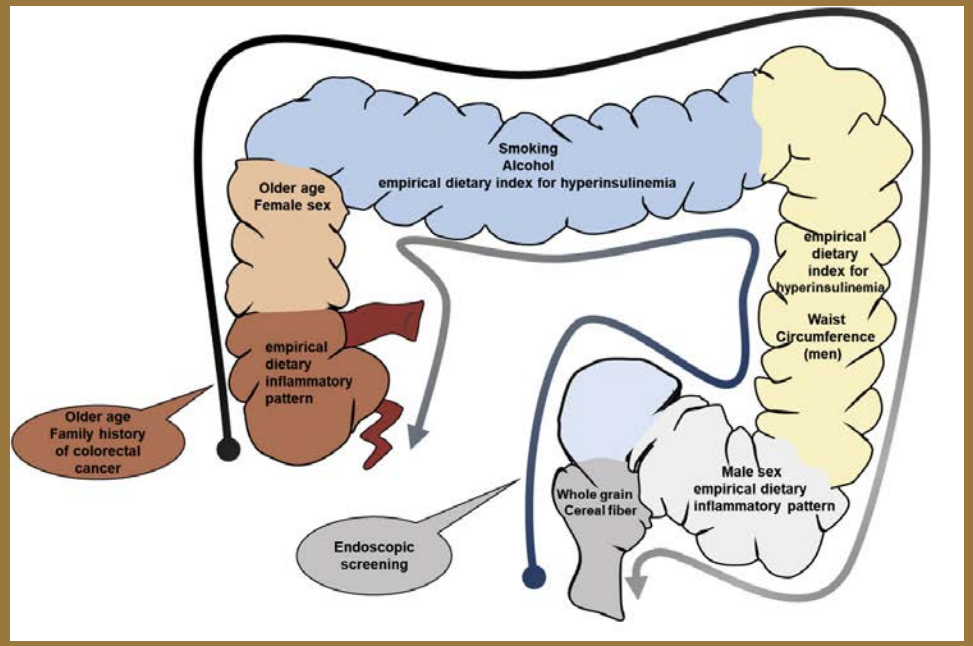
Stern et al. *Cancer Causes Control*. 2017.

Conclusions

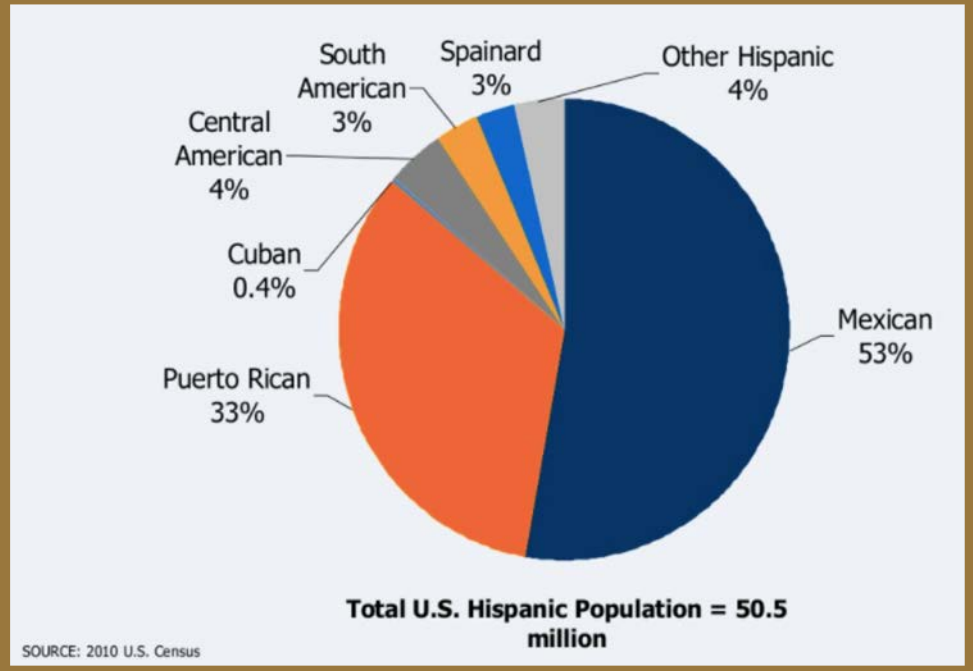
- Younger age at diagnosis is associated with a higher propensity for right-sided tumors
  - Tumor site-specific risk factor profiles
  - Avoid conflation of appendix & right-sided colon tumors

- Hispanics diagnosed with early-onset CRC at younger ages vs Whites
  - Differences in cancer determinants among Latinos?

- **Need for studies within early-onset CRC population subgroups**



Wang et al. *Gastroenterology*. 2020.



Early-onset CRC survival is significantly worse among non-Hispanic blacks vs non-Hispanic whites

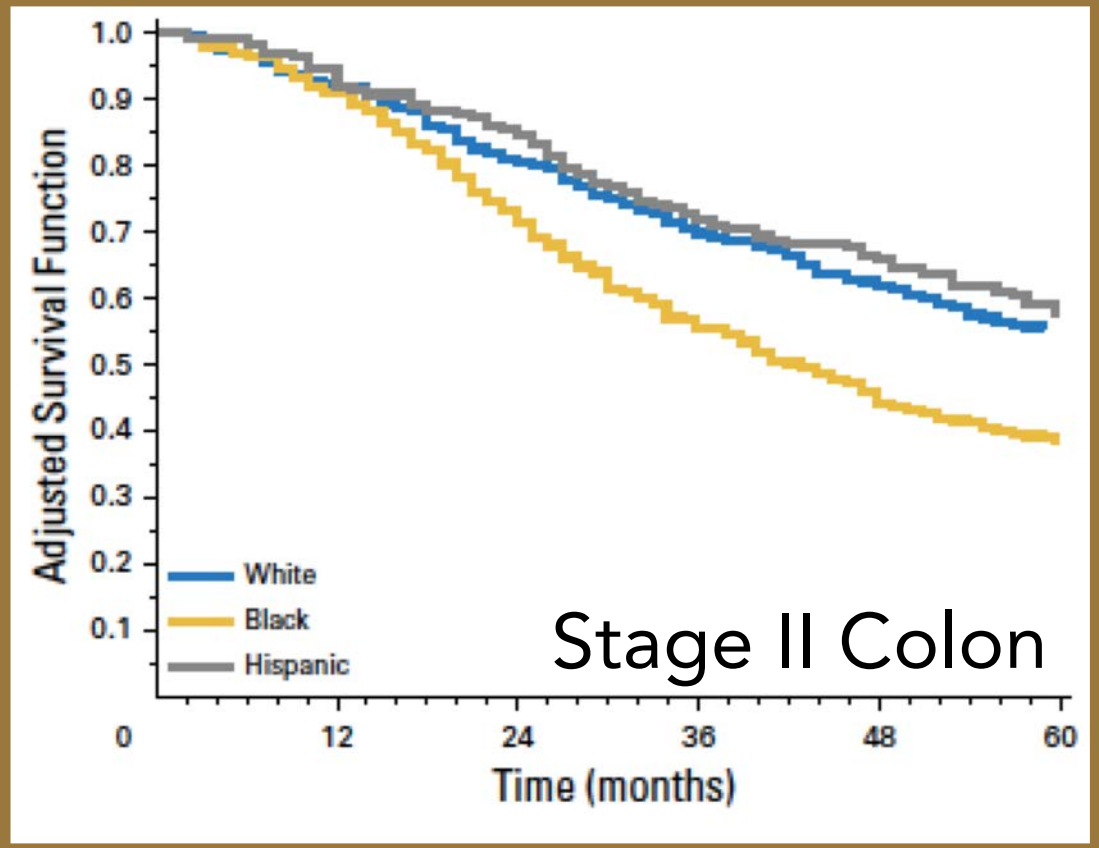
SEER18: 28,145 cases age 20-49 at CRC diagnosis, 2000-2009.

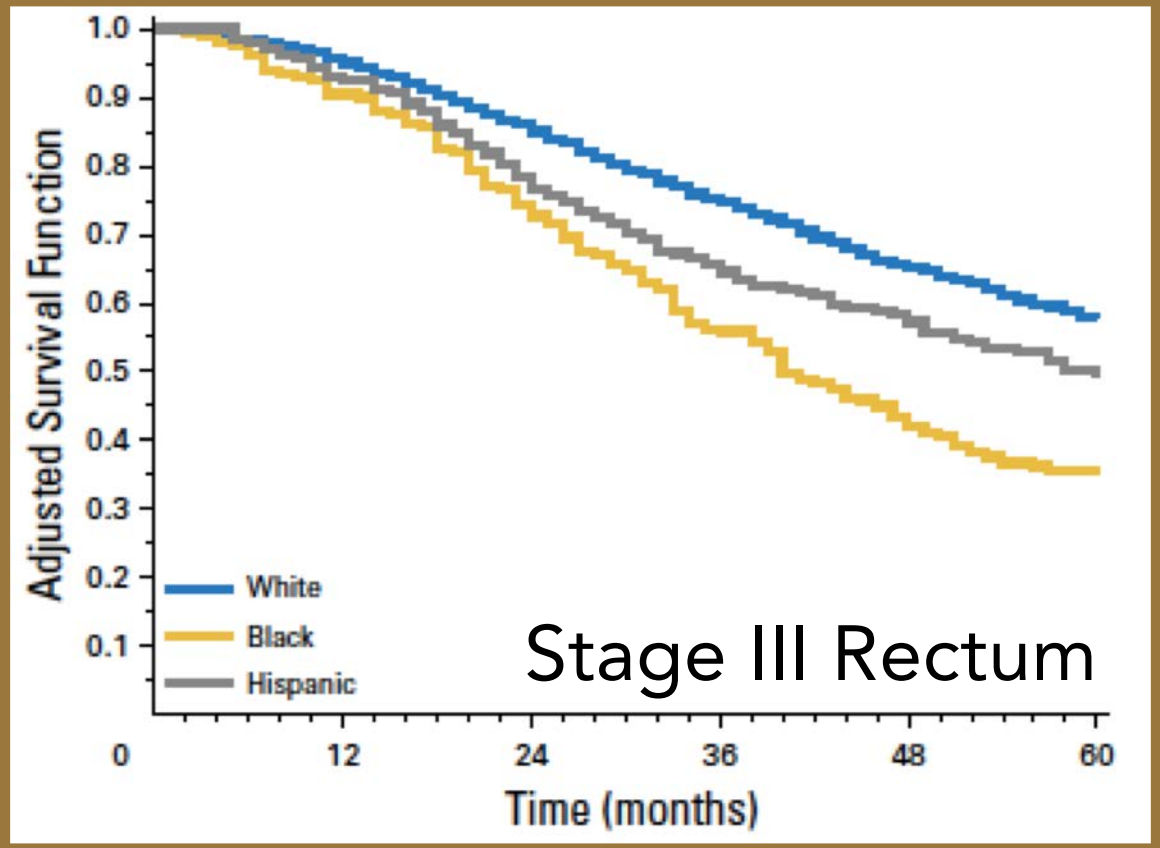
Characteristic	NHW		NHB		H	
	No.	%	No.	%	No.	%
Total	19,497	69.3	4,384	15.6	4,264	15.1
Age at diagnosis, years						
20-29	708	3.6	146	3.3	268	6.3
30-39	3,664	18.8	811	18.5	1,110	26.0
40-49	15,125	77.6	3,427	78.2	2,886	67.7
Mean (SD), years	43.0	(5.7)	42.9	(5.6)	41.4	(6.5)

- Blacks had a 35% and 51% higher hazard of death in colon and rectum/rectosigmoid junction cancers, respectively, vs Whites.

Holowatyj et al. *J Clin Onc.* 2016.

Early-onset CRC survival is significantly worse among blacks vs whites, even in early-stage disease



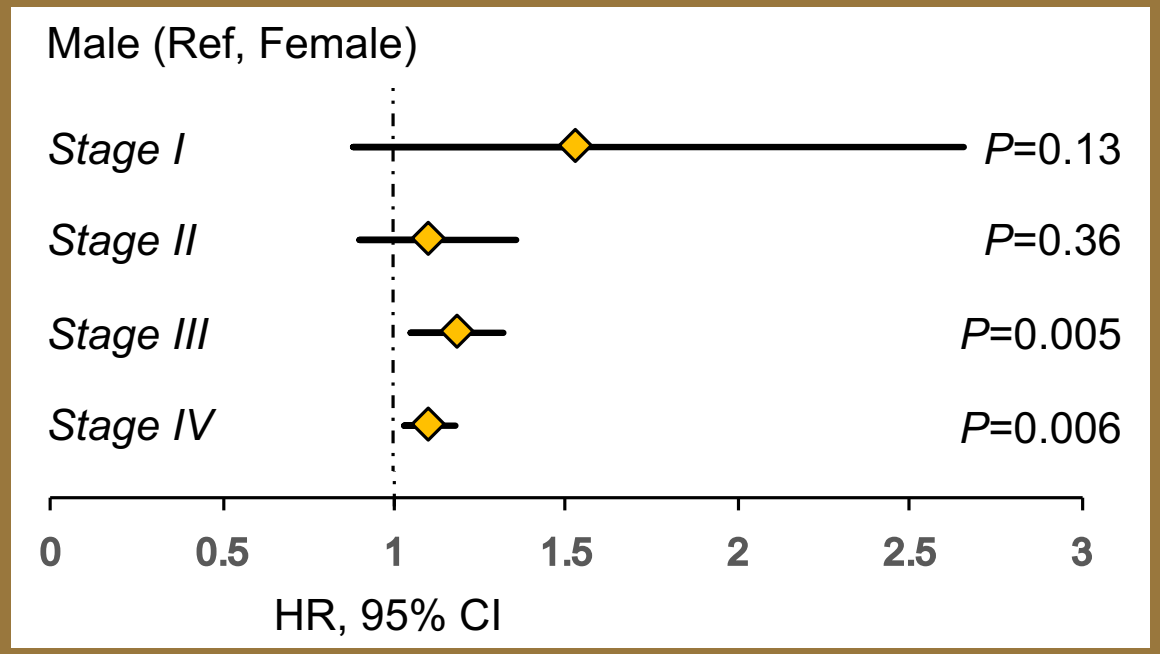


Overall survival curves adjusted for age, poverty, sex, surgery, and radiation therapy.

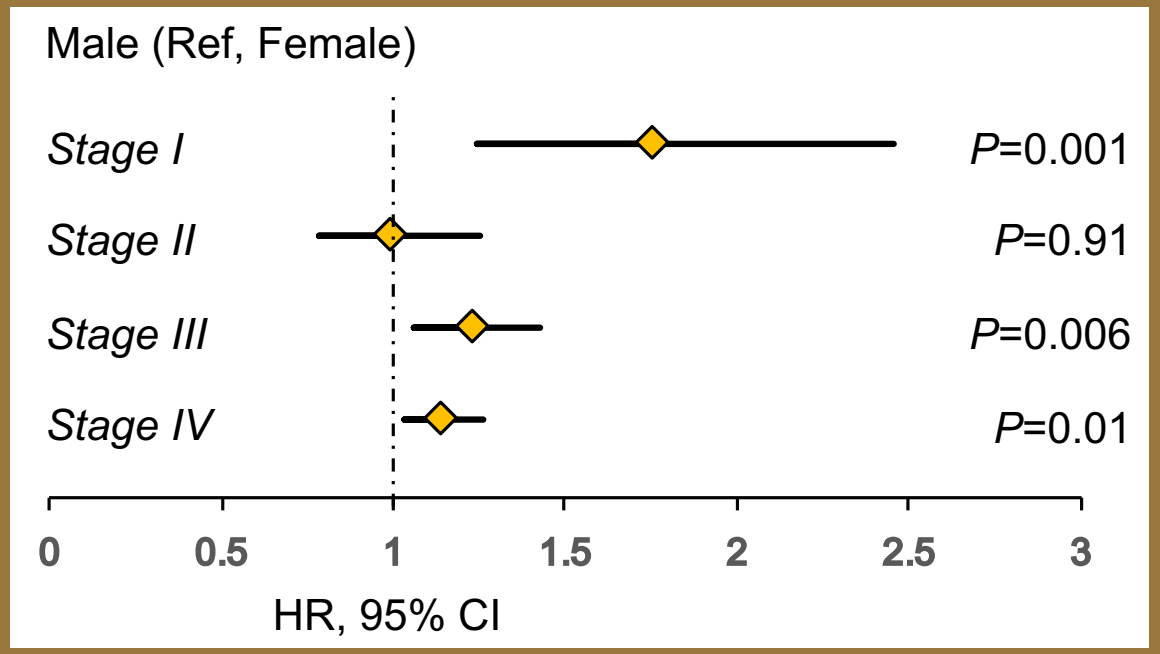
Holowatyj et al. *J Clin Onc*. 2016.

Early-onset CRC survival is significantly worse among males compared with females

Colon



Rectum/Rectosigmoid Junction



- Males had a 15% and 20% higher hazard of death in colon and rectum/rectosigmoid junction cancers, respectively, vs females.

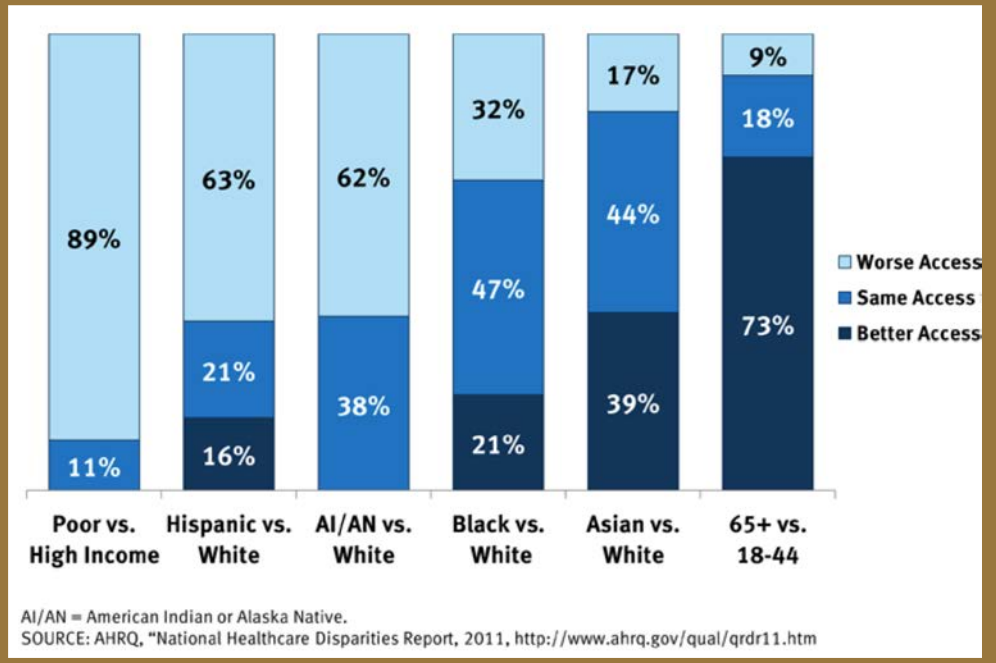
Holowatyj et al. *J Clin Onc.* 2016.

Conclusions

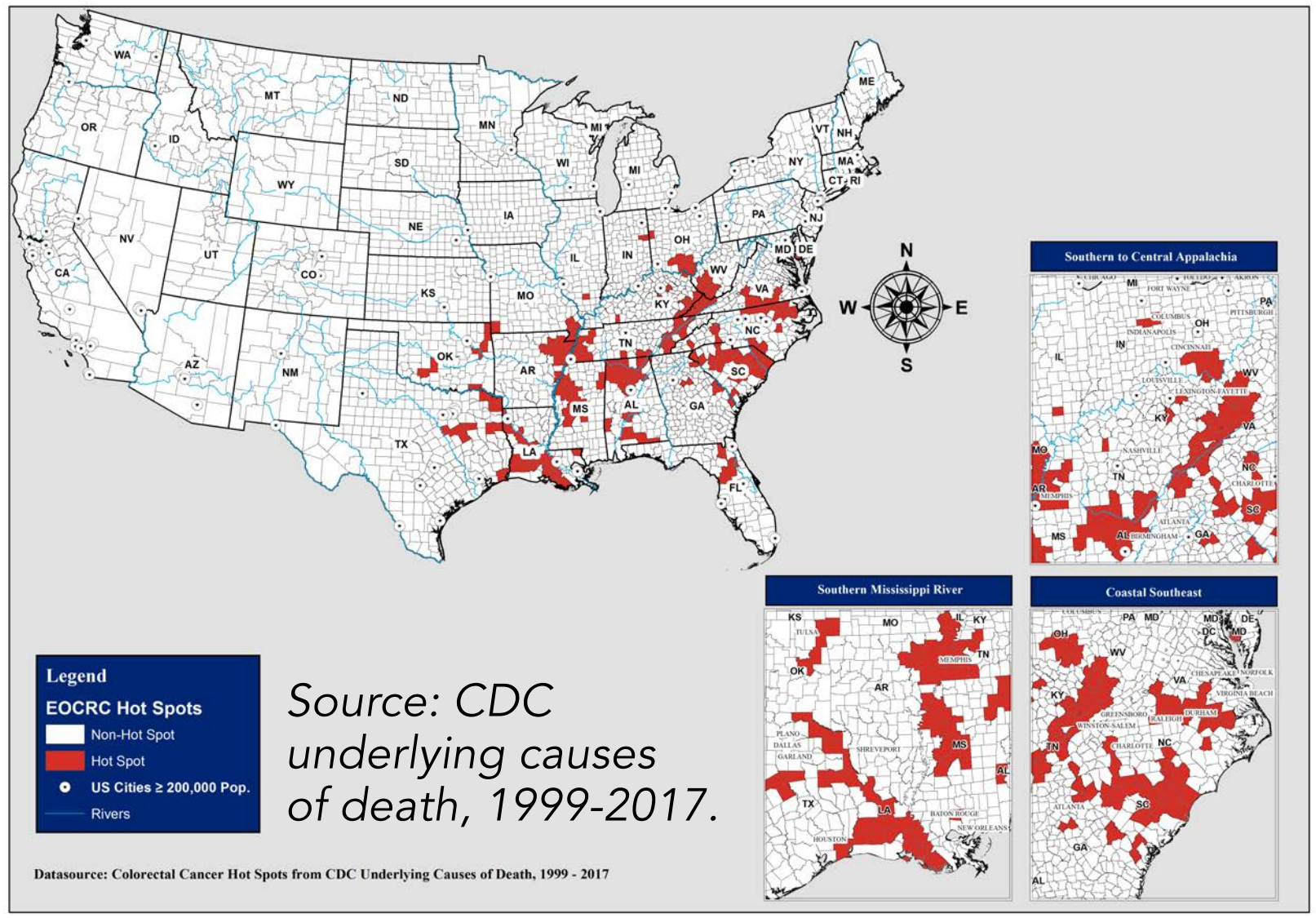
- Survival after early-onset CRC diagnosis is significantly worse among NHB vs NHWs, even among patients with early-stage disease
- Men experienced significantly poorer CRC survival vs women
- **Further study needed to determine whether differences in tumor biology and/or treatment are associated with disparities in outcomes**

Table 2. Mean Overall and Cancer-Specific Survival Months for Patients With Colorectal Cancer by Tumor Stage and Site by Race/Ethnicity, SEER 18, 2000-2009

	Colon			Rectum and Rectosigmoid Junction		
Survival	White	Black	Hispanic	White	Black	Hispanic
Overall survival						
Stage 0-I	58.8	57.9	52.4	56.7	54.8	53.6
Stage II	55.7	54.1	56.6	54.7	50.6	53.7
Stage III	51.4	48.2	50.1	53.3	47.2	50.3
Stage IV	27.3	22.8	26.1	28.6	22.6	26.1
Cancer-specific survival						
Stage 0-I	59.6	48.2	53.3	57.2	55.8	54.0
Stage II	55.6	55.1	57.6	55.6	51.7	54.5
Stage III	51.9	49.1	50.9	53.7	47.7	50.8
Stage IV	27.9	23.4	27.0	29.0	23.2	27.2



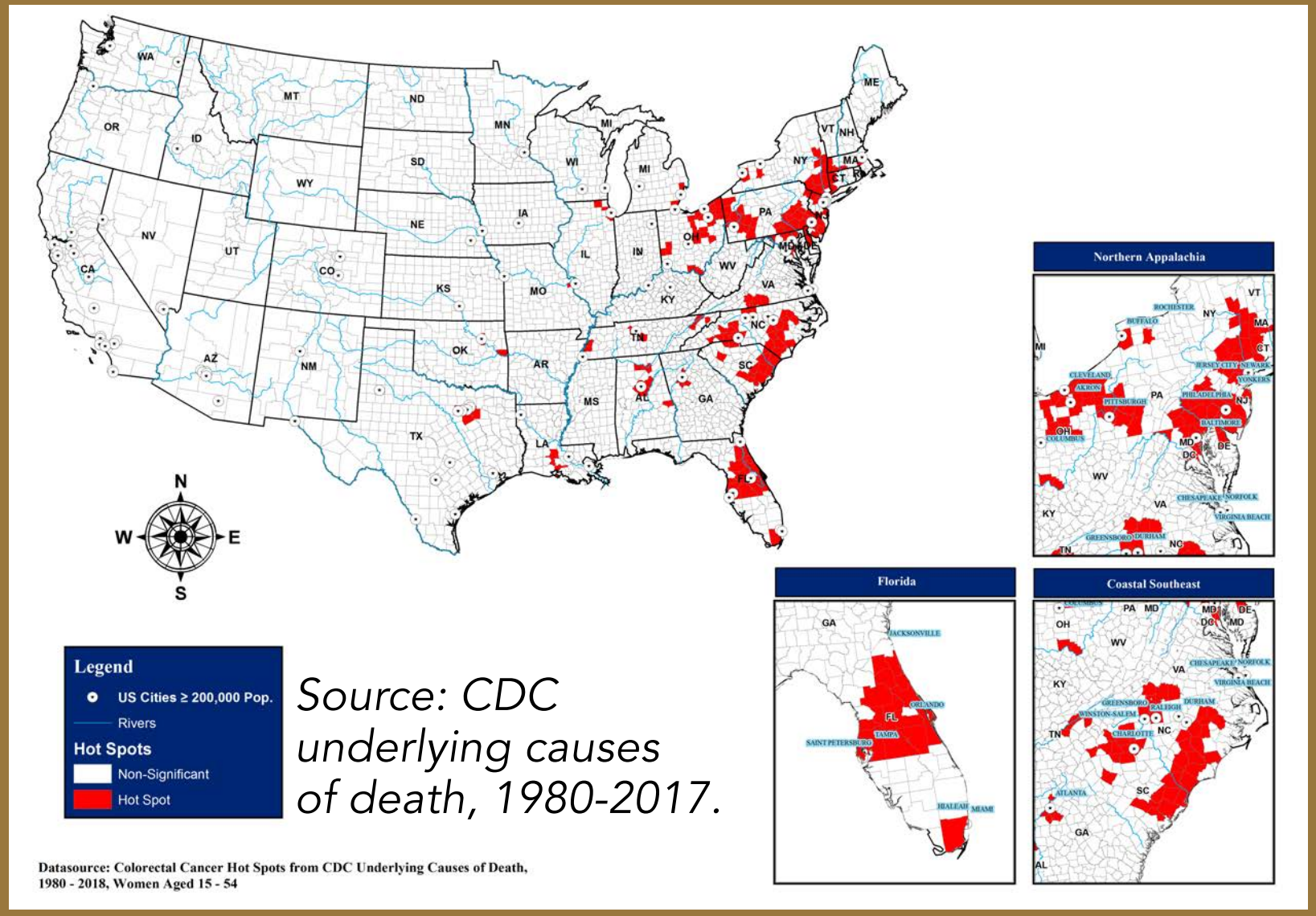
Counties with high early-onset CRC mortality are concentrated in the Southern US



Hot spots: counties with high rates of early-onset CRC mortality **among men and women**, based on 3 geospatial methodologies.

Rogers…Holowatyj. *Am J Can Res.* 2020.

Marked shifts in early-onset CRC mortality hot spots specifically among women



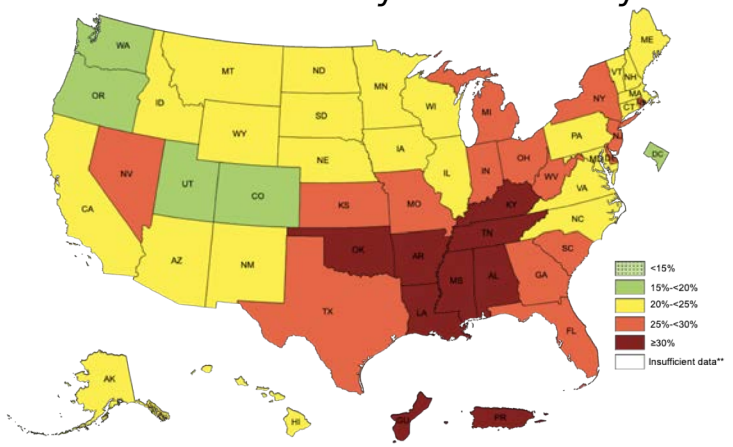
- Approximately 1 in every 16 contiguous U.S. counties are female early-onset CRC hot spots
- 47% of female hot spot counties were located in the Midwest/Northeast

Holowatyj et al. *Under review*. 2020.

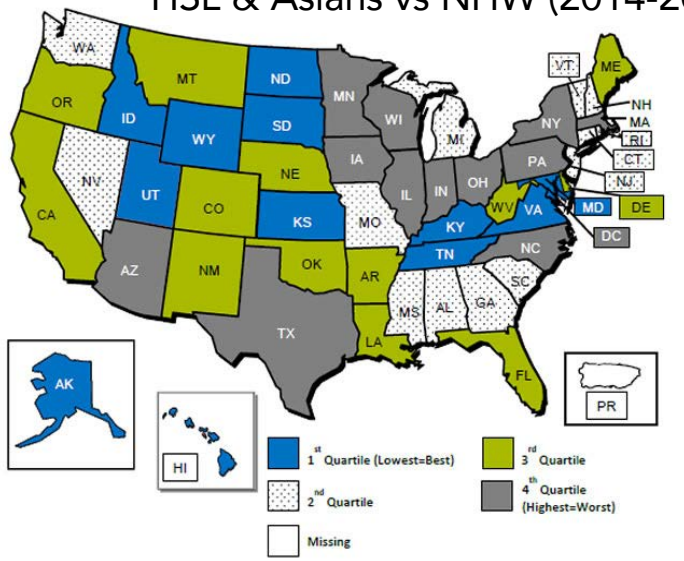
Conclusions

- Geographic disparities in early-onset CRC mortality persist across the US
- Individual & community-level features accounted for distinct variance patterns in early-onset CRC survival by hot spot classification
- **Understanding the impact of community health behaviors—particularly in regions with high early-onset CRC mortality rates—is critical for tailoring strategies to reduce early-onset CRC disparities**

BRFSS 2015-2018
Physical Inactivity



Differences in quality of care for NHB, HSL & Asians vs NHW (2014-2015)



https://www.ahrq.gov/research/findings/nhqrdr/nhqdr16/overview.html


Madrid,
Spain
USA
Zaria,
Nigeria
Makassar,
Indonesia

The burden of early-onset CRC among rural Nigerians

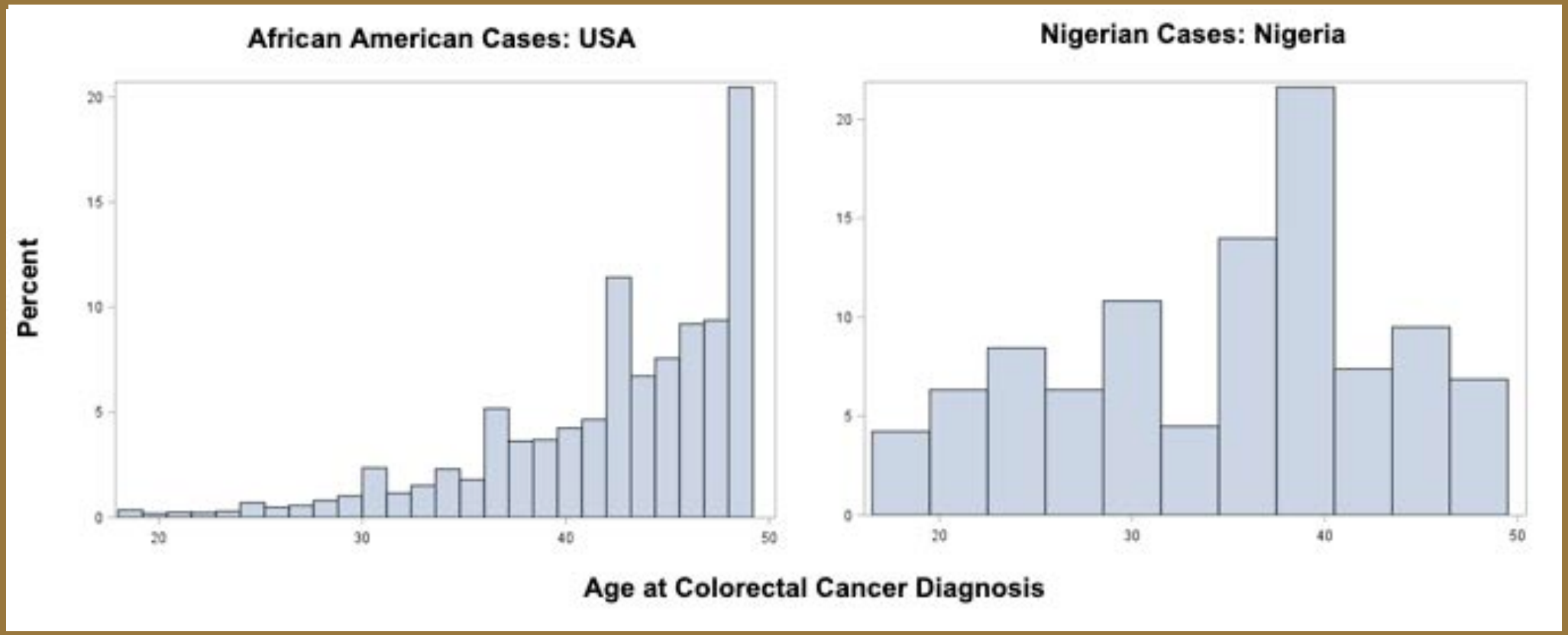
- No current organized CRC screening programs in Nigeria

	Study Population	
Characteristic	N	%
Total	379	
Age at Diagnosis		
<30 Years	103	27.2
30-39 Years	124	32.7
40-49 Years	152	40.1
Mean, Years (std)	34.8 (8.4)	
Sex		
Female	158	41.7
Male	221	58.3
Tumor Site		
Colon	86	22.7
Rectosigmoid Junction/Rectum	290	76.5
Unspecified	3	0.8
Histology		
Adenocarcinoma	352	92.9
Signet Ring Cell Carcinoma	7	1.8
Squamous Cell Carcinoma	7	1.8
Other**	13	3.4

**Other histological subtypes include, but are not limited to: carcinoid tumor, small cell carcinoma, neuroendocrine tumor, gastrointestinal stromal tumor (GIST), medullary carcinoma, and carcinoma, not otherwise specified.

Holowatyj et al. *JCO Global Oncology*. 2020.

Age patterns of early-onset CRC among Nigerian and African American individuals



70.3% vs 92.6% of US & Nigerian populations are age younger than 54 years

Holowatyj et al. *JCO Global Oncology*. 2020. CIA World Factbook.

Distinct patterns of early-onset CRC among Nigerian and African American individuals

Young Nigerian patients with CRC were eight-fold more likely to be diagnosed with rectal tumors compared with young AA individuals in the US.

	Nigerian vs African American Cases*		
Observational Study Estimate	OR	(95% CI)	*P*
Age at Diagnosis			
Years	0.87	(0.86-0.89)	<0.0001
Sex			
Female	Ref		
Male	1.16	(0.91-1.48)	0.23
Tumor Site			
Colon	Ref		
Rectosigmoid Junction/Rectum	8.14	(6.23-10.62)	<0.0001
Histology			
Adenocarcinoma	Ref		
Signet Ring Cell Carcinoma	0.51	(0.21-1.26)	0.14
Squamous Cell Carcinoma	0.59	(0.25-1.40)	0.23
Other**	0.11	(0.06-0.19)	<0.0001

*Adjusted for patient age, sex, tumor site and histology, as appropriate.
**Other histological subtypes include, but are not limited to: carcinoid tumor, small cell carcinoma, neuroendocrine tumor, gastrointestinal stromal tumor (GIST), medullary carcinoma, and carcinoma, not otherwise specified.
OR, odds ratio; CI, confidence interval; Ref, referent.

Holowatyj et al. *JCO Global Oncology*. 2020.

Conclusions

- Nearly 2/3 of Nigerian population with CRC were diagnosed with early-onset disease vs 1 of every 8 African Americans in the US

- Potential left-sided CRC shift in sub-Saharan Africa
  - Young Nigerians more likely to present with rectal tumors vs young African Americans
  - Rectal tumors more likely to present with signs/symptoms vs colon tumors
  - **Distinct CRC presentation may be due to limited resources, unique biology, and patient beliefs**

- *Need to implement organized CRC screening programs in Nigeria*


Madrid, Spain
USA
Zaria, Nigeria
Makassar, Indonesia

Prognostic factors of microsatellite stable CRC in young Spanish patients

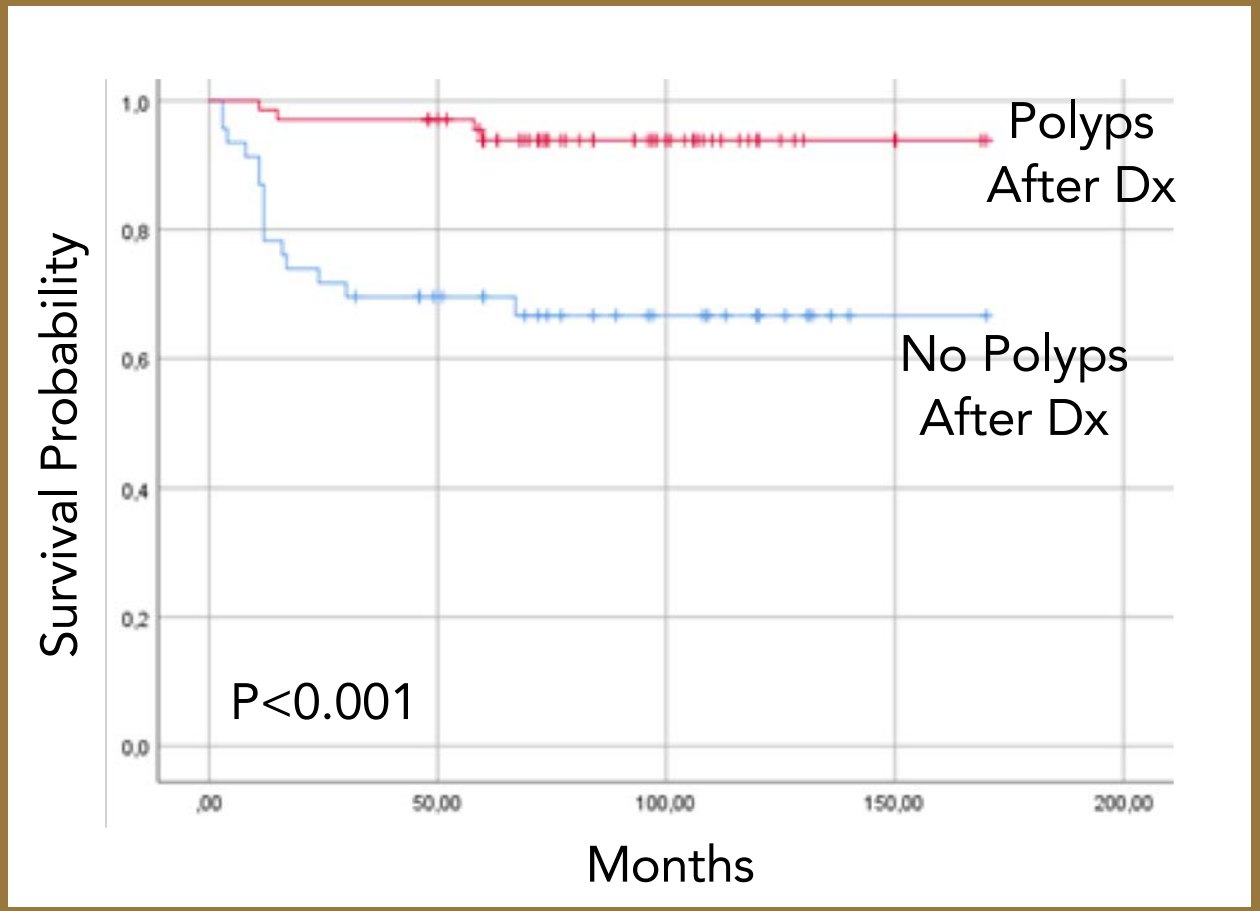
Characteristic	Study Population N (%)
Total	177 (100)
Sex	
Male	95 (54)
Female	82 (46)
Tumor Site	
Right-sided colon	43 (24)
Left-sided colon	61 (35)
Rectum/rectosigmoid junction	73 (41)
History of Colorectal Polyps	
None	84 (47)
Yes	93 (53)
Before CRC	20 (22)
Synchronous to CRC	38 (41)
After CRC	86 (92)
Mean number of polyps (SD)	2.14 (3.6)
Recurrence	19 (11)
CRC-Related Death	47 (27)
Overall survival, months (±SD) [1]	80.6 (±49.6)
Disease-free survival, months (±SD) [1]	72 (±42.8)

- *Nearly half of patients with early-onset MSS CRC had a positive history of colorectal polyps*
- *92% of young patients with a polyp history presented with 1+ polyps after CRC diagnosis*

Perea…Holowatyj. *Under review*. 2020.

Prognostic factors of microsatellite stable CRC in young Spanish patients

- *Patients who presented with polyps after early-onset MSS CRC diagnosis had significantly improved survival vs cases with no polyps*
- *Polyps were associated with >80% reduced hazard of CRC-specific death in adjusted models*

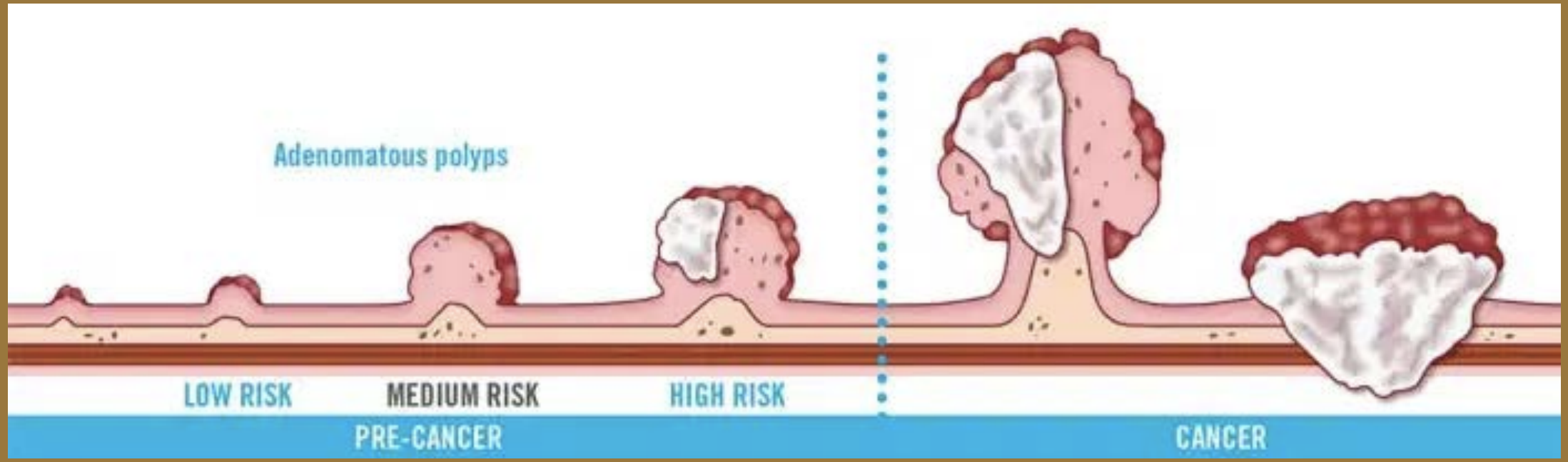


Perea…Holowatyj. *Under review*. 2020.

Conclusions

- Importance of comprehensive colorectal polyp characterization among patients with early-onset CRC
  - Clinical and molecular features unique to young patients

- **Unknown prevalence of polyps among early-onset CRC patients, especially across population subgroups**

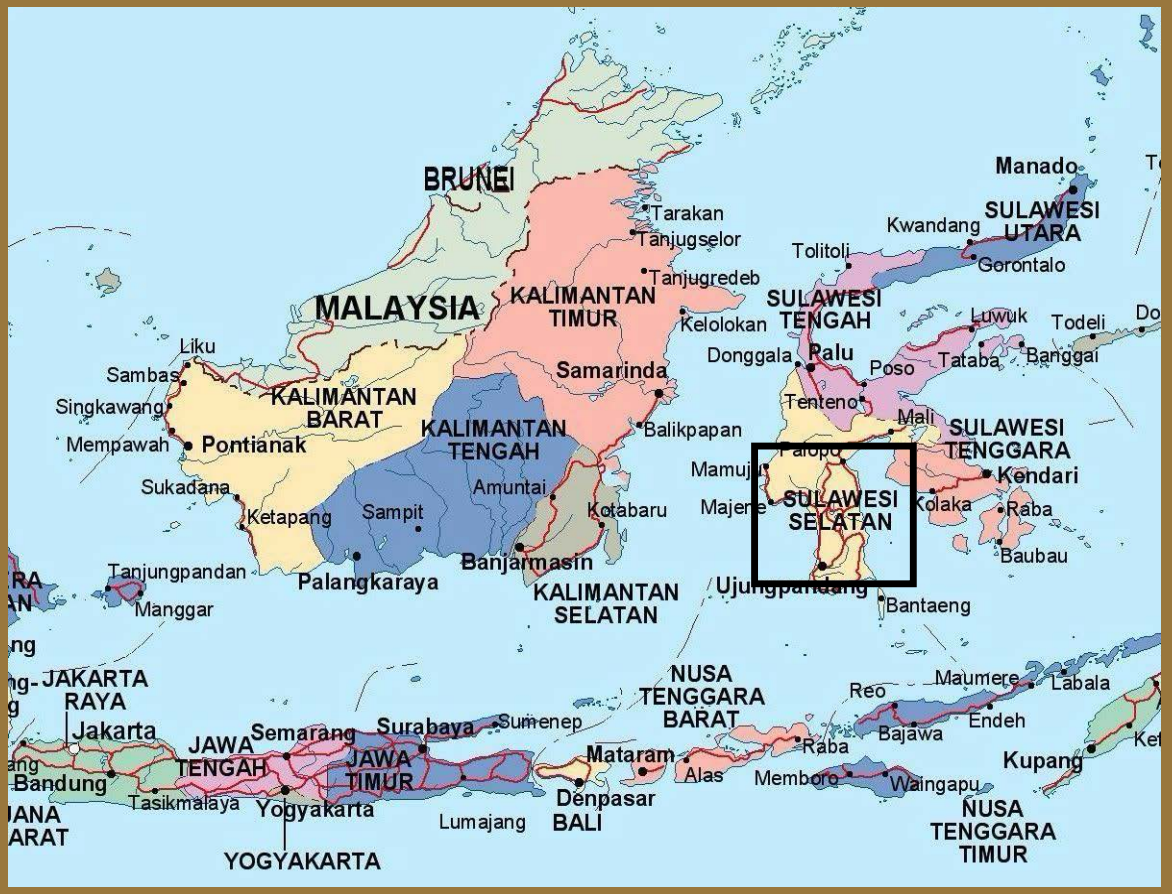



Madrid,
Spain
USA
Zaria,
Nigeria
Makassar,
Indonesia

Unique patterns of early-onset CRC among multiethnic Indonesians

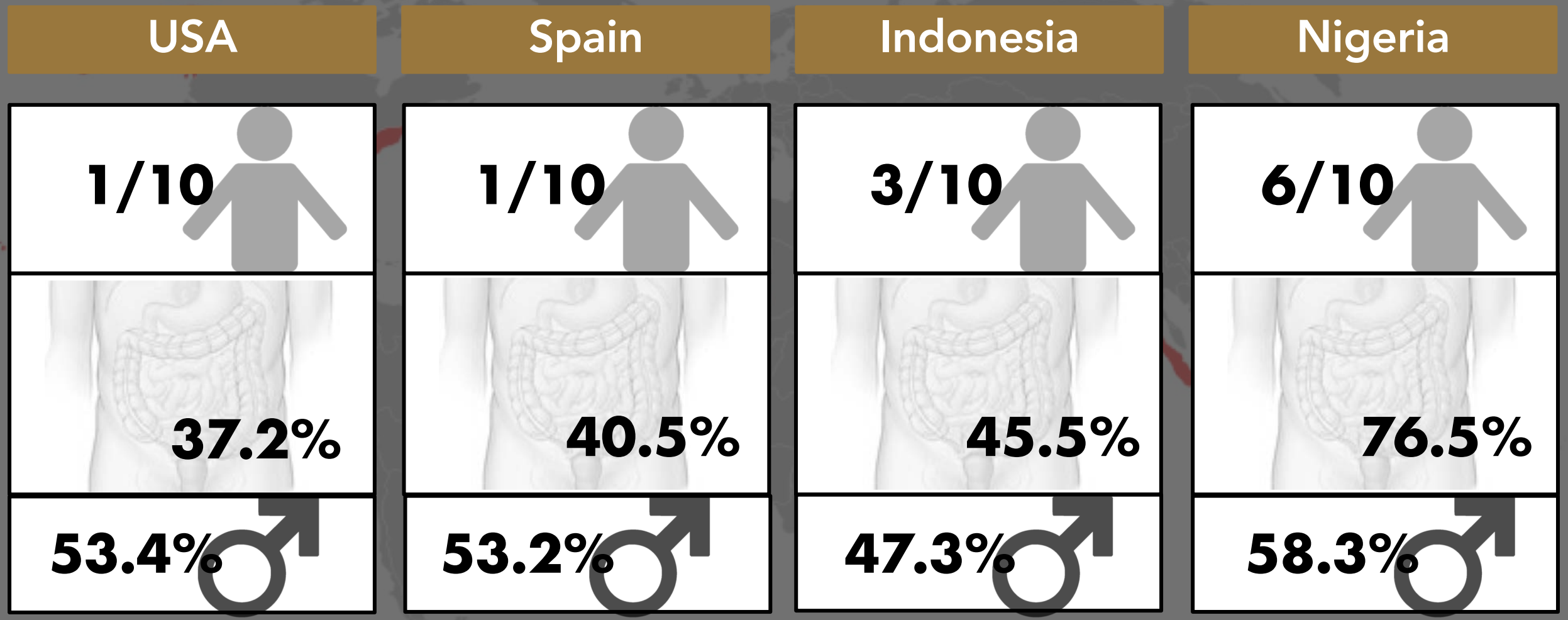
- One-third of all Indonesians with CRC are diagnosed with early-onset disease
  - *83.2% of Indonesia's population is younger than age 54 years*

- No current organized CRC screening programs in Indonesia
- 6.9% of adult population is obese



Unpublished data; CIA World Factbook.

Distinct patterns of early-onset CRC persist worldwide: do phenotypes differ?



Future early-onset CRC research directions

- Additional multi-omic studies of early-onset sporadic CRC across *and within* diverse population subgroups
- Multilevel research on dynamic relationships between individual factors, macroenvironmental influences, & health disparities in early-onset CRC
- Laboratory-based studies of early-onset CRC disparities
- Understanding survivorship needs among young CRC patients by population subgroups
- **Large-scale international investigation of early-onset CRC to decipher potential phenotypic differences in disease burden worldwide**

Global Early-Onset Colorectal Cancer Database (GEOCODE)

The overarching goal of GEOCODE is to decipher geographic variations in phenotypes of early-onset CRC worldwide.

Acknowledgements

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Questions & Discussion

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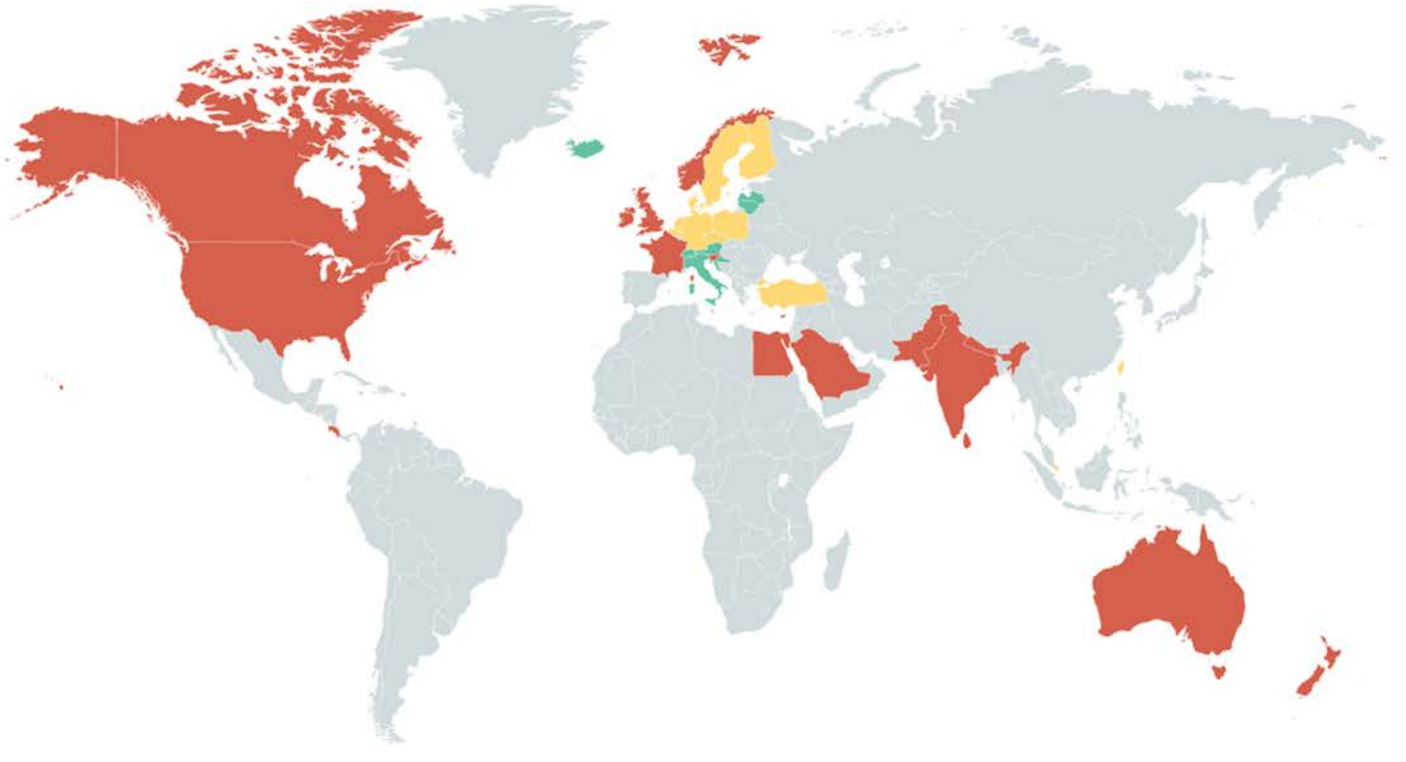
VANDERBILT HEALTH

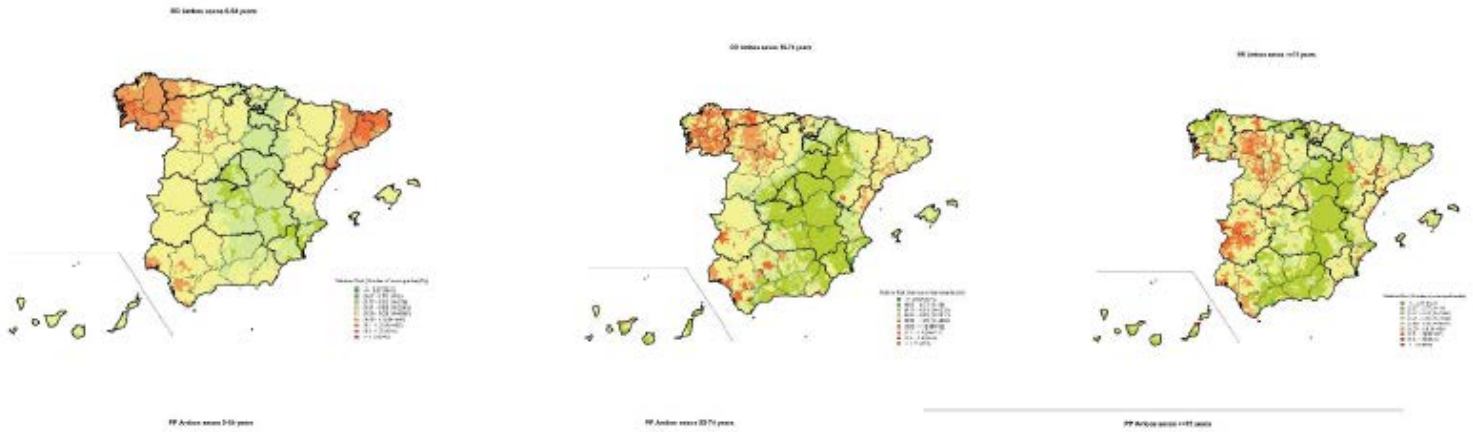
Discussion

Discussion. Increasing incidence.



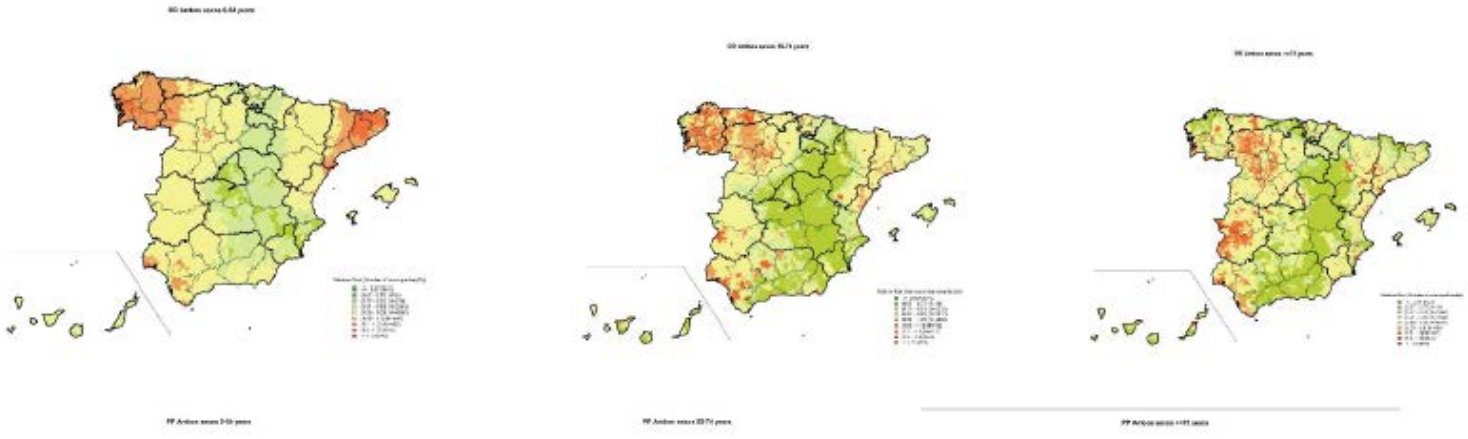
Discussion. CRC-related deaths in Spain.

Figure 2. Colorectal cancer mortality in Spain between 2010 and 2014 (classified by age intervals: 0-54, 55-74 and ≥75, respectively). Municipal distributions of the relative risks of death (A, B and C) and probabilities of having a relative risk greater than 1 (D, E, and F).

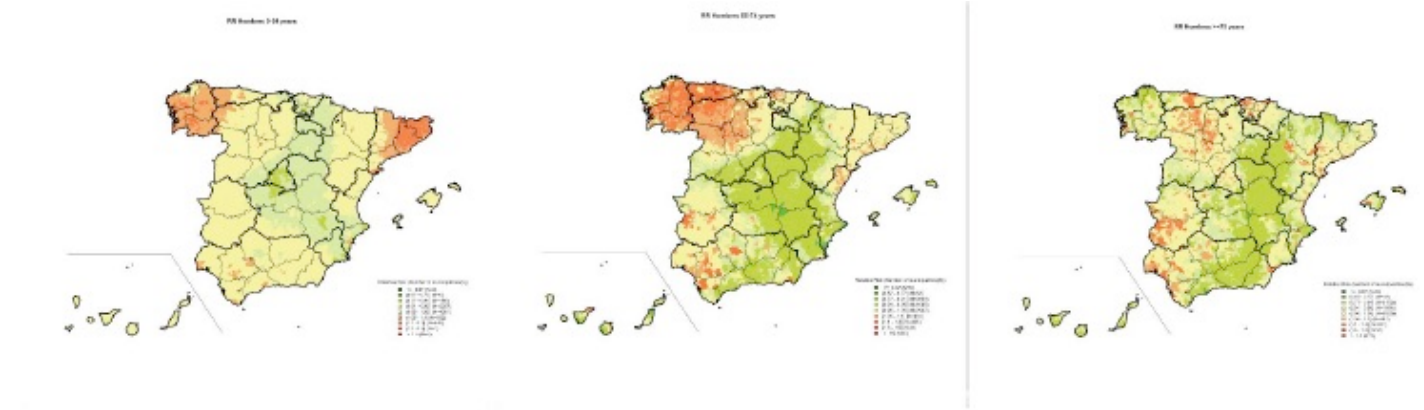


Discussion. CRC-related deaths in Spain.

M/F

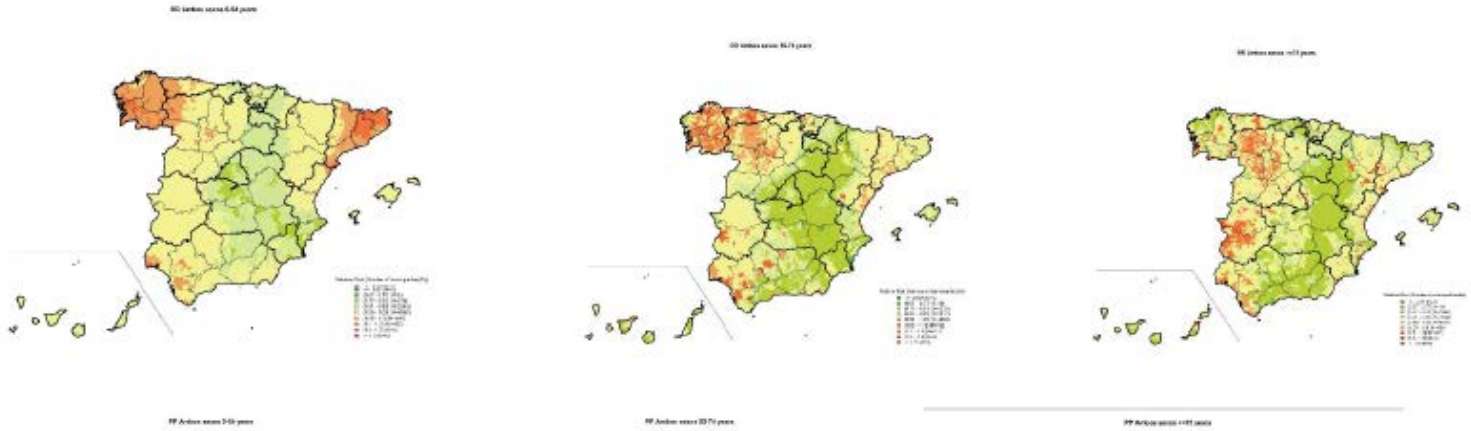


M



Discussion. CRC-related deaths in Spain.

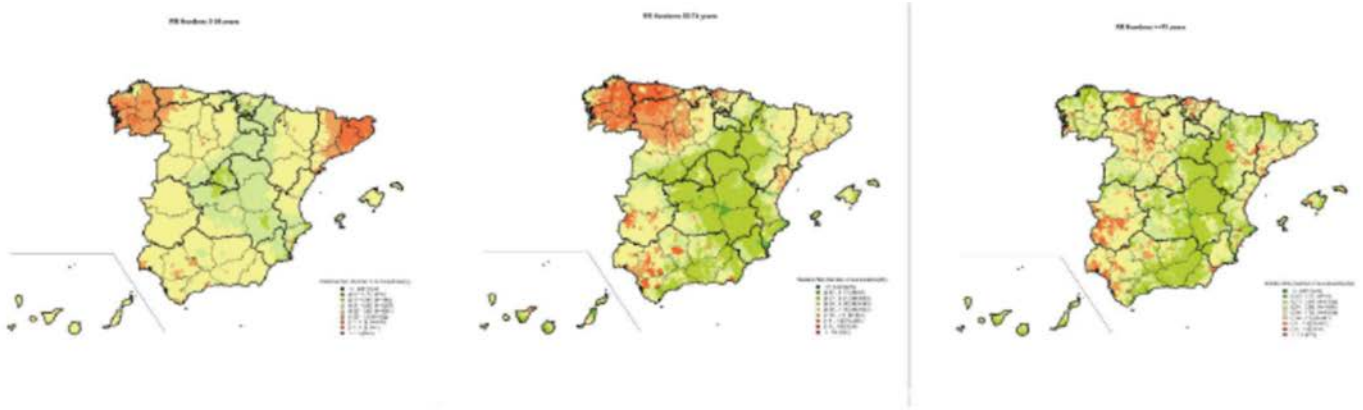
M/F



F

Discussion. CRC-related deaths in Spain.

M



F

Worldwide Consortium on EAOCRC characterization: GEOCODE.

Addressing Pre-Webinar Questions

Discussion

Research literature.

Open

Personal History of Diabetes as Important as Family History of Colorectal Cancer for Risk of Colorectal Cancer: A Nationwide Cohort Study

Uzair Ali Khan, MSc[1,2], Mahdi Fallah, MD, PhD[1,3], Yu Tian, PhD[1,2], Kristina Sundquist, MD, PhD[3,4,5], Jan Sundquist, MD, PhD[3,4,5], Hermann Brenner, MD, PhD[1,6,7] and Elham Kharazmi, MD, PhD[1,3]

Am J Gastroenterol 2020;115:1103–1109.

Current Overview of EAOCRC initiatives.

Research literature.

AIM: Analysis of the association of CRC risk, especially early-onset CRC, with DM, family history of CRC, and age at DM diagnosis.

MATERIAL AND METHODS:

- Nationwide cohort study (Swedish family cancer data sets)

- All individuals born after 1931 and their parents (12,614,256 individuals; 559,375 diabetic patients; 162,226 CRC patients).

- Period of follow-up: 1964–2015.

-

Am J Gastroenterol 2020;115:1103–1109.

Research literature.

RESULTS:

DM diagnosis before 50: 1.9-fold increased risk of CRC before 50 vs 1.3-fold risk of CRC at/after the age of 50 years.

DM diagnosis before 50 in those with a family history of CRC was associated with 6.9-fold risk of CRC before 50, and 1.9-fold risk of CRC at/after the age of 50 years.

Diabetic patients had a similar lifetime risk of CRC before 50 (0.4%) to those with only a family history of CRC (0.5%), double that of the population (0.2%, 0.2%–0.2%).

Am J Gastroenterol 2020;115:1103–1109.

Research literature.

CONCLUSIONS:

- DM is associated with increased risk of CRC in a magnitude close to having family history of CRC.

- Associations of DM and CRC family history with increased CRC risk were most prominent in young adults.

- These findings warrant further studies on CRC screening in patients with diabetes, especially type 2, at earlier ages than in the general population.

Am J Gastroenterol 2020;115:1103–1109.

Current Overview of EAOCRC initiatives.

Research literature.

Systematic Review of Prevalence, Risk Factors, and Risk for Metachronous Advanced Neoplasia in Patients With Young-Onset Colorectal Adenoma.

Ngozi Enwerem, Moo Y. Cho, Joshua Demb, Ashley Earles, Karen M. Heskett, Lin Liu, Siddharth Singh, Samir Gupta

Clin Gastroenterol Hepatol 2020 May 16;S1542-3565(20)30679-0

Research literature.

AIM: Systematic review of young-onset adenoma (YOA) prevalence, associated risk factors, and rate of metachronous advanced neoplasia after YOA diagnosis.

RESULTS:

- The pooled overall prevalence of YOA was 9.0% (95% CI, 7.1%-11.4%) based on 24 studies comprising 23,142 individuals.
- Only advancing age was identified as a consistent risk factor for YOA (4 studies, 78,880 individuals).
- Pooled rate of metachronous advanced neoplasia after baseline YOA diagnosis was 6.0% (95% CI, 4.1%-8.6%)(3 studies, 1493) undergoing follow-up colonoscopy, with only 1 CRC case reported.
- few studies reported metachronous advanced neoplasia and none evaluated whether routine surveillance colonoscopy decreases risk of CRC

Clin Gastroenterol Hepatol 2020 May 16;S1542-3565(20)30679-0

Research literature.

CONCLUSION:

More research is needed to understand the prevalence, risk factors, and risk of CRC associated with YOA.

Clin Gastroenterol Hepatol 2020 May 16;S1542-3565(20)30679-0

EAO CRC Funding Opportunities

Closing.

- **Next webinar:**

  November, 3rd, 2020 (Tuesday, 12pm ET)**.**

- **3rd EOCRC International Symposium.**

  Definitive days / Abstract submission.

Closing.

LET´S KEEP UP THE EFFORTS.