The Causes and Consequences of Cancer Health Disparities

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Overview

- **Part 1:** Discussion of key cancer health disparities in the US
- **Part 2:** Discussion of key factors that contribute to disparities
- **Part 3:** Looking forward

Race and Ethnicity

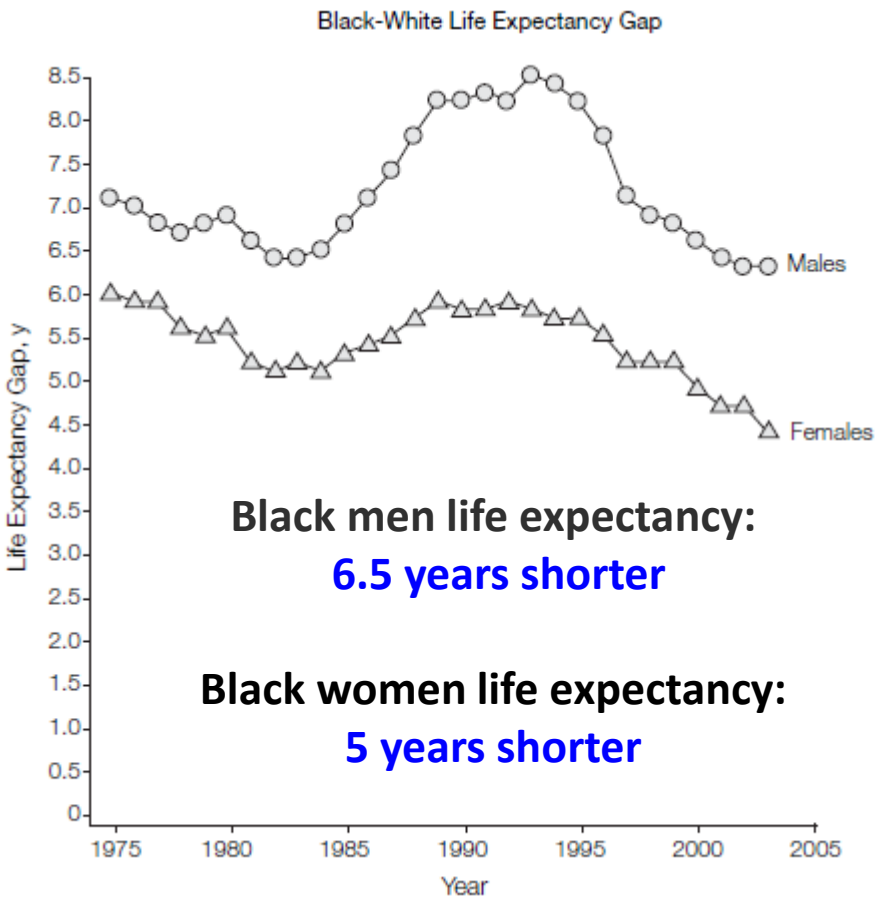
- **Race:** Biological differences between groups assumed to have different bio-geographical ancestries or genetic makeup

- **Ethnicity:** A multi-dimensional construct reflecting biological factors, geographical origins, historical influences, shared customs, beliefs and traditions among populations that may not have common genetic origin

- Both are important factors to consider in trying to research, understand and diminish cancer disparities

Health Disparities in the United States

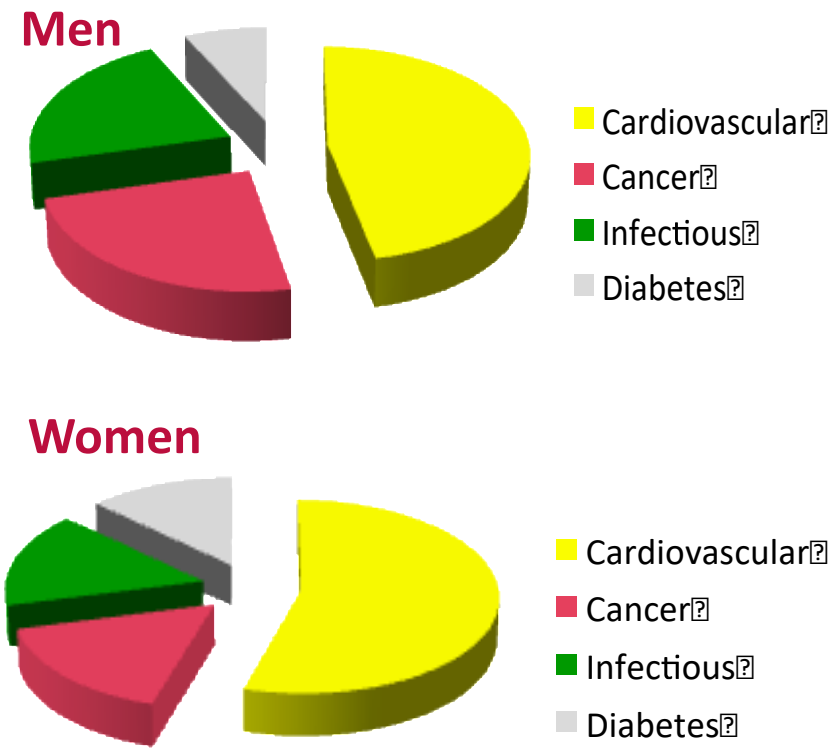
Racial differences in life expectancy in the United States



Black men life expectancy:
6.5 years shorter

Black women life expectancy:
5 years shorter

Contributing Factors



Adapted from JAMA 2007 297:11 1227

Cancer Disparities: Definition

The NCI defines "cancer health disparities" as:

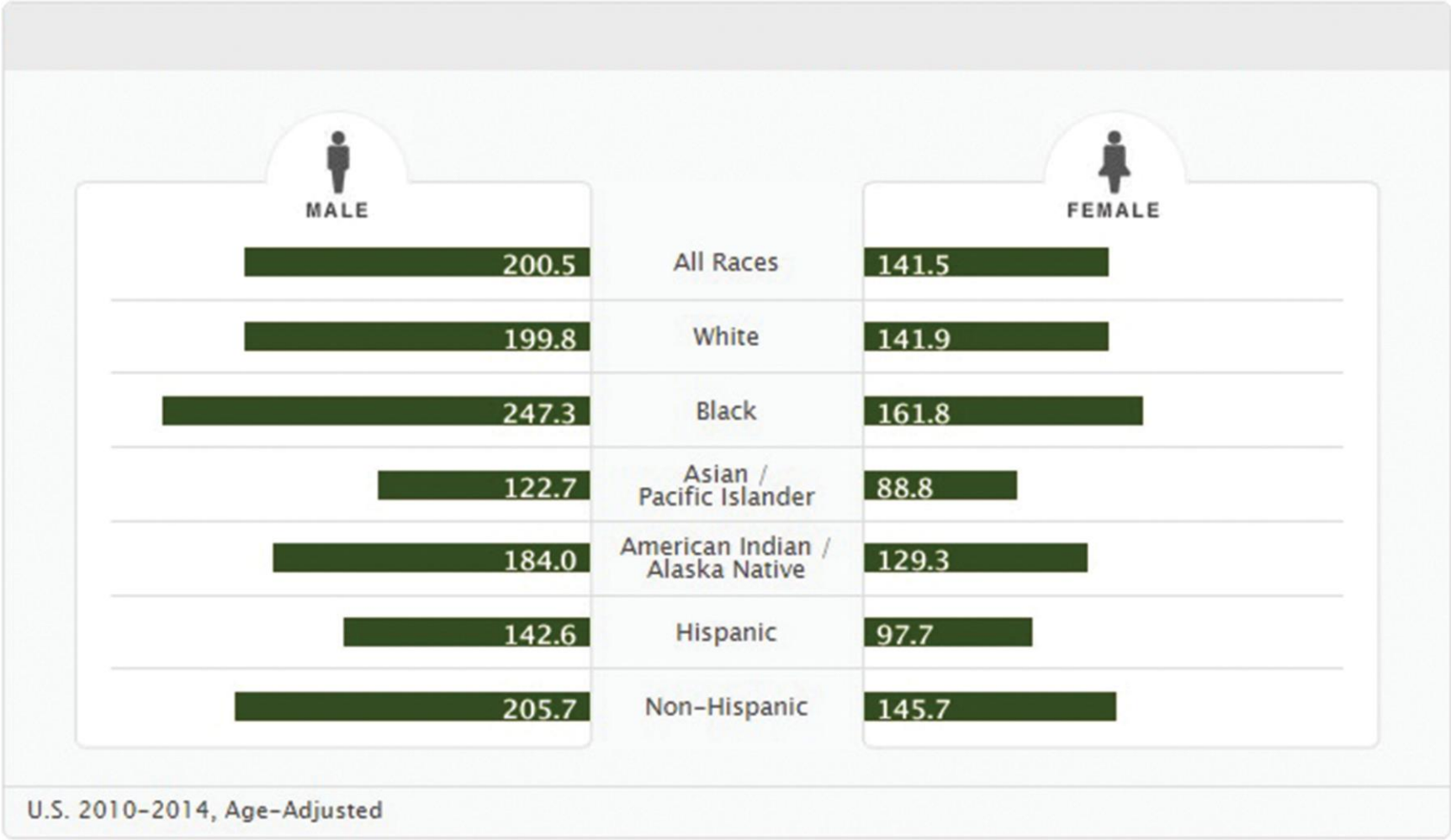
"differences in the incidence, prevalence, mortality, and burden of cancer and related adverse health conditions that exist among specific population groups in the United States."

Cancer Disparities: Definition

Excess Burden of Cancer in the African-American Community

"African-Americans have the highest death rates from all cancer sites combined, and from malignancies of the lung, colon and rectum, breast, prostate, and the cervix of all racial groups in the United States"

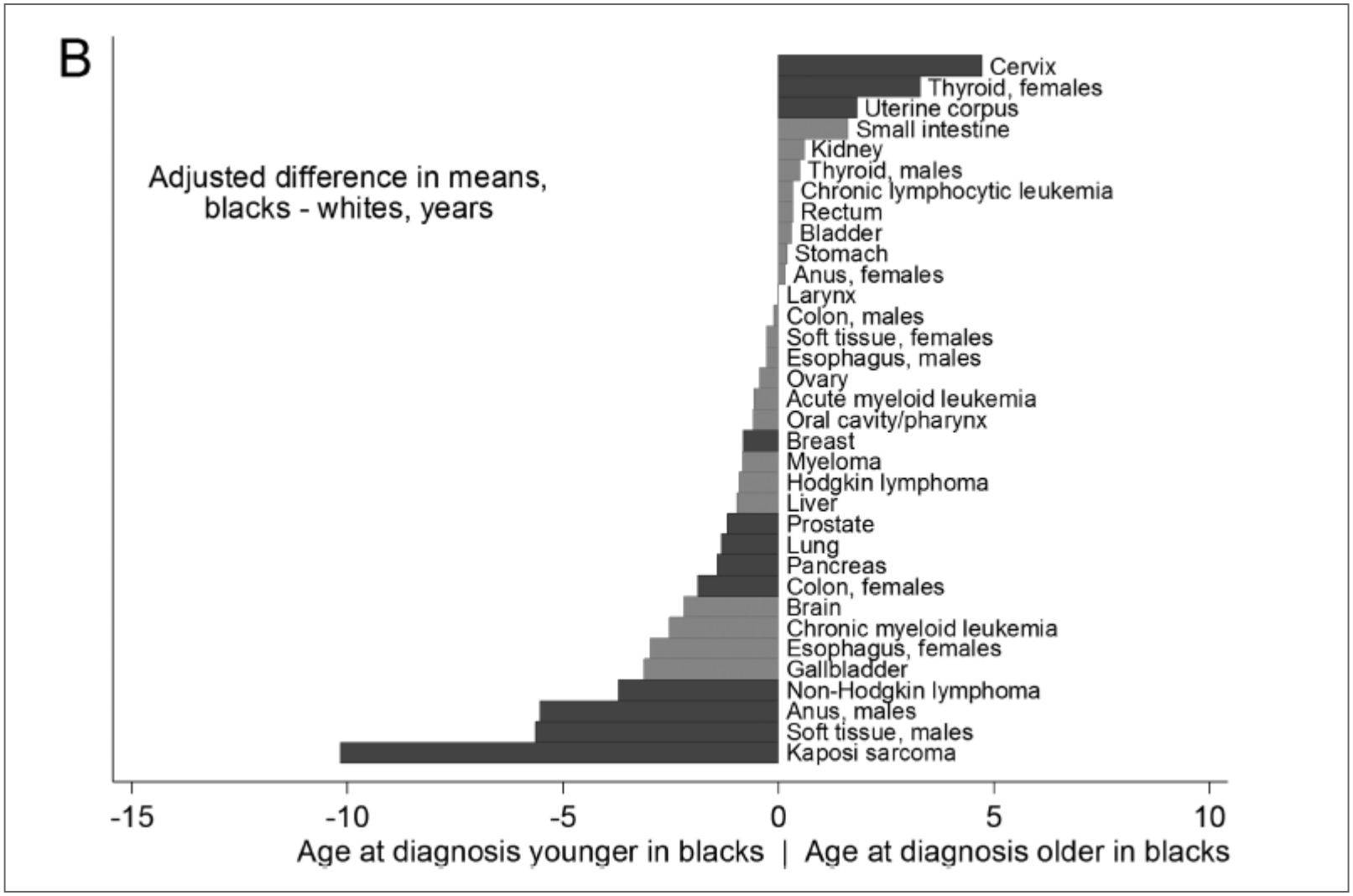
Cancer Disparities



From: Number of Deaths per 100,000 Persons by Race/Ethnicity & Sex: Cancer of Any Site

J Natl Cancer Inst. 2017;109(10). doi:10.1093/jnci/djx222

Younger age at diagnosis for most cancers



Robbins et al., J Natl Cancer Inst (2015) 107 (3)

Younger age at diagnosis for most cancers

Cancers mainly diagnosed at younger age in black men and women

NHL, anal cancer, Kaposi sarcoma and soft tissue

Etiologic heterogeneity

Cause of the cancer differs across groups, causes cancer at different ages

Subtypes can be caused by different factors – can contribute to disparities

Timing or intensity of exposure

For example, exposure to tobacco could occur earlier in one population

Timing, prevalence and frequency of early cancer detection

Screening, or through follow after an incidental finding

NCI Early Onset Malignancy Initiative

The Center for Cancer Genomics (CCG) in collaboration with the Division of Cancer Prevention's NCI Community Oncology Research Program (NCORP) invited the twelve Minority/Underserved NCORP sites to participate in this project

Cancer Health Disparities: Second cancers

African Americans also have a higher risk of certain second cancers
Site-specific risk of second primary cancer in women with endometrial cancer according to race (1973-2007)

Second Cancer Site	White (n = 10,584)	Black (n = 463)
	SIR (95% CI)	SIR (95% CI)
All sites (N = 11,047)	0.85 (0.84–0.87)	1.19 (1.08–1.31)
Solid tumors (N = 9744)	0.85 (0.83–0.87)	1.19 (1.08–1.31)
Digestive system (N = 2854)	0.97 (0.93–1.01)	1.37 (1.16–1.61)
Colon and rectum (N = 1949)	1.02 (0.97–1.07)	1.53 (1.24–1.87)
Liver (N = 40)	0.58 (0.41–0.80)	1.17 (0.32–2.99)
Pancreas (N = 356)	0.88 (0.79–0.98)	0.97 (0.56–1.55)
Respiratory system (N = 1382)	0.72 (0.68–0.76)	1.09 (0.84–1.39)
Breast (N = 3448)	0.98 (0.95–1.01)	1.01 (0.82–1.23)
Female genital system (N = 448)	0.65 (0.59–0.71)	1.48 (1.03–2.07)
Urinary system (N = 801)	1.19 (1.11–1.28)	1.80 (1.25–2.52)

Digestive system: esophagus, stomach, small intestine, colon and rectum, liver, gallbladder, and pancreas.
Respiratory system: lung and bronchus.
Female genital system: ovary, cervix, vagina, and vulva.
Urinary system: urinary bladder, ureter, kidney, and renal pelvis.

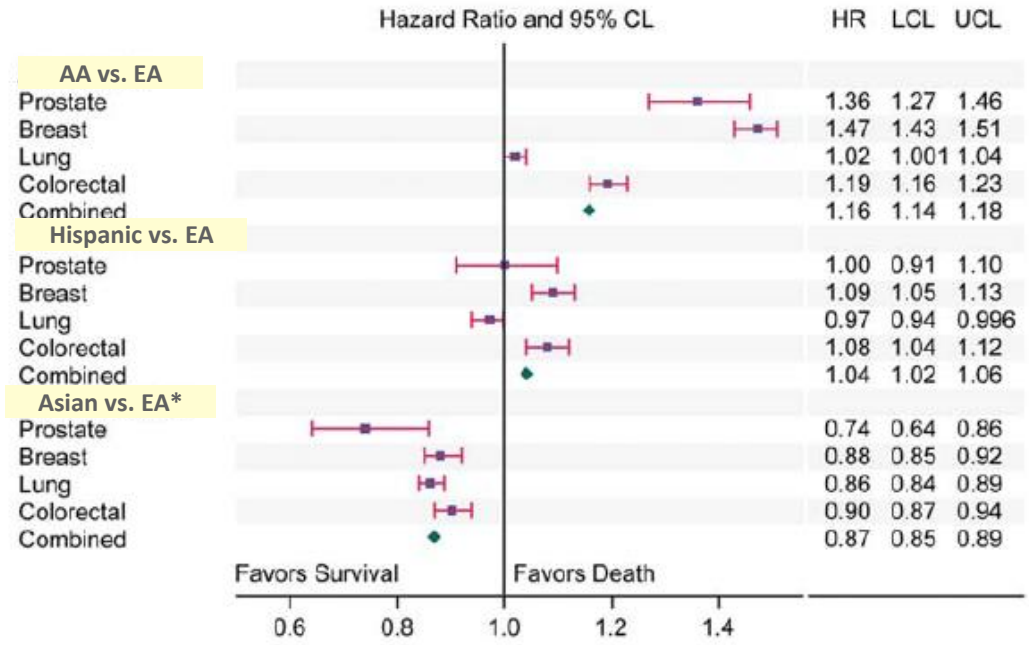
INTERNATIONAL JOURNAL OF GYNECOLOGICAL CANCER

Int J Gynecol Cancer. 2011 21(2): 309–315

Survival Health Disparities by Cancer Site

1. African Americans have the highest rate of cancer specific mortality
2. Racial differences are not reducing over time (overall)
3. Breast cancer—disparities might be increasing
4. Prostate cancer—disparities might be improving

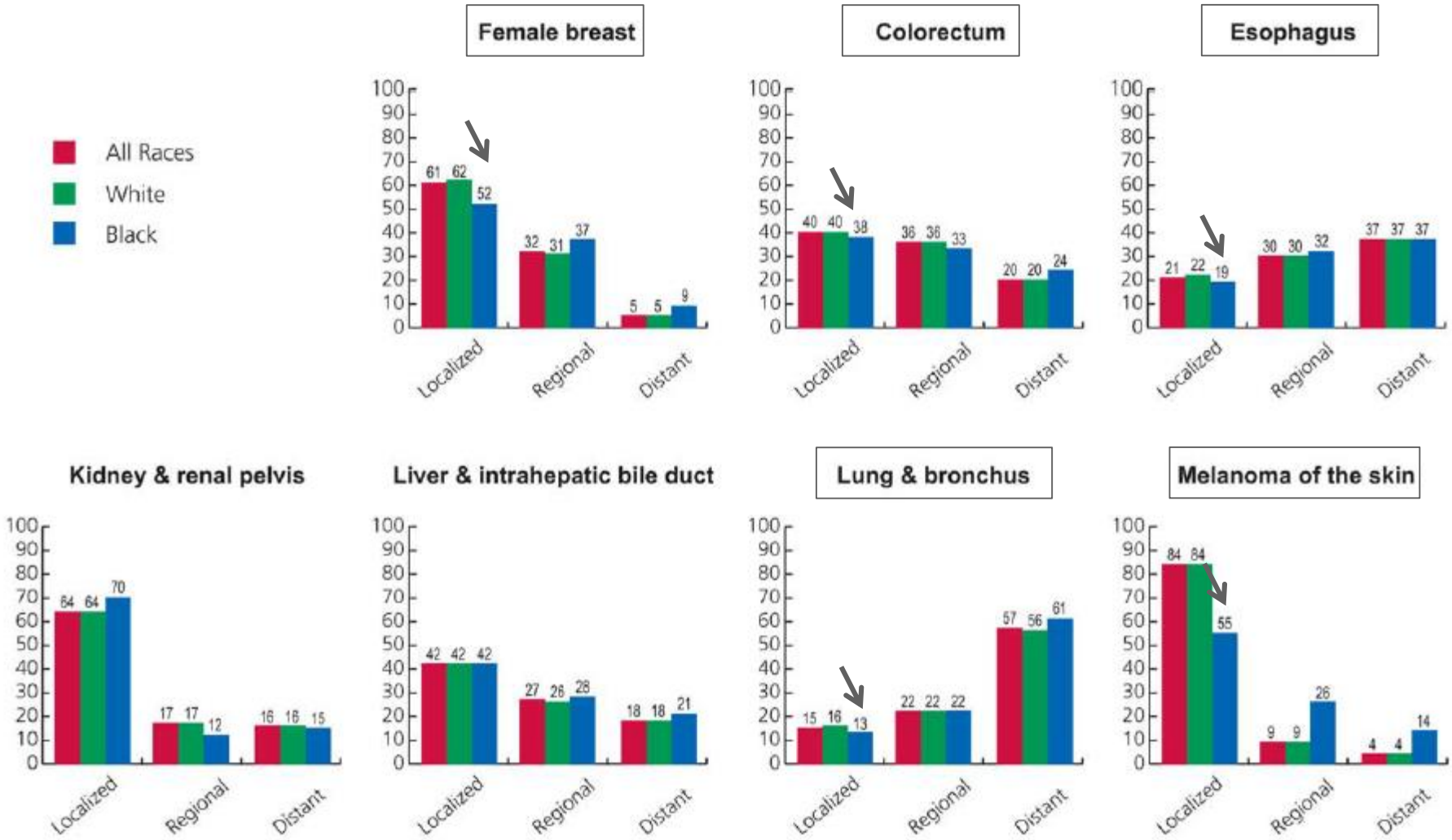
Survival health disparities between population groups



AA = African-American; EA = European-American

Aizer et al., Cancer 2014, 120: 1532-9
Zeng et al., Jama Oncology 2015 1: 88-96

Some of the reasons for disparities in cancer mortality: Lack of early detection?



CA CANCER J CLIN 2015;65:5–29

Some of the reasons for disparities in cancer mortality: Access to screening?

- Barriers to screening exist in some populations, including minority and rural
- Breast cancer mammography use similar in equal access to care setting (Cancer 2013 119(19):3531-8)
- Colorectal cancer screening is lower among African Americans even in an equal access to care setting (Cancer. 2013; 4(3): 270–280)
- Uptake of screening for other cancers, such as HPV, may also be lower in minority populations
- But mortality differences exist even in cancers where there is no validated screening modality (liver, esophagus, etc)

Lung Cancer Screening

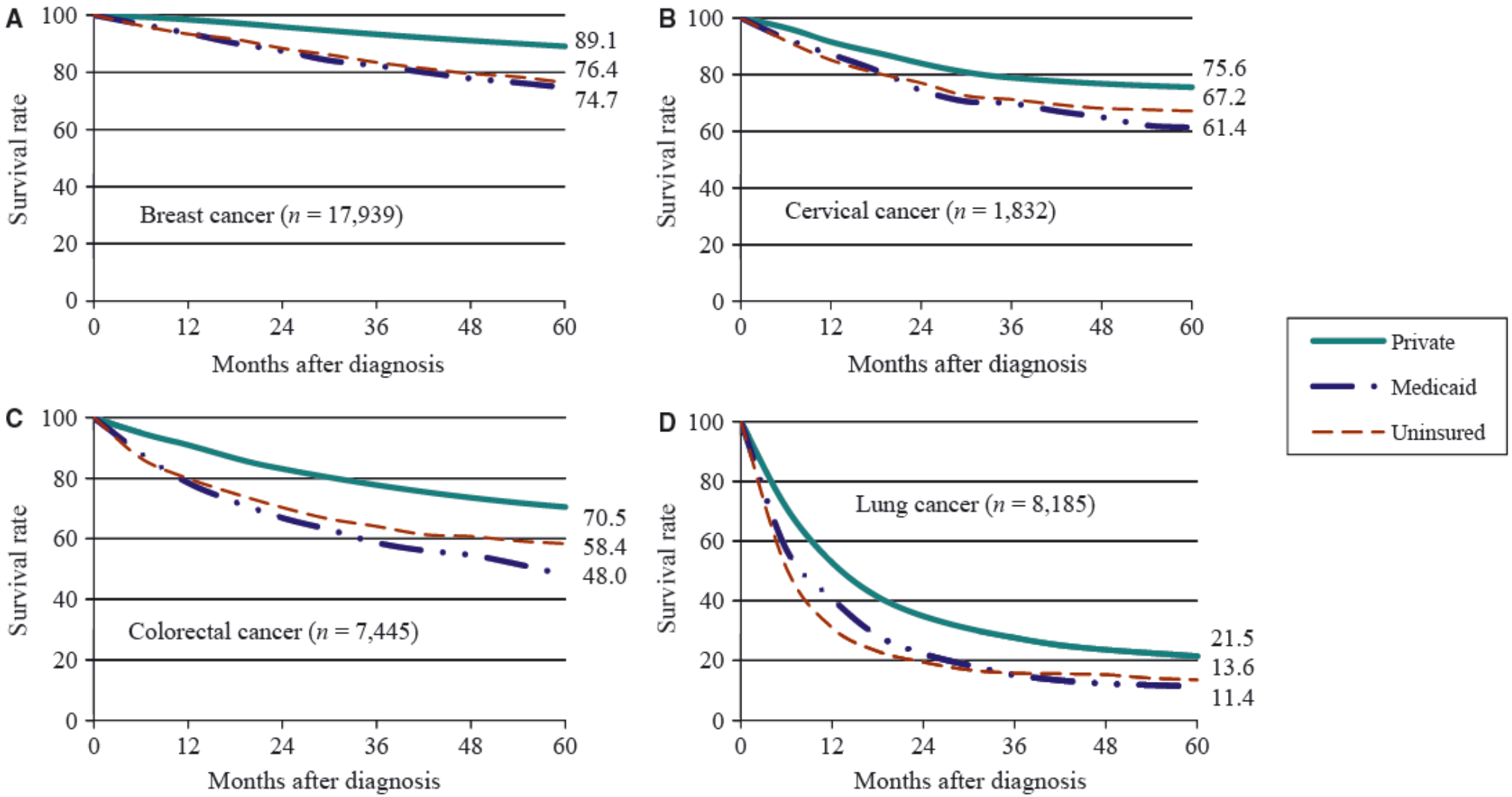
Table 2 Numbers and per cent of lung cancers diagnosed in the NCI-MD case–control study from 1998 to 2015 that fall within guidelines for lung cancer screening

	Criteria					
	NLST*		USPSTF†		CMS‡	
	EA	AA	EA	AA	EA	AA
All (n=1141 EA, n=517 AA)	381 (33.4%)	161 (31.1%)	449 (39.4%)	176 (34.0%)	421 (36.9%)	171 (33.1%)
p Value	0.355		***0.036***		0.134	
Men (n=600 EA, n=270 AA)	231 (38.5%)	98 (36.3%)	269 (44.8%)	110 (40.7%)	255 (42.5%)	105 (38.9%)
p Value	0.392		0.119		0.168	
Women (n=541 EA, n=247 AA)	150 (27.7%)	63 (25.5%)	180 (33.3%)	66 (26.7%)	167 (30.9%)	66 (26.7%)
p Value	0.350		***0.007***		0.083	

Bold signifies statistical significance.
Data based on smoking status, pack-years of smoking, time since quitting and age.
*NLST criteria: aged 55–74, current or former smoker, at least 30 pack-years of smoking, if former smoker, having quit within the last 15 years.
†USPSTF criteria: aged 55–80, current or former smoker, at least 30 pack-years of smoking, if former smoker, having quit within the last 15 years.
‡CMS criteria: aged 55–77, current or former smoker, at least 30 pack-years of smoking, if former smoker, having quit within the last 15 years.
AA, African American; CMS, Centers for Medicare & Medicaid Services; EA, European Americans; NLST, National Lung Screening Trial; USPSTF, US Preventive Services Task Force.

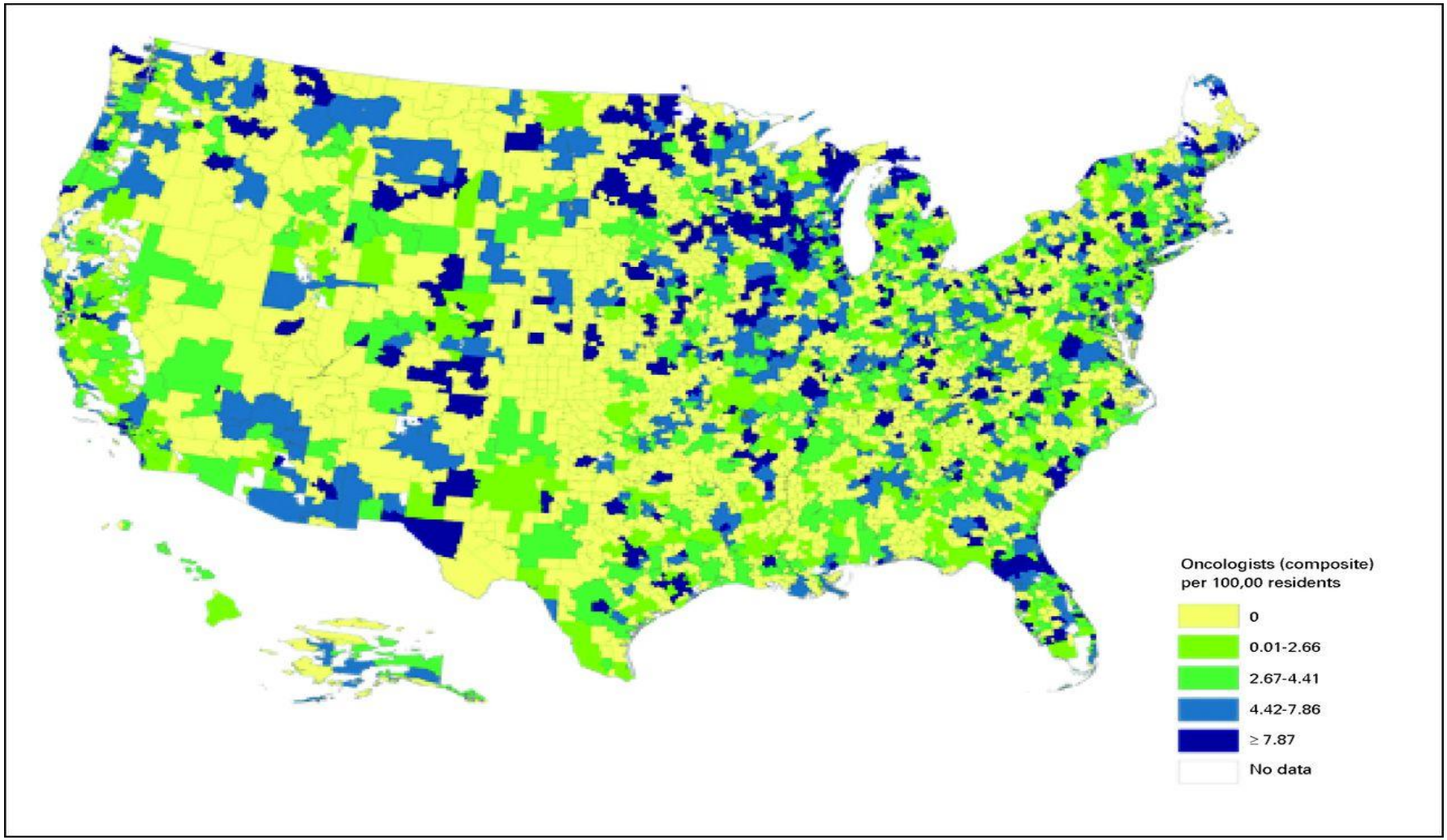
Ryan, BM BMJ Open Resp Res 2016;3: e000166

Some of the reasons for disparities in cancer mortality: Access to care?



Cancer Medicine 2013; 2(3): 403–411

Oncologists per 100,000 residents by hospital service area

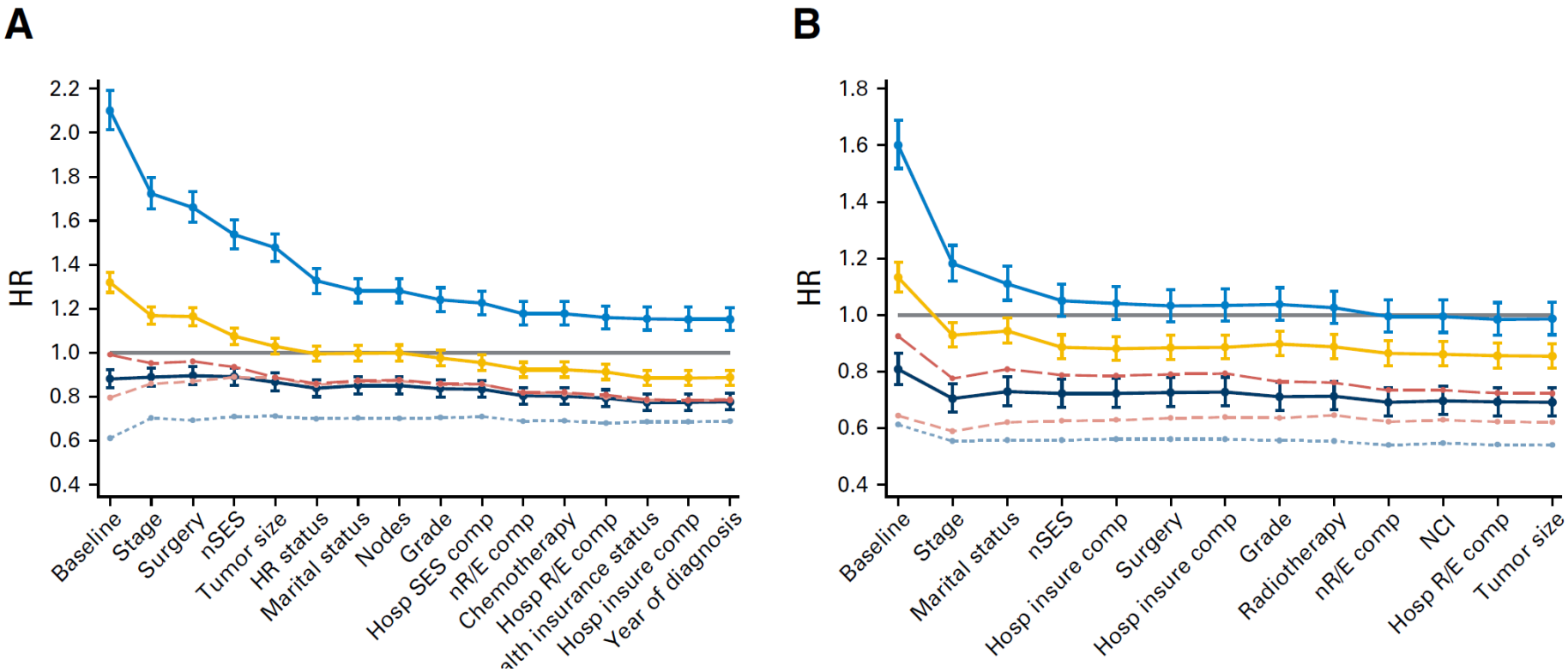


JOURNAL OF CLINICAL ONCOLOGY ASCO

Chun Chieh Lin et al. JCO 2015.61.1558

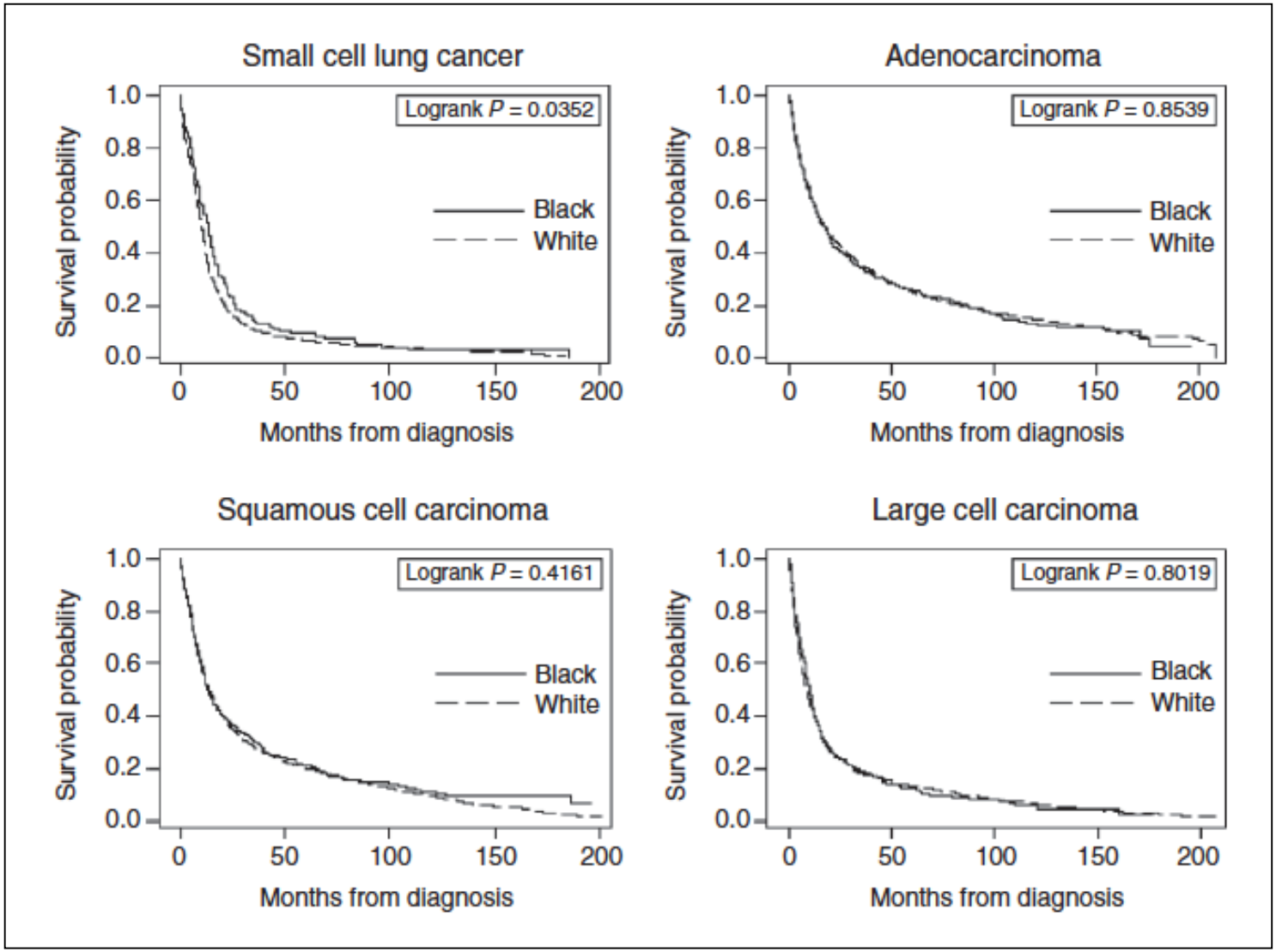
Factors affecting disparities in cancer mortality

"Stage at diagnosis had the largest effect on racial/ethnic survival disparities, but earlier detection would not entirely eliminate them. The influences of neighborhood socioeconomic status and marital status suggest that social determinants, support mechanisms, and access to health care are important contributing factors."



JCO 2018 36(1):25-33

Some of the reasons for disparities in cancer mortality: Access to care?



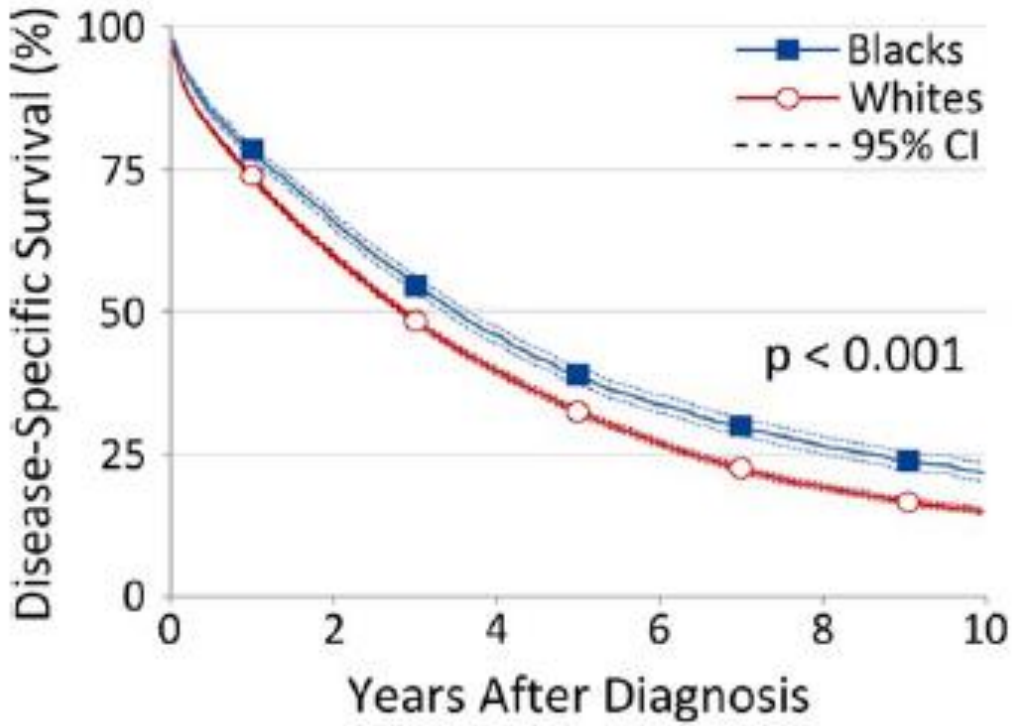
Cancer Epidemiol Biomarkers Prev; 21(10) 2012

Some of the reasons for disparities in cancer mortality: Access to care?

Multiple myeloma

Increased incidence among African Americans but adverse disparities in outcome not observed

African Americans may have a more indolent form of MM



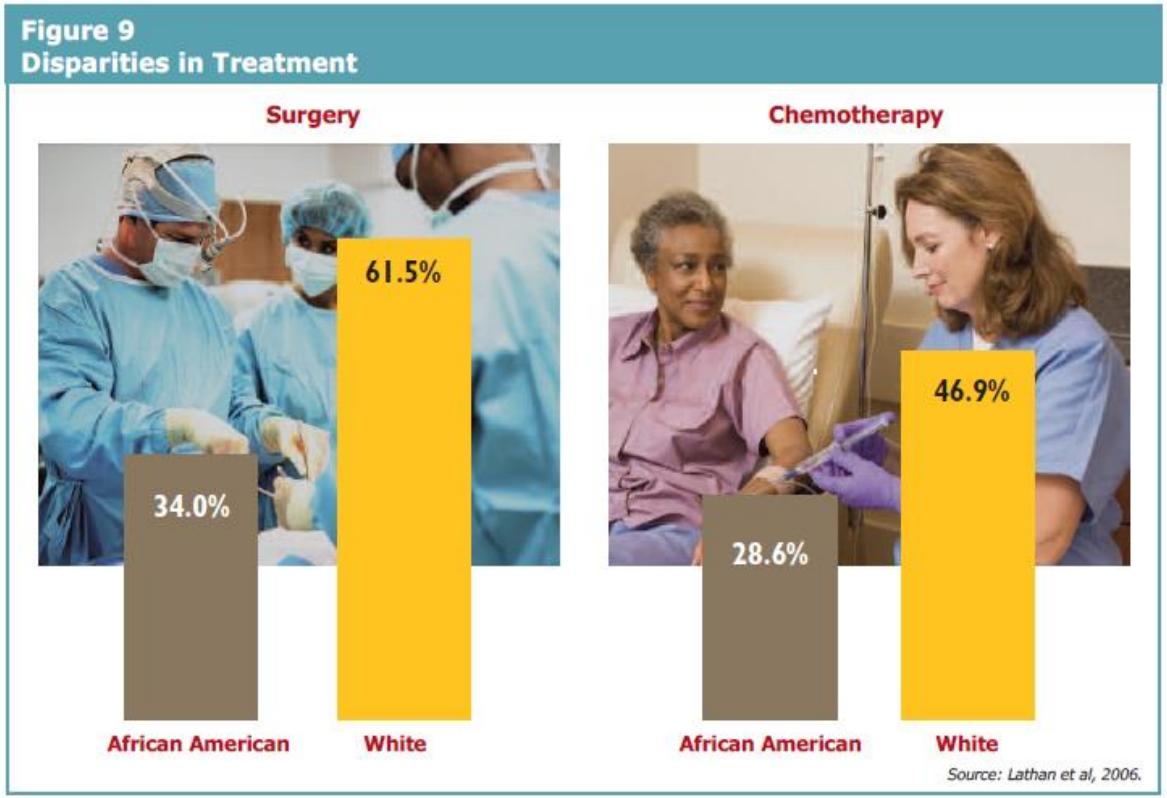
AA patients with myeloma have better survival than EA patients

Waxman et al. *Blood 2010*

Some of the reasons for disparities in cancer mortality: Access and uptake of care?

- Even among those with medicare, AA are less likely to receive treatment for lung cancer (Cancer 2008 112 900-908)

- African American renal cancer patients are less likely to receive surgical treatment (nephrectomy) and die more often from competing causes than European American patients (*J Clin Oncol 2007, 25: 3589 – 3595*)



ALA – Too Many Cases Too Many Deaths 2010

Some of the reasons for disparities in cancer mortality: Access and uptake of care?

TABLE 4. Multivariate regression analyses assessing race and the odds of treatment among all of the study subjects and by tumor stage, age, and sex

Parameter	*OR*[a]	*95% CI*[a]
Surgery, all subjects	0.75	0.37–1.53
Chemotherapy, all subjects	0.79	0.59–1.04
Tumor stage		
I	2.52	0.64–9.98
II	0.98	0.61–1.60
III	0.55	0.30–1.00
IV	0.80	0.40–1.58
Age at diagnosis, y		
<50	1.10	0.47–2.59
50–64	0.74	0.48–1.15
≥65	0.93	0.60–1.44
Sex		
Men	0.80	0.56–1.14
Women	0.74	0.45–1.22

N = 2560.

[a]ORs and 95% CIs of race (non-Hispanic black versus non-Hispanic white) and treatment after adjusting for race, year of diagnosis, age at diagnosis (continuous), sex, marital status at diagnosis, active duty status at diagnosis, service branch of active duty member/sponsor, colon cancer site, tumor stage, tumor grade, surgery, chemotherapy, recurrence, and comorbidities. Respective treatments and stratified variables were not included in stratified analysis.

In a setting of equal access to care, African Americans with colon cancer are as less likely to receive surgery and chemotherapy as European Americans

Diseases of the Colon & Rectum Volume 57: 9 (2014)

Perception and Behavior

African Americans were more likely to hold beliefs about lung cancer that could interfere with prevention and treatment (Health Information National Trends Survey)

- 3 times less likely to get a lung cancer check up
- 2 times more likely to expect symptoms before diagnosis
- 2 times less likely to agree that getting checked for lung cancer could help find the disease early
- Perceptions expressed unlikely to affect lung cancer incidence – more related to outcome

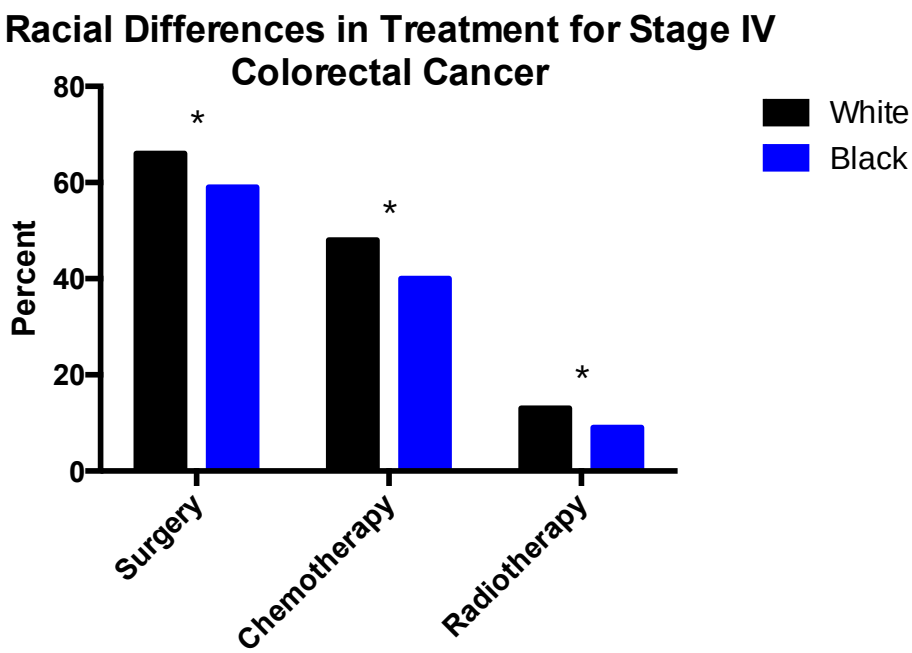
Cancer 2010;116:1981–6

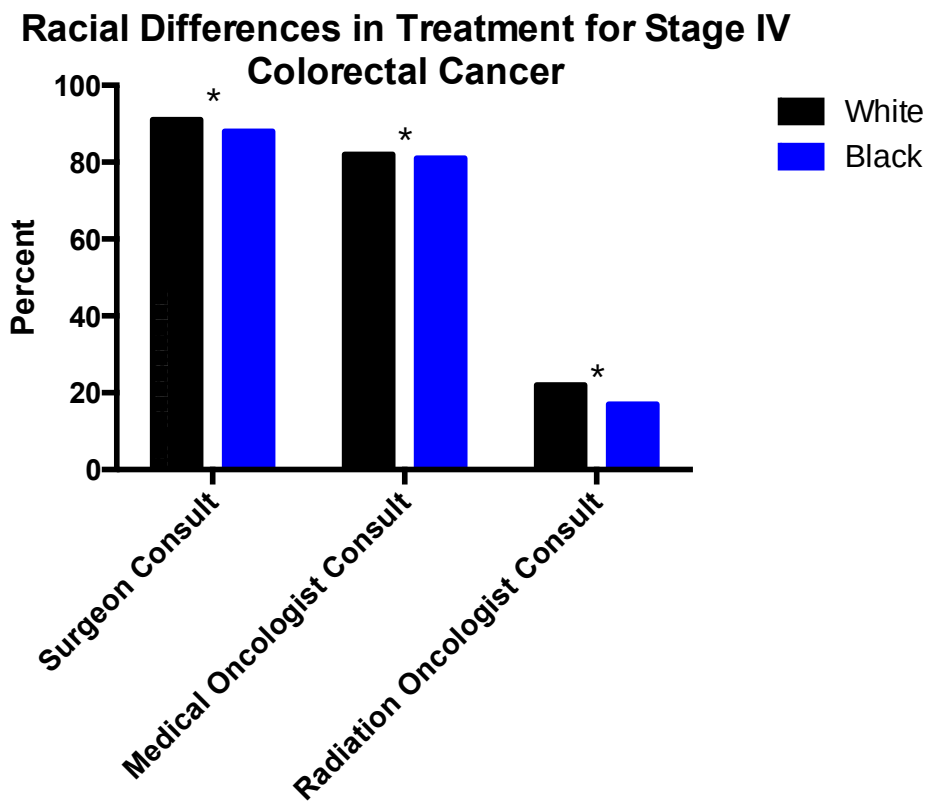
Potential factors that influence uptake of care

- Personal beliefs
- Fear
- Culture
- Patient-doctor relationship
- Patient bias
- Provider bias
- Patient-doctor communication
- Co-morbid conditions

Similar access to care does not equate to equal access to quality care

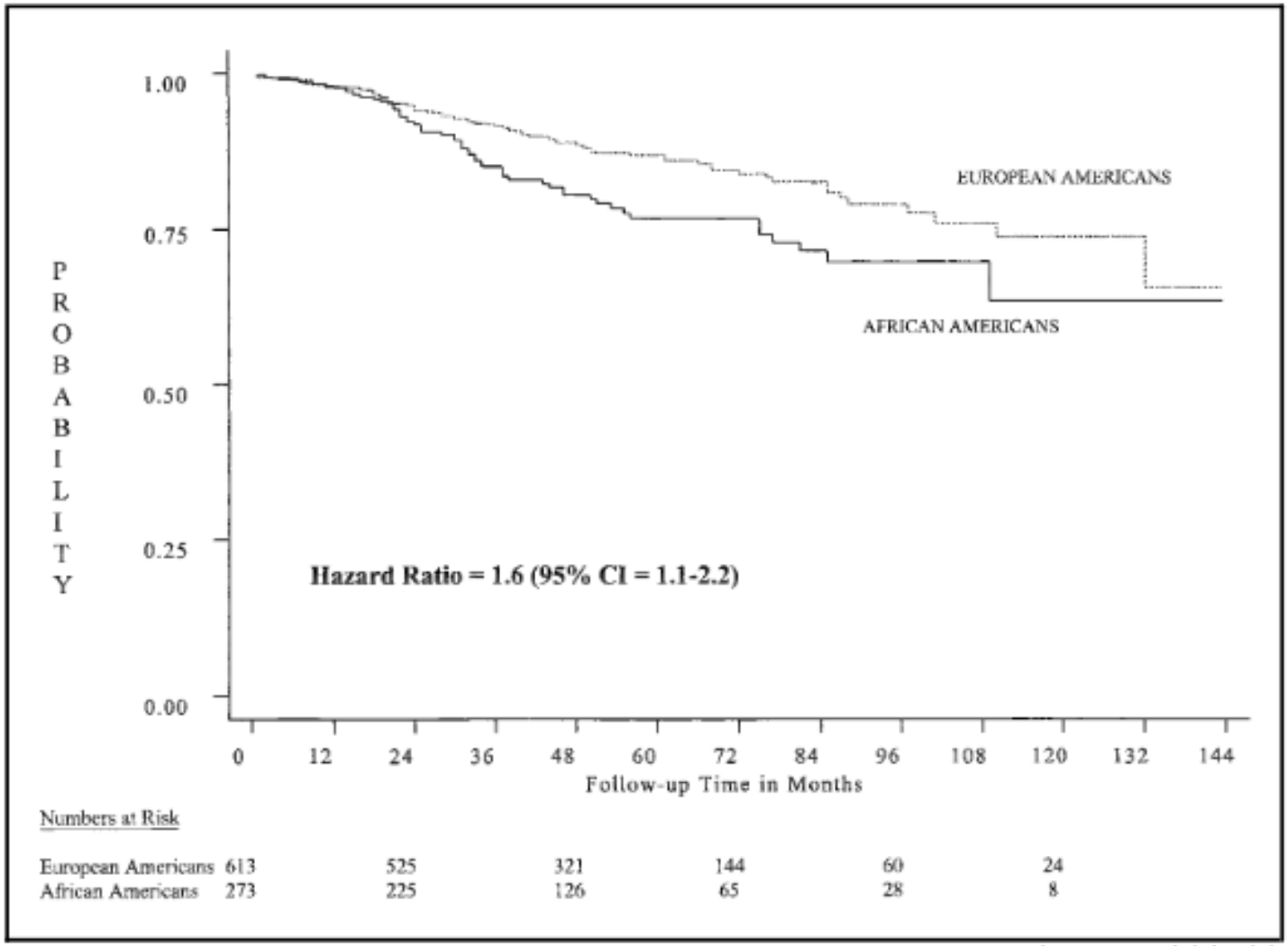
In a "regular" medical setting, studies show that racial disparity in specialist consultation as well as subsequent treatment with multimodality therapy for metastatic colorectal cancer exists.





Adapted from JNCI 2013 105(23):1814-20

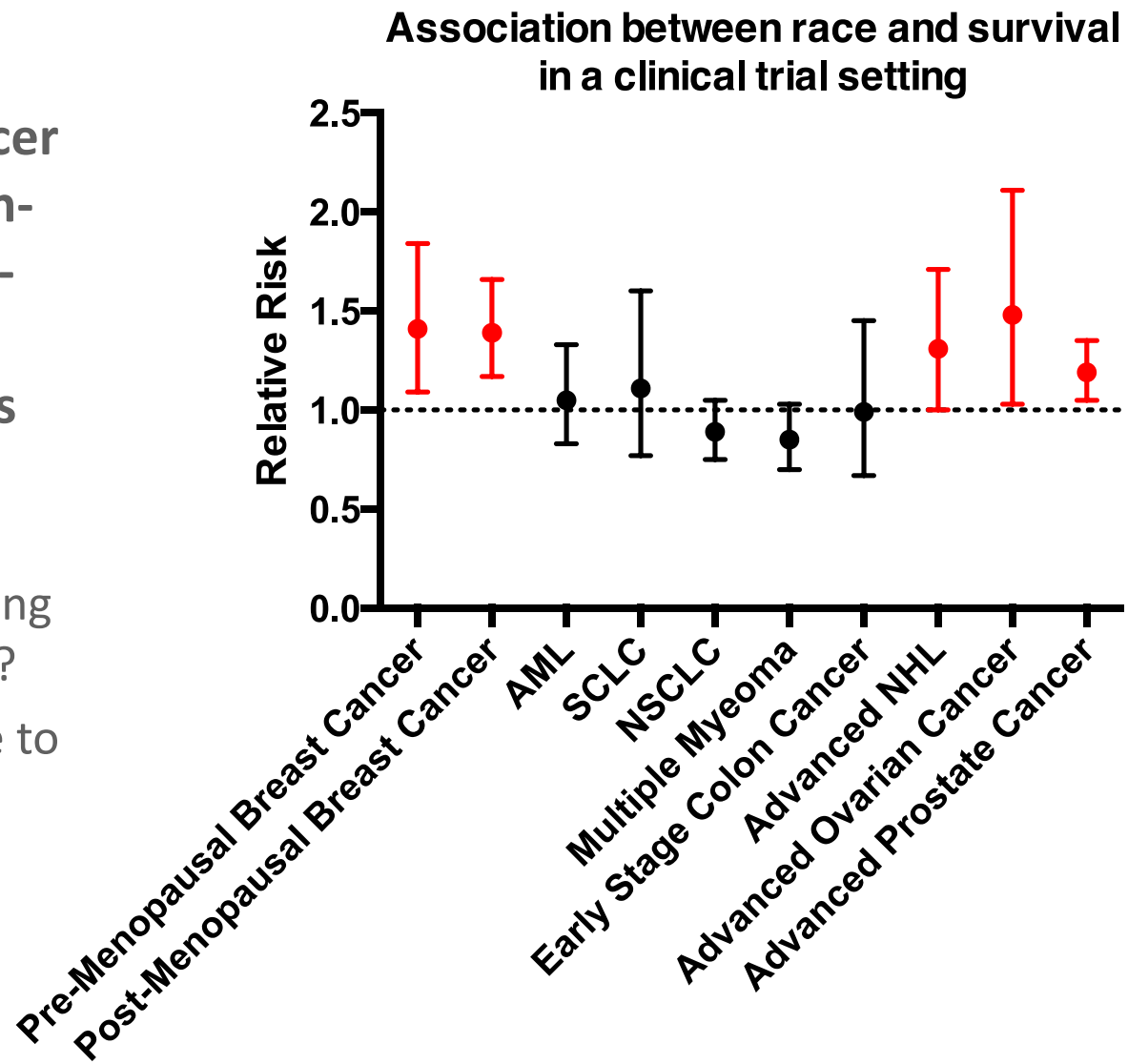
For some cancers, disparities persist even in equal access to care settings



Cancer 1998, 82: 1310 - 1318;
Cancer 2003, 98: 894 – 899
JNCI 91:17, 1999
JNCI Monographs, No. 35, 2005

Is biology a contributing factor?

- **Racial disparities in prostate and breast cancer survival between African-American and European-American persist in randomized clinical trials (*JNCI 2009, 101: 984 – 92*)**
  - Intrinsic differences in tumor biology influencing disease aggressiveness?
  - Differences in response to therapy?

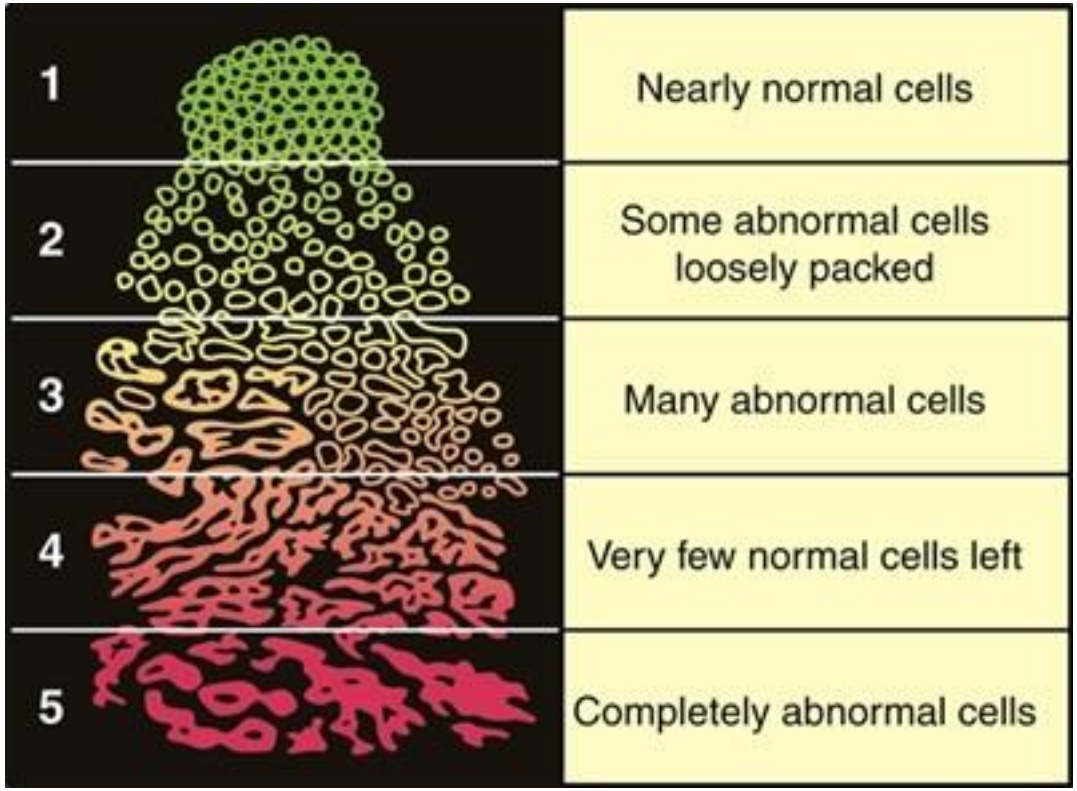


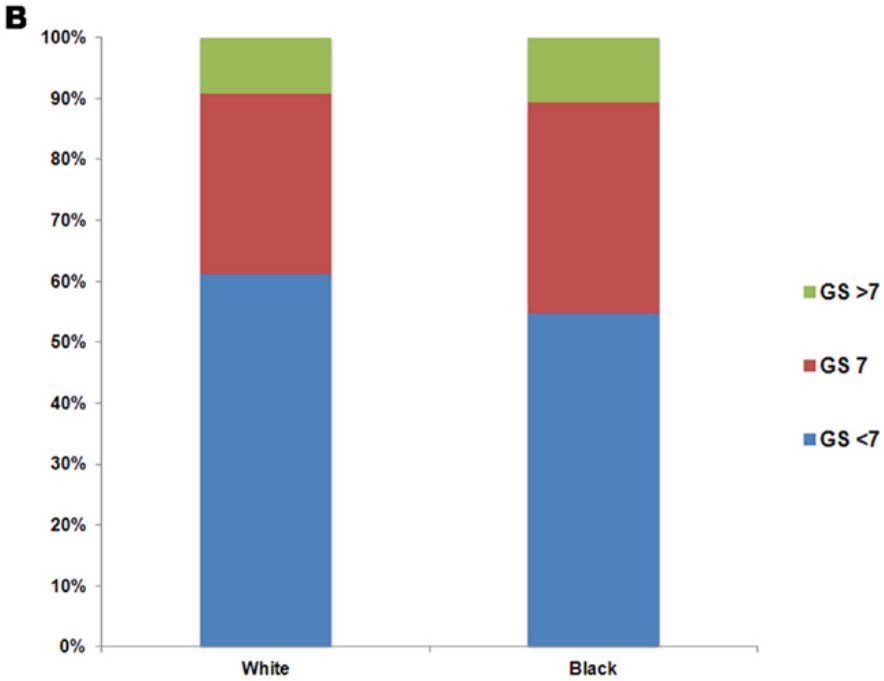
Biological factors that contribute to cancer disparities

- What role, if any, does biology play in cancer health disparities?

African Americans are more likely to be diagnosed with Aggressive Prostate Cancer

Gleeson Score





Front Oncol 2013 23;3:312

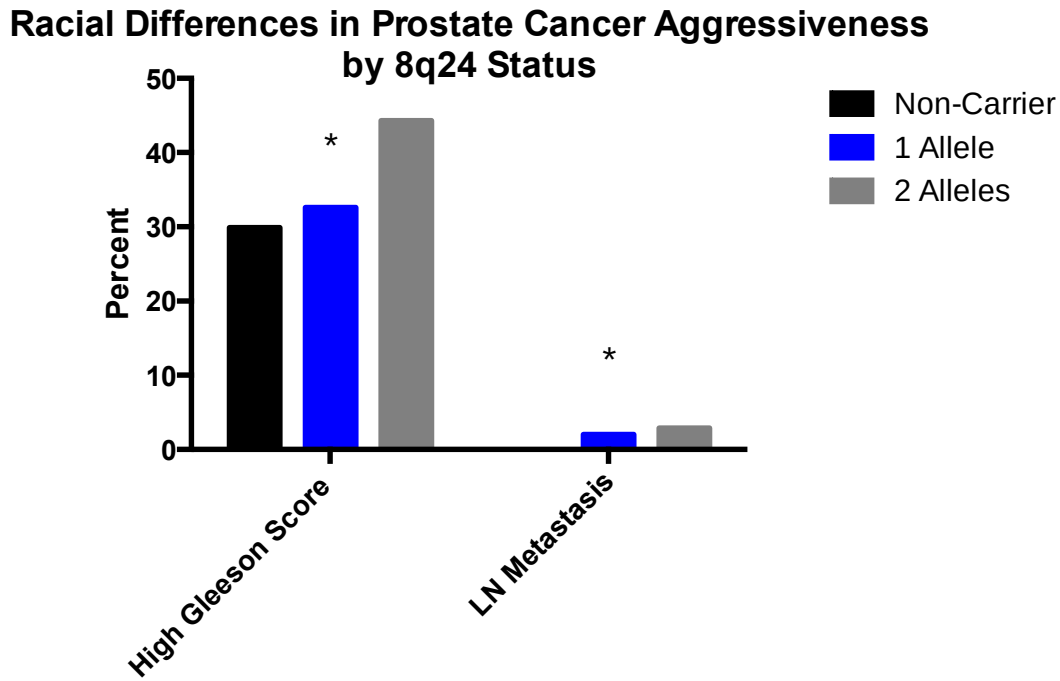
Genetic susceptibility

- **Racial differences in prevalence of 8q24 prostate cancer susceptibility variants (~ 50%)**
  - **Admixture mapping identified 8q24 as a locus of increased risk for African-American men when compared to European-American men** *(PNAS 2006, 103: 14068-73)*
  - **Risk alleles are more common among African-American men, leading to the highest population attributable risk conferred by 8q24 in this population** *(Nat Genet 2007, 39: 638 – 44 & 954 – 6)*
  - **Excess of African ancestry at 8q24** *(Hum Genet 2009 Nov;126(5):637-42)*
  - **Risk variants rs114798100 and rs111906923 are only found in men of African descent** (JNCI 2016 108 (7))

- **Racial differences in prevalence of 17q21 prostate cancer susceptibility variants (~ 10%)**
  - **Risk alleles of a new locus, rs7210100 are more common in populations of African descent** *(Nat Gen 2011, 43: 570-573)*

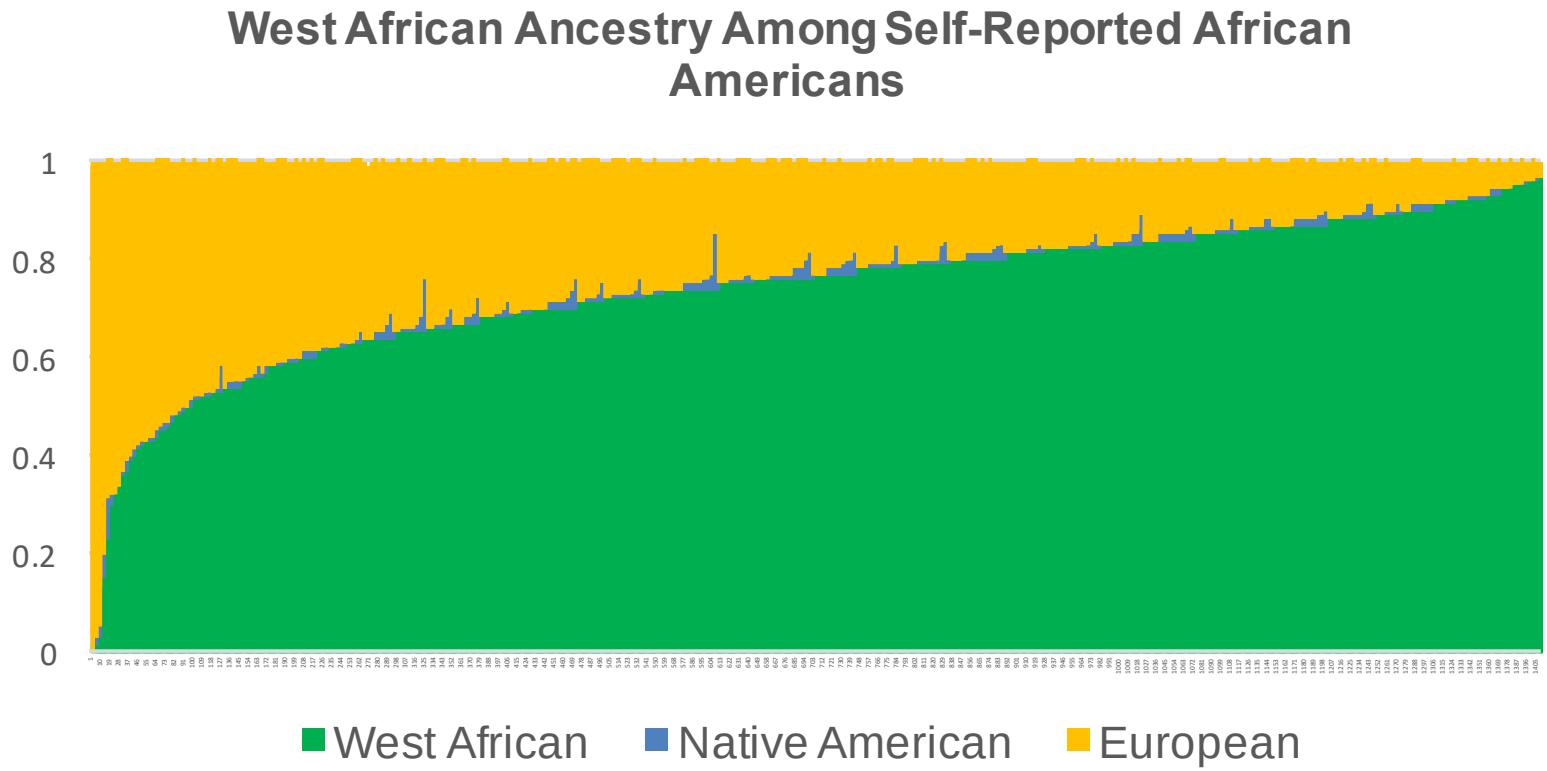
Germline Genetics

- **8q24 is associated with higher grade, more aggressive prostate cancers**
  - Risk alleles are more common among AA men, *(Powell et al., J Urology 2010, 183: 1792 – 7)*
- **Faster disease progression in AA men (vs. EA men)** *(Powell et al., J Urology 2010, 183: 1792 – 7)*



Germline Genetics: Admixture

African and European ancestry in self-identified African Americans can vary widely



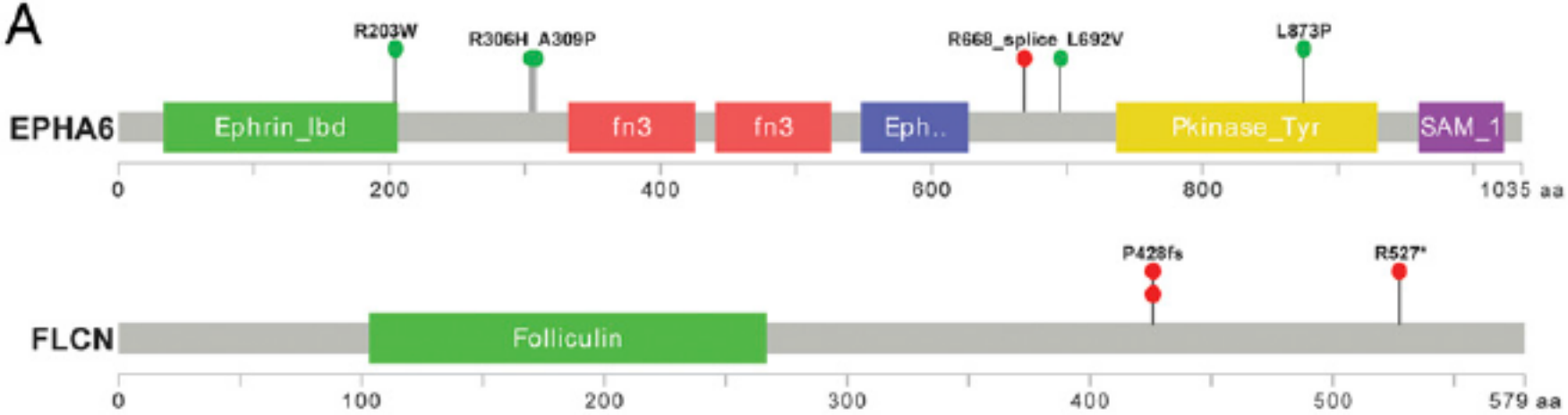
Ryan, unpublished

Germline Genetics

- Increased proportion of Native American ancestry is associated with increased risk of childhood acute lympoblastic leukemic
- Screening implications
- Also related to treatment—Children with more than 10% Native American ancestry need an additional round of chemotherapy to respond to the treatment (Yang et al., Nature Genetics 2011 43(3); 237-241)
- Ancestry informative markers provide a greater granularity to studying race in genetic and genomics studies

Somatic Genetics

A



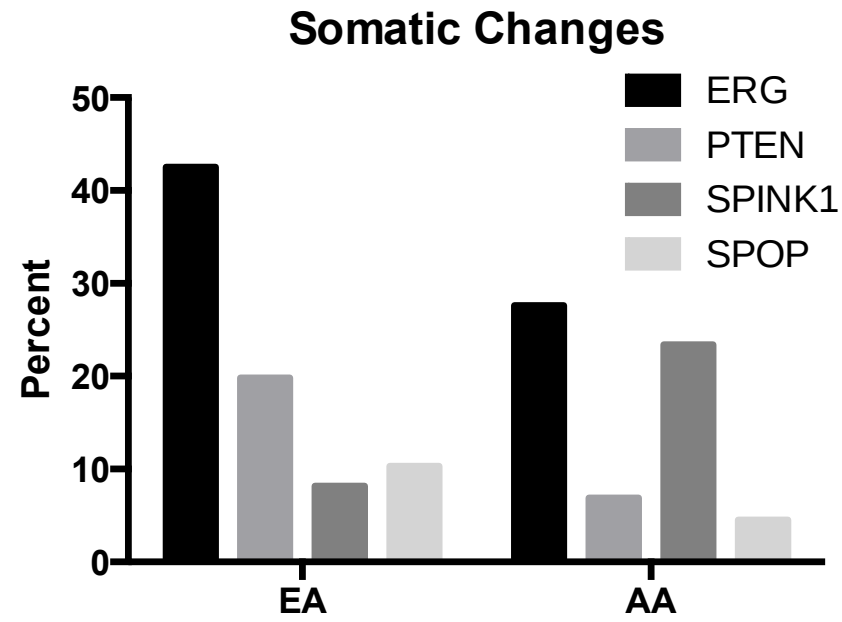
B

Hugo_ Symbol	Tumor ID	Race	Colon cancer Stage	Screen	Variant_ Class	Protein_ Change	Tumor_Mutant allele frequency	PPH2_Class
EPHA6	11843	AA	Stage IV	Discovery	Missense	R203W	0.20	Deleterious
EPHA6	15873	AA	Stage IV	Discovery	Missense	R306H	0.35	Deleterious
EPHA6	16765	AA	Stage IIIB	Validation	Missense	A309P	0.25	Deleterious
EPHA6	13129	AA	Stage IIB	Validation	Splice	R668_splice	0.47	
EPHA6	16700	AA	Stage IIB	Validation	Missense	L692V	0.21	
EPHA6	16714	AA	Stage IIB	Validation	Missense	L873P	0.10	Deleterious
FLCN	16670	AA	Stage IIA	Validation	FS ins	P428fs	0.66	
FLCN	16518	AA	Stage IIIB	Validation	FS ins	P428fs	0.46	
FLCN	11604	AA	Stage IV	Discovery	Nonsense	R527*	0.80	

Guda PNAS 2015 112:4 1149-1154

Somatic Genetics

- **Global heterogeneity in acquired mutational events in prostate tumors: Evidence of a different disease etiology?**
  (*Cancer Res 2010, 70: 5207 – 12; Prostate 2011, 71: 489 – 97; Urology 2012, 80: 749 – 53; Clinical Cancer Res 2014, 20: 4925 – 34*)



- High frequency of oncogenic TMPRSS2:ERG gene fusion events in European/European-American patients (about 50%), intermediate frequency in African-American patients (24%-31%), but rather uncommon in Asian patients (2%-16% among Chinese, Japanese patients)

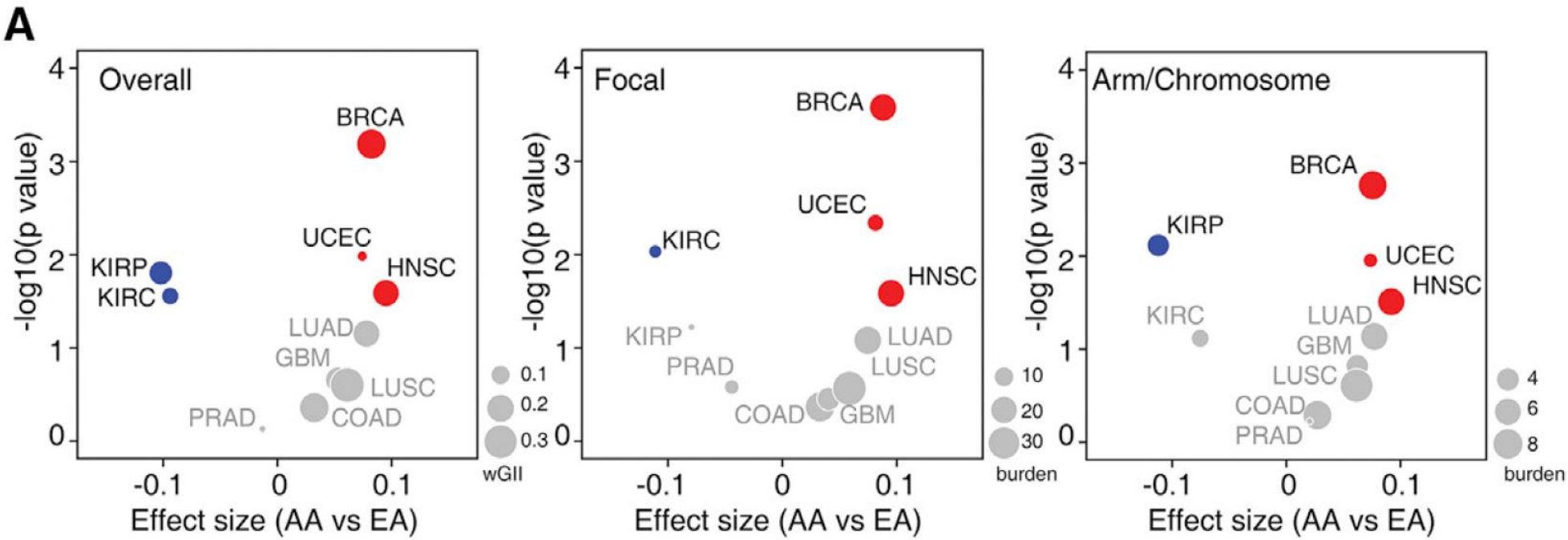
- Common PTEN loss in European/European-American patients (30%-50%) but uncommon in Asian and African-American patients (5%-15%)

Int J Mol Sci. 2013 Jul 25;14(8):15510-31

Somatic Genetics

- **Breast, head and neck, and endometrial cancers of African Americans have higher levels of chromosomal instability than those of European Americans**

- **The frequency of genetic alternations in the PI3K pathway in AA patients is lower**



Cancer Cell 2018 34(4):549-560

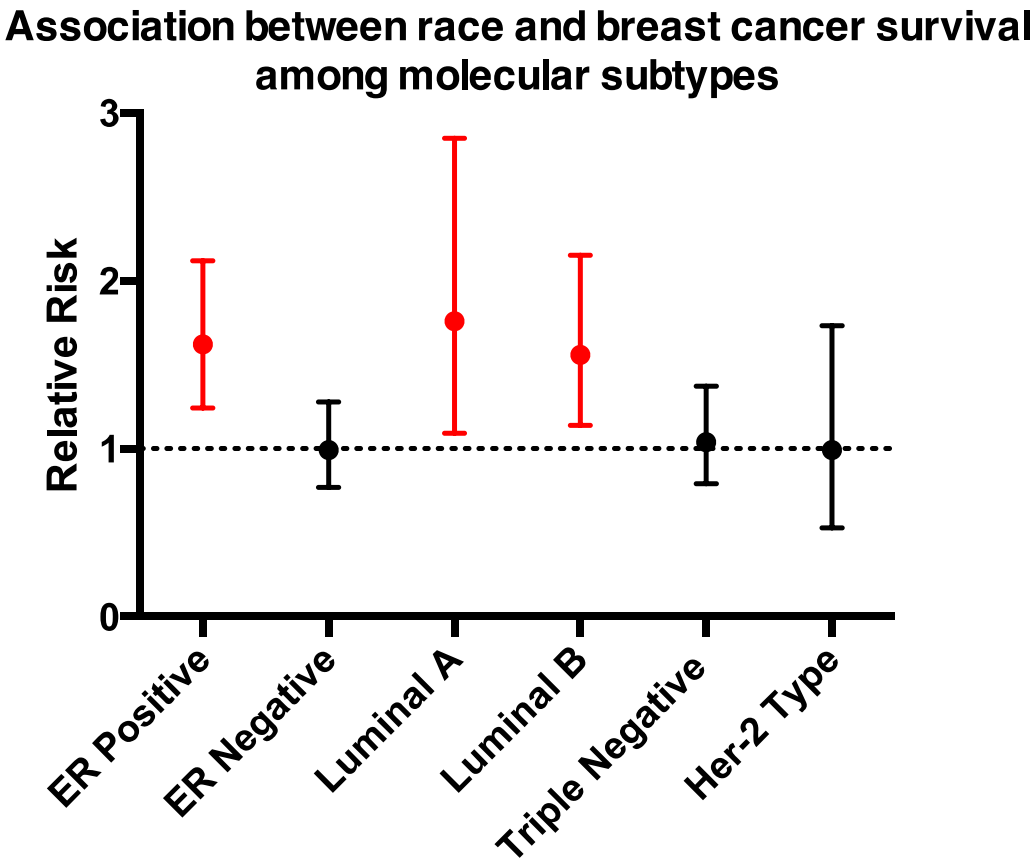
Molecular subtype

- Population differences in molecular subtypes and disease grade
- Race/ethnic disparity in prevalence of basal-like/triple-negative breast tumors *(JAMA 2006, 295: 2492 – 2502;* J Clin Oncol 2009, 27: 4514 – 21; CEBP 1994, 3: 127-135)

Table 3 Relative odds of specific tumor characteristics among black breast cancer patients compared with whites

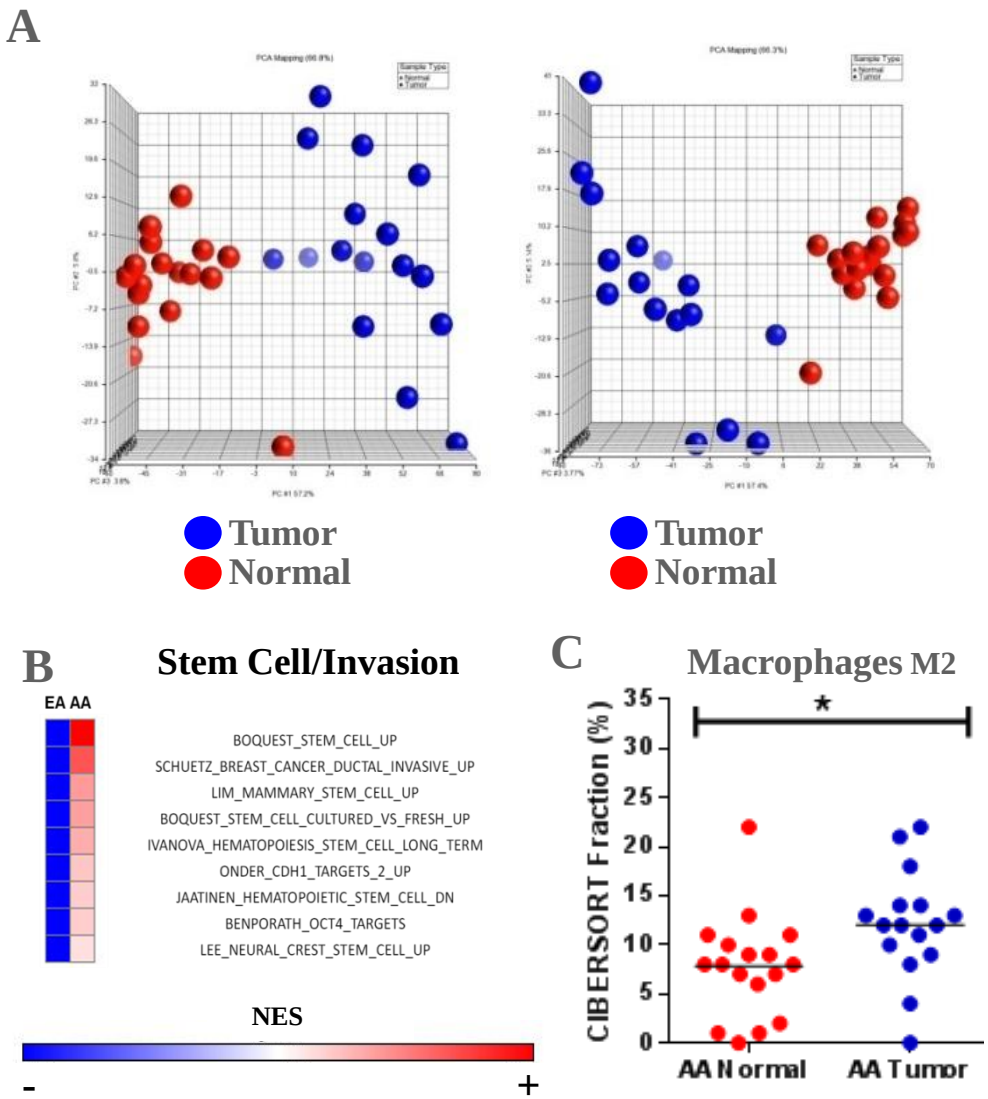
Variables	Black		White		Crude		Adjusted[a]	
	n	%	*n*	%	OR	95% CI	OR	95% CI
Nuclear atypia								
1	153	30.7	218	47.8	1.00		1.00	
2	263	52.7	187	41.0	2.00	(1.52–2.65)	1.90	(1.42–2.55)
3	83	16.6	51	11.2	2.32	(1.55–3.47)	1.97	(1.27–3.04)
Mitotic activity								
1	249	50.6	291	64.7	1.00		1.00	
2	154	31.3	115	25.6	1.57	(1.17–2.10)	1.47	(1.08–2.00)
3	89	18.1	44	9.8	2.36	(1.59–3.52)	2.05	(1.34–3.14)
Tubular formation[b]								
None or few	377	77.6	266	63.9	1.00		1.00	
Moderate and well	109	22.4	150	36.1	0.51	(0.38–0.69)	0.57	(0.42–0.77)
Grade								
1	109	21.8	129	28.4	1.00		1.00	
2	295	59.0	262	57.7	1.33	(0.98–1.81)	1.19	(0.87–1.64)
3	96	19.2	63	13.9	1.80	(1.20–2.71)	1.58	(1.02–2.45)
Estrogen receptor								
Negative and border	185	44.5	143	36.7	1.00		1.00	
Positive	231	55.5	247	63.3	0.72	(0.55–0.96)	0.78	(0.58–1.05)

Molecular subtype



However, breast cancer survival disparity in US is irrespective of some tumor subtypes (JNCI 2009, 101: 993-1000)

Transcriptome



- **Lung tumors from African Americans a greater representation of stem cell pathways**

Mitchell….. Ryan Clin Cancer Res 2017 23(23):7412-7425.

Cell biology

- **Identification of an Interferon signature in prostate cancer tumors from African American men**
- **The signature is linked with a germline mutation**

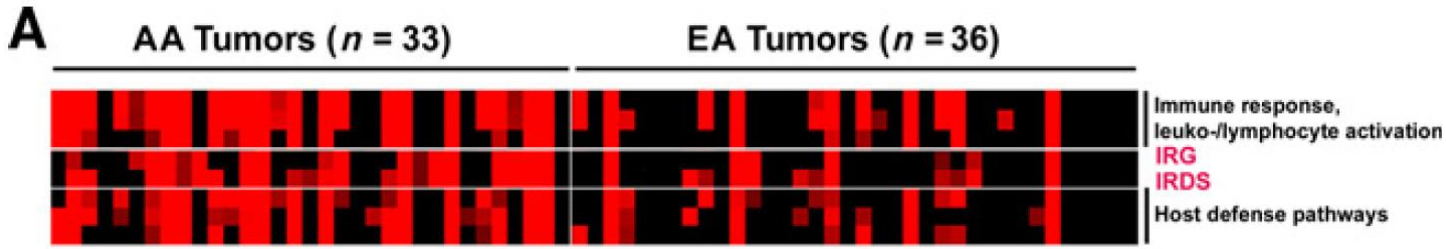


Table 1. *IFNL4* rs368234815-ΔG allele is associated with occurrence of IRDS in prostate tumors

	***IFNL4* genotype, *N* (%)**		**Fisher's exact test**	**OR**
All tumors, $N = 44$	TT/TT or TT/ΔG	ΔG/ΔG	*P*	Adjusted OR (95% CI)[a]
IRDS-negative	23 (92%)	2 (8%)	< 0.001	15.7 (2.7–90.6)
IRDS-positive	8 (42%)	11 (58%)		
Only tumors from AA men, $n = 23$				
IRDS-negative	6 (75%)	2 (25%)	0.04	8.2 (1.1–60.4)
IRDS-positive	4 (27%)	11 (73%)		

[a]Adjusted for age at diagnosis and pathological stage.

Wallace…. Ambs, Cancer Res 2008, 68: 927– 36
Tang…… Ambs Clin Cancer Res. 2018.

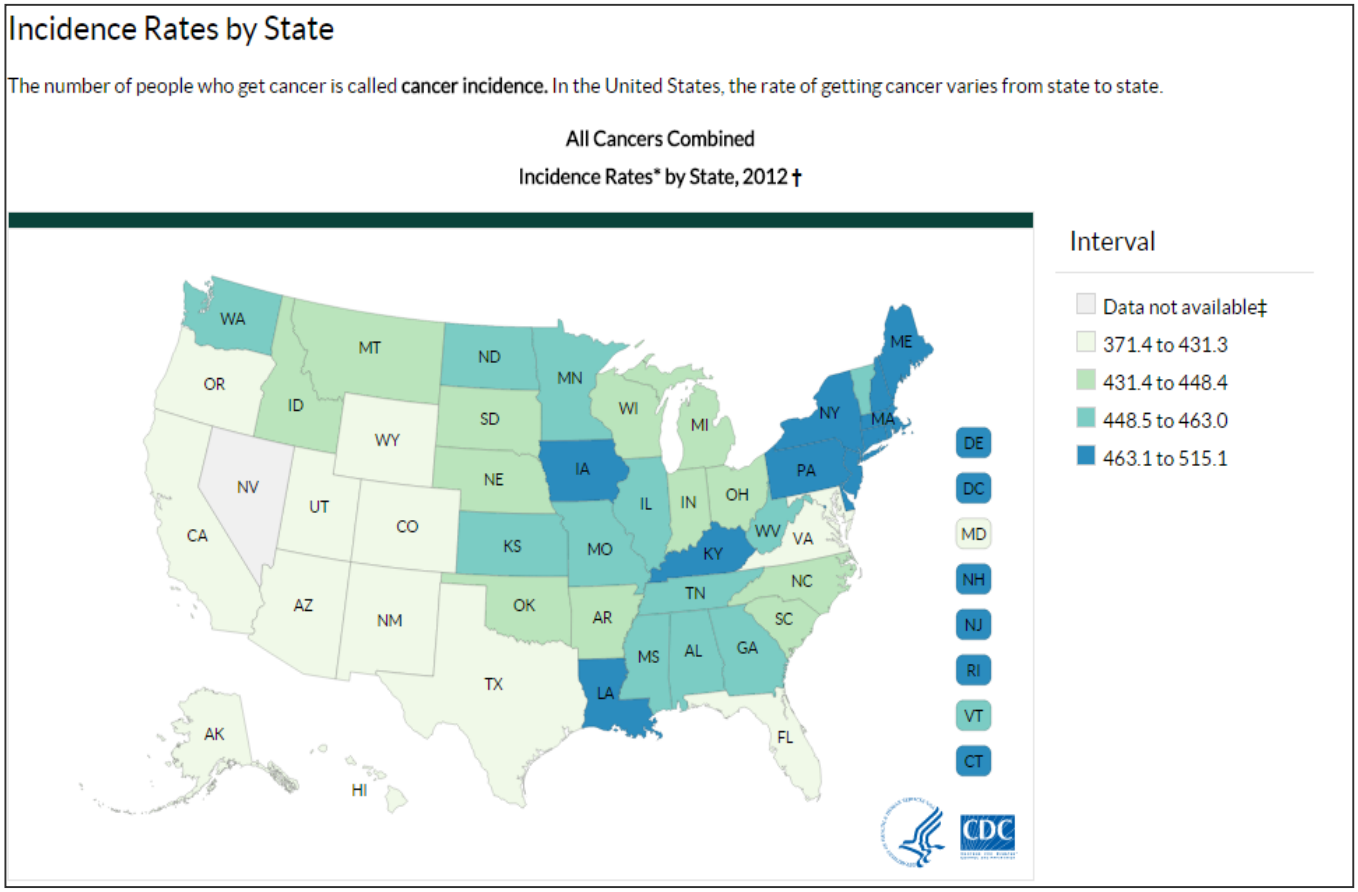
Biological differences can translate to a need for different biomarkers

Inflammation proteins are higher at the time of diagnosis-potential use for early detection
Cancer-associated inflammation profile is different in African and European Americans

	African Americans (N = 255)			European Americans (N = 566)		
	Cases/ Controls	OR (95% CI)*	P	Cases/ Controls	OR (95% CI)*	P
IL-1β	12/57	1.00 (referent)		61/59	1.00 (referent)	
	20/35	2.28 (0.87 – 5.99)		52/77	0.69 (0.40 – 1.19)	
	24/41	2.58 (1.02 – 6.50)		91/80	1.09 (0.66 – 1.81)	
	29/37	3.61 (1.46 – 8.95)	0.007	66/80	0.69 (0.41 – 1.17)	0.47
IL-10	16/55	1.00 (referent)		44/61	1.00 (referent)	
	16/41	1.35 (0.53 – 3.40)		63/75	1.09 (0.63 – 1.91)	
	31/38	4.11 (1.69 – 9.99)		78/80	1.21 (0.70 – 2.07)	
	22/36	2.19 (0.88 – 5.24)	0.02	85/80	1.36 (0.79 – 2.32)	0.23

* Adjusted for age (continuous), sex, smoking pack-years (continuous), smoking status (never, former quit ≤15 years, former quit >15 years, and current),

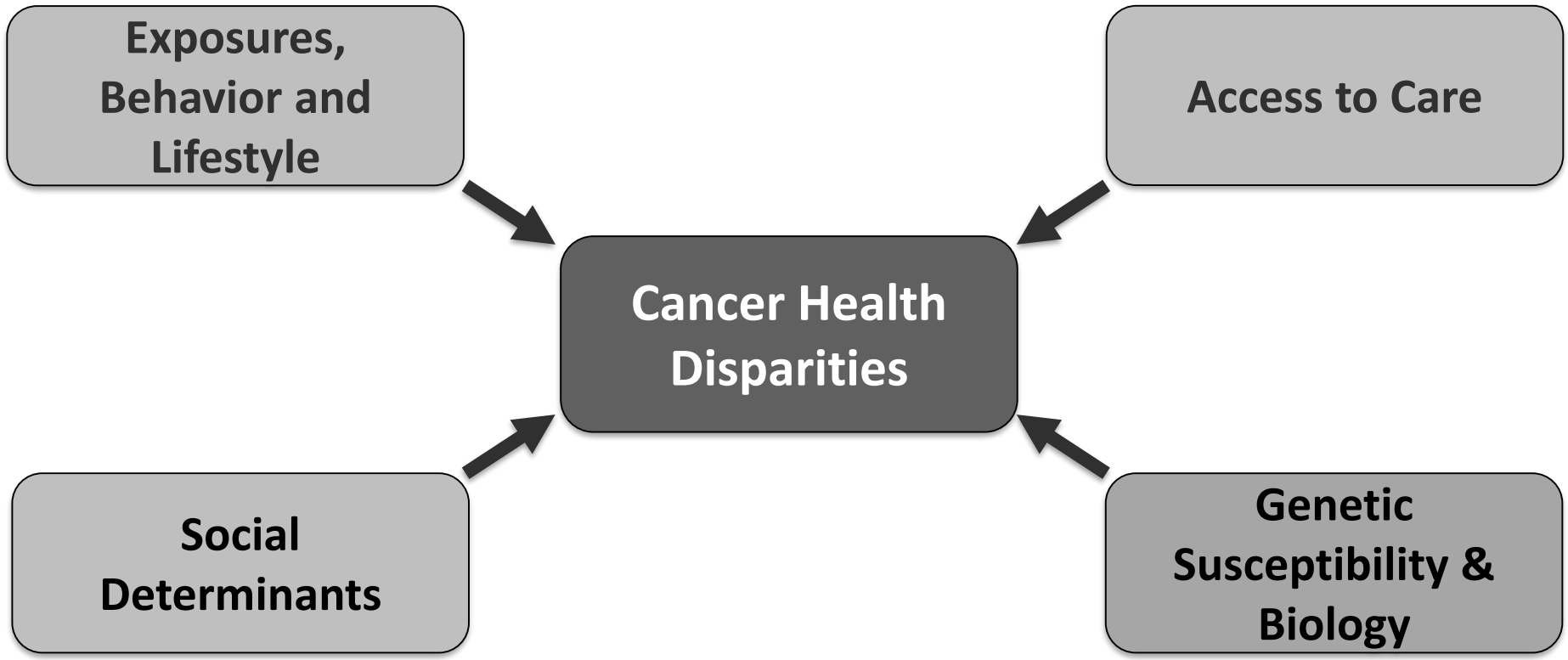
Geographical factors contribute to cancer disparities



Highest
Kentucky
Rhode Island
Delaware
Louisiana
New Jersey

Lowest
New Mexico
Arizoma
Wyoming
Alaska
Virginia

Cancer Health Disparities: Contributing Factors are Multifactorial



Geographical factors contribute to cancer disparities

- A low socioeconomic status (SES) neighborhood confers additional incidence or mortality risk beyond individual SES *(J. Epidemiol. Community Health 2003, 57:444-52)*
  - Unequal burden of pollution
  - Access to preventative services (eg tobacco cessation)
  - Areas with the highest percentage of African Americans have the highest exposure to cancer-associated pollutants *(Environ Health Perspect. 2005 113(6): 693–699)*

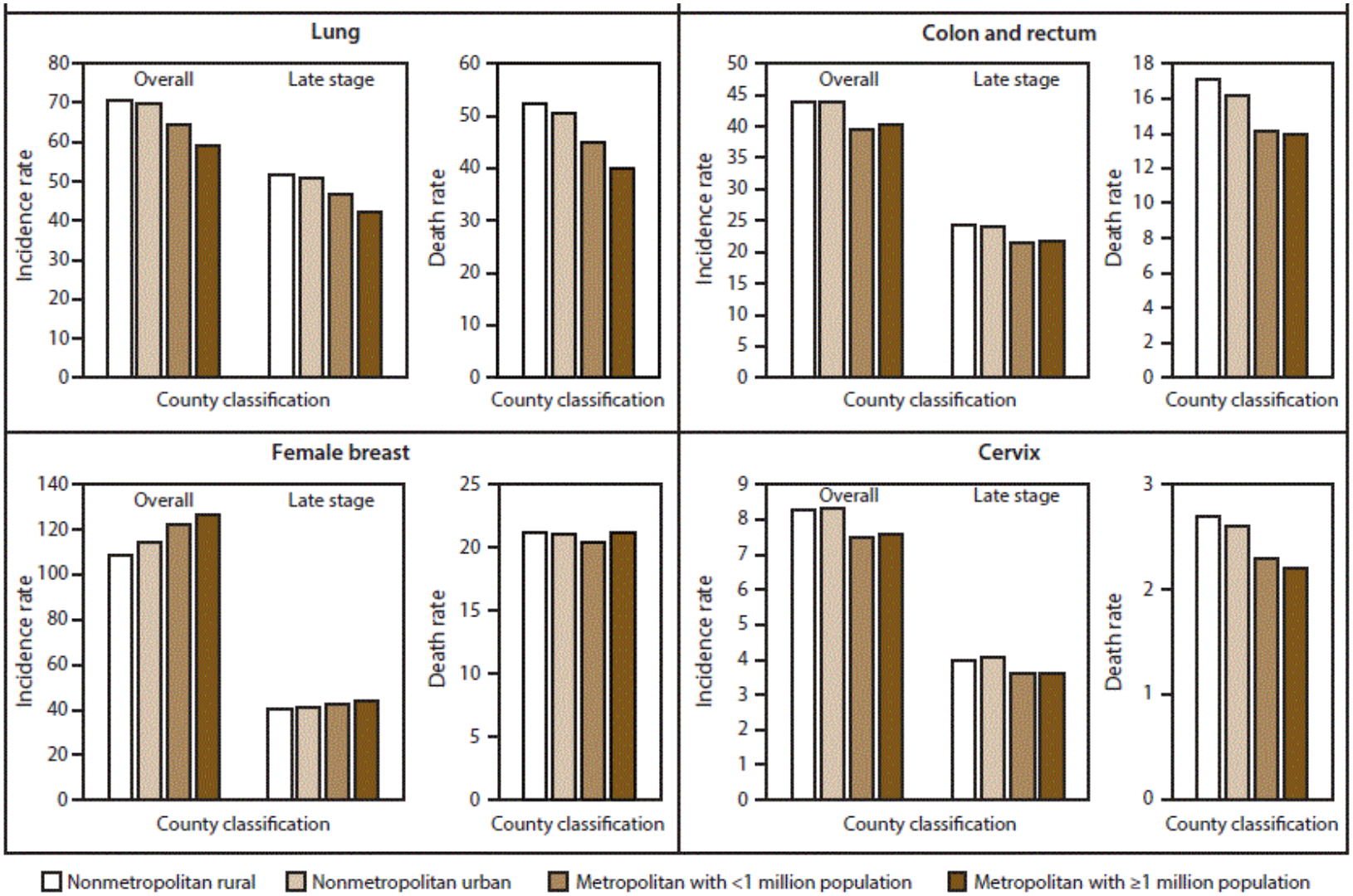
- Rural populations are more likely to have increased cancer incidence, unequal burden of pollution
  - Forego medical care and prescriptions due to cost
  - Report fair/poor heath and health-related unemployment
  - Experience psychosocial distress

Rural-Urban Disparities in Cancer Incidence

- Rural cancer disparities included higher rates of tobacco associated, HPV associated, lung and bronchus, cervical and colorectal cancers across most population groups.
- HPV-associated cancer incidence rates increased in rural areas (APC=0.724, $p<0.05$) while temporal trends remained stable in urban areas.
- Cancer rates associated with modifiable risks - tobacco, HPV, and some preventive screening modalities (e.g. colorectal and cervical cancers) - were higher in rural compared to urban populations.
- Impact: Population-based, clinical, and/or policy strategies and interventions that address these modifiable risk factors could help reduce cancer disparities experienced in rural populations.

Palmer NR et al, Cancer Epidemiol Biomarkers Prev, 2013.
Weaver KE et al., Cancer Causes Control, 2013.
Weaver KE et al., Cancer, 2013.
Zahnd et al. CEBP 2017

Rural-Urban Disparities in Cancer Mortality



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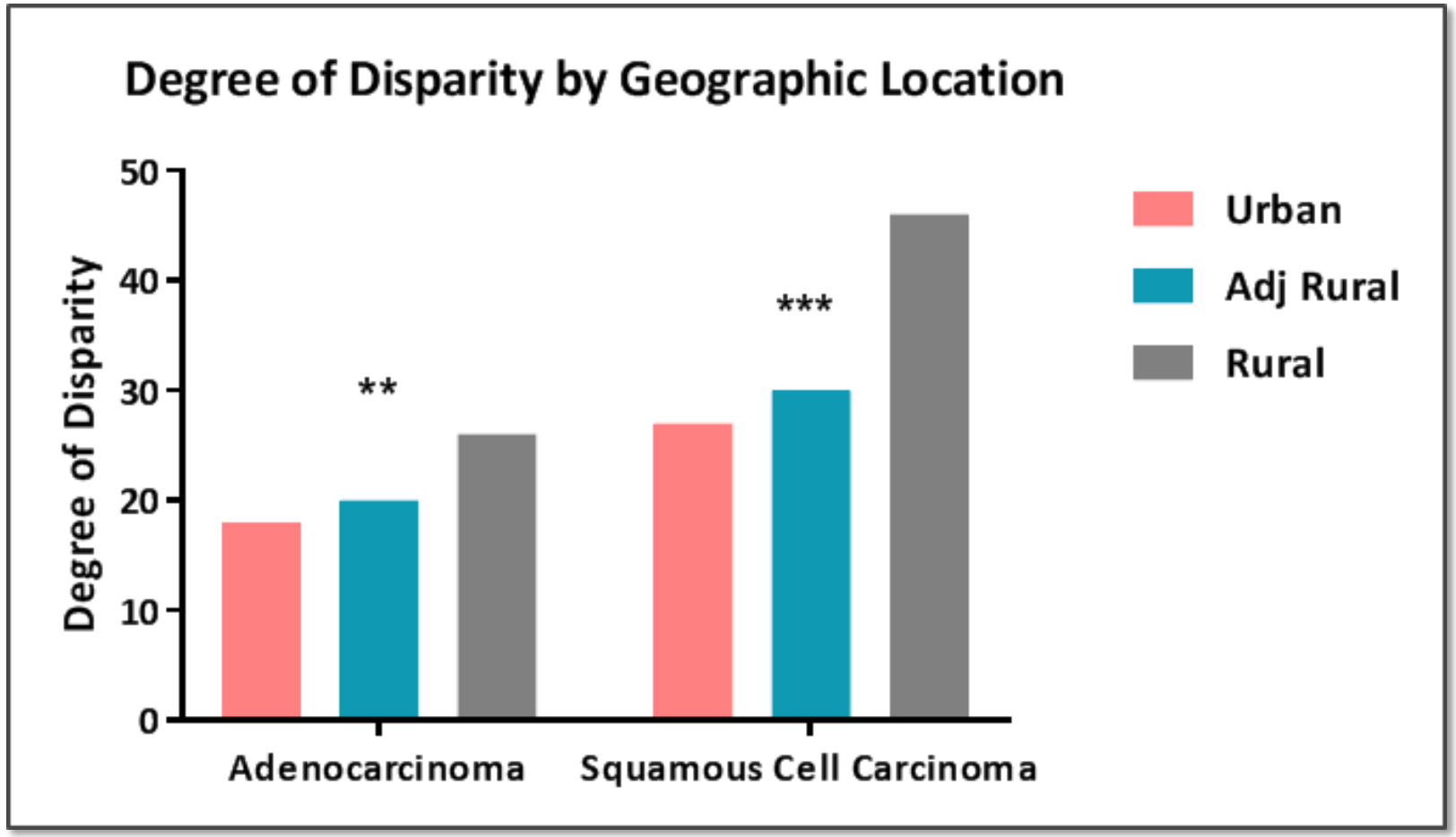
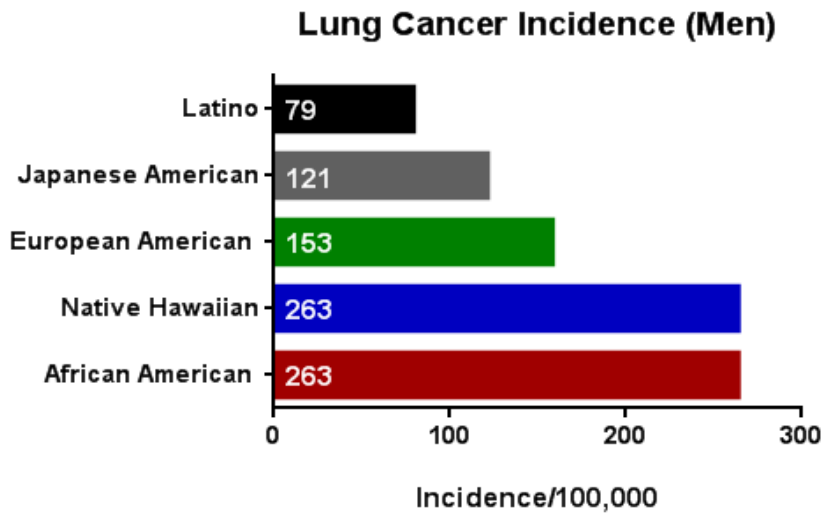
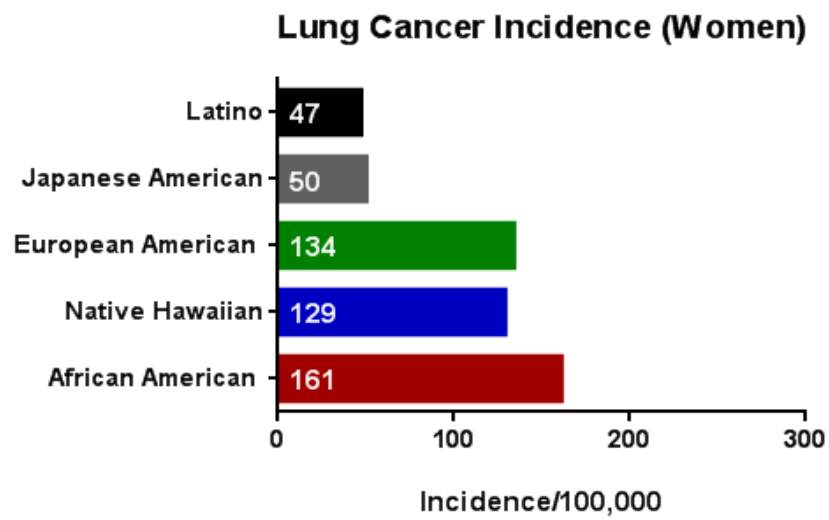
Rural-Urban Cancer Disparities

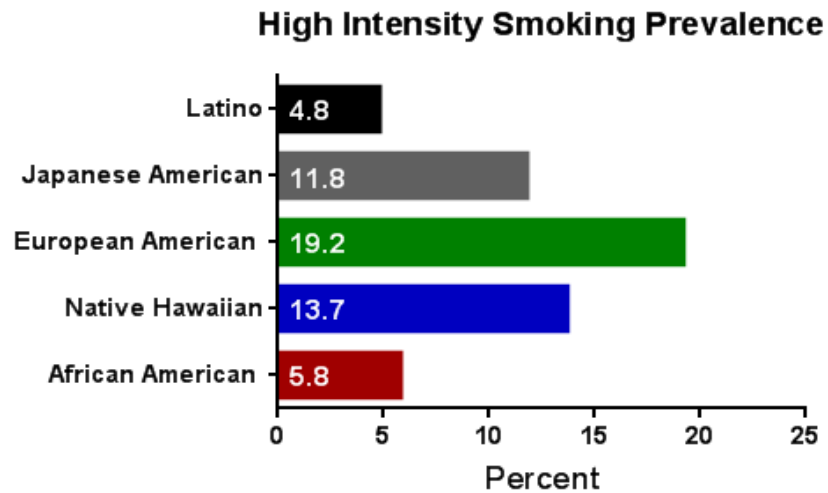


Houston….. Ryan… *Journal Thoracic Oncol* 2018 (13) 4: 497-509

Tobacco Disparities







Lung cancer incidence is highest in African Americans despite having the second to lowest prevalence of high intensity smoking

Adapted from N Engl J Med 2006; 354:333-342

Tobacco Disparities

- Initiate smoking later (average age at onset, 17.4 years for blacks versus 14.7 years for whites; $p < .05$)
- Smoke fewer cigarettes (14.1 versus 18.4 cigarettes per day)
- Disparities observed in never smokers
- Menthol cigarettes not associated with increased risk of lung cancer relative to non-menthol cigarettes
- Less likely to quit smoking

Tobacco Disparities

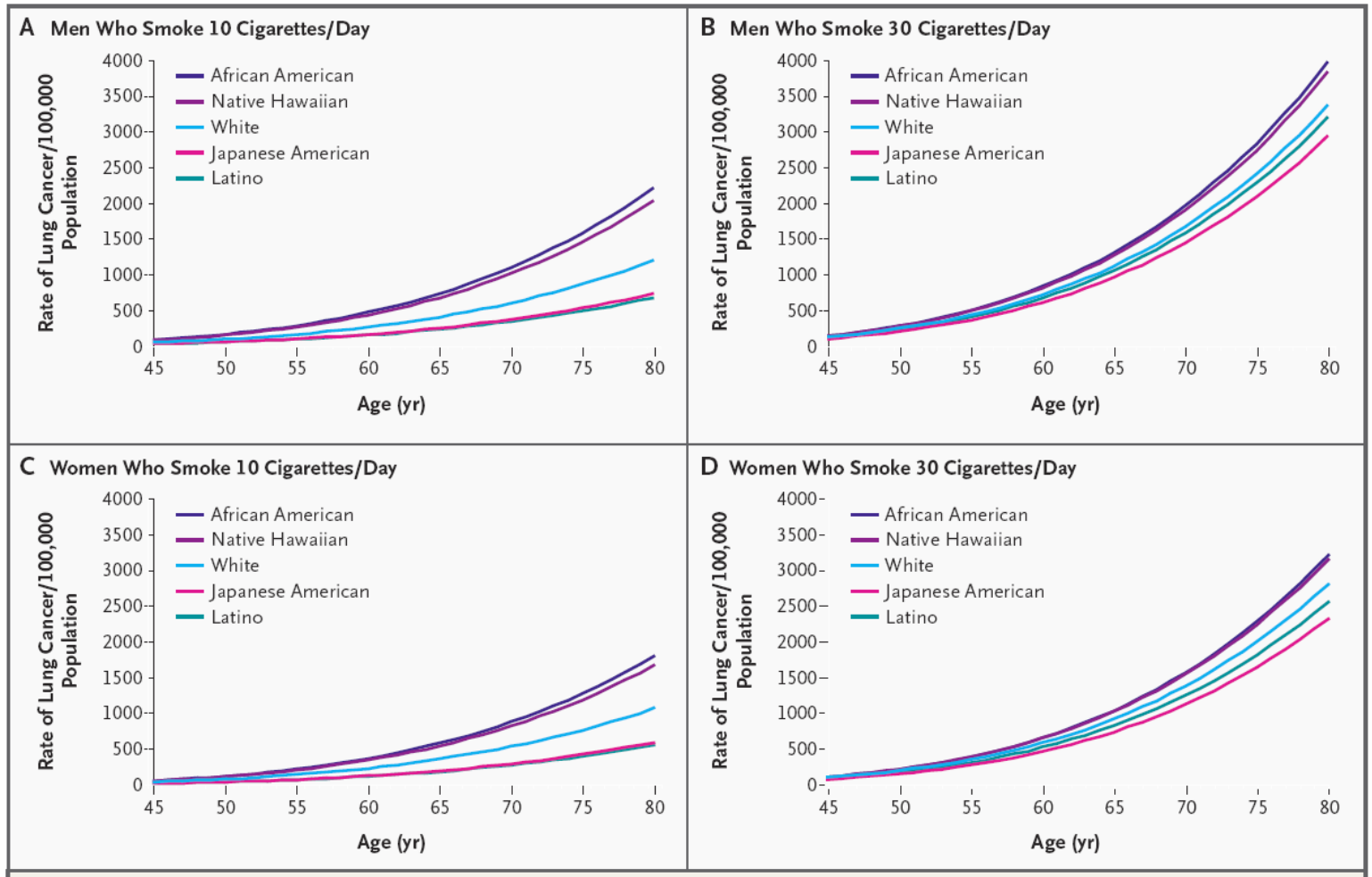


Figure 1. Predicted Rates of Lung Cancer among Men Who Currently Smoke 10 Cigarettes per Day (Panel A) or 30 Cigarettes per Day (Panel B) and among Women Who Currently Smoke 10 Cigarettes per Day (Panel C) or 30 Cigarettes per Day (Panel D).

Adapted from N Engl J Med 2006; 354:333-342

Tobacco Disparities

- Evidence for population differences in the amount of nicotine extracted per cigarette, unclear yet if this explains the disparity in lung cancer incidence

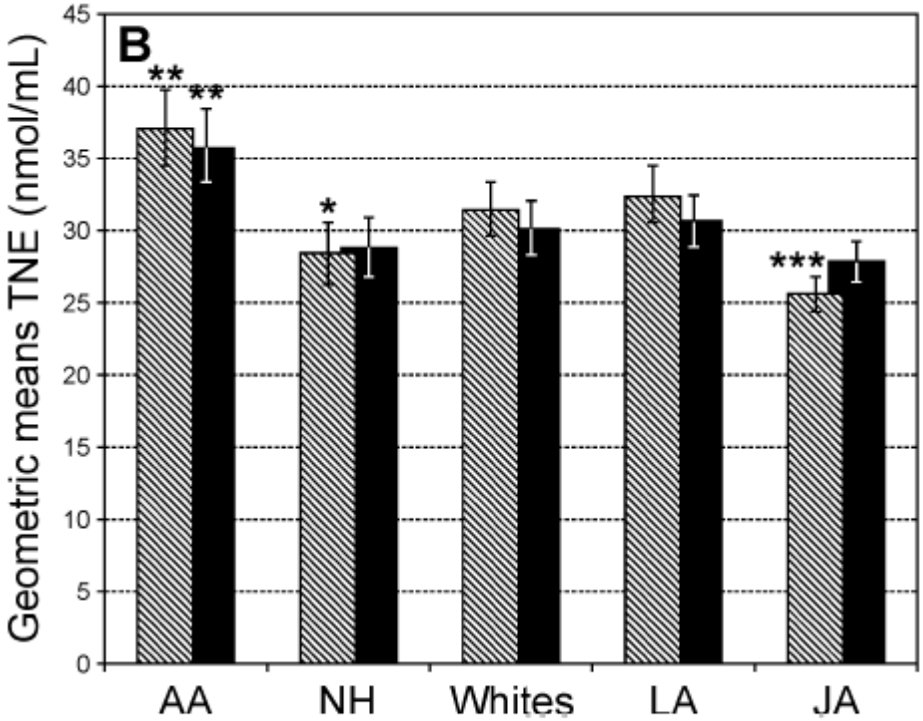


Figure 1. CYP2A6 activity and TNE stratified by racial/ethnic group. (**A**) The urinary ratio of total 3-HCOT to cotinine adjusted for age, sex, CPD and TNE; (**B**) TNE by racial/ethnic group adjusted for age, sex, BMI and CPD (hatched bars) and additionally adjusted for CYP2A6 activity (black bars). *$P < 0.04$, **$P < 0.001$, ***$P < 0.0001$ for difference between this group and Whites.

Carcinogenesis, 2016, Vol. 37, No. 3, 269–279

Racial differences in continued smoking may be attributable to several factors

- Socioeconomic vulnerabilities (including poverty, stress, and secondhand smoke exposure)
- Although the majority of black smokers express a desire to quit, they are less likely to receive and use evidence-based treatments (e.g., screening for tobacco use and advice to quit, smoking cessation pharmacotherapy, and counseling).
- In addition, black smokers are less likely to enroll in smoking cessation trials.
- Black smokers are more likely to smoke mentholated cigarettes, which might be harder to quit than nonmentholated cigarettes, which leads to poorer cessation outcomes
- Less accurate knowledge about the risks and prevalence of smoking and about the benefits and risks of effective smoking cessation treatments.

Cancer Health Disparities Summary

RESEARCH PRIORITIES (Joint AACR, ASCO, ACS and NCI statement)

1) Defining and improving data measures for cancer disparities research
2) Addressing disparities in cancer incidence
3) Addressing cancer survival disparities
4) Improving community engagement in cancer research
5) Redesigning cancer clinical trials to acknowledge and address cancer disparities

Rural-Urban Disparities in Cancer Mortality

- The U.S. Preventive Services Task Force recommends population-based screening for colorectal, female breast, and cervical cancers among adults at average risk for these cancers and for lung cancer among adults at high risk

- Screening adults for tobacco use and excessive alcohol use, offering counseling and interventions as needed; and using low-dose aspirin to prevent colorectal cancer among adults considered to be at high risk for cardiovascular disease based on specific criteria.

- Recommendation for vaccination against cancer-related infectious diseases including human papillomavirus and hepatitis B virus.

- *The Guide to Community Preventive Services* describes program and policy interventions proven to increase cancer screening and vaccination rates and to prevent tobacco use, excessive alcohol use, obesity, and physical inactivity.

CDC Surveillance Summaries / July 7, 2017 / 66(14);1–13

Key determinants of disparities

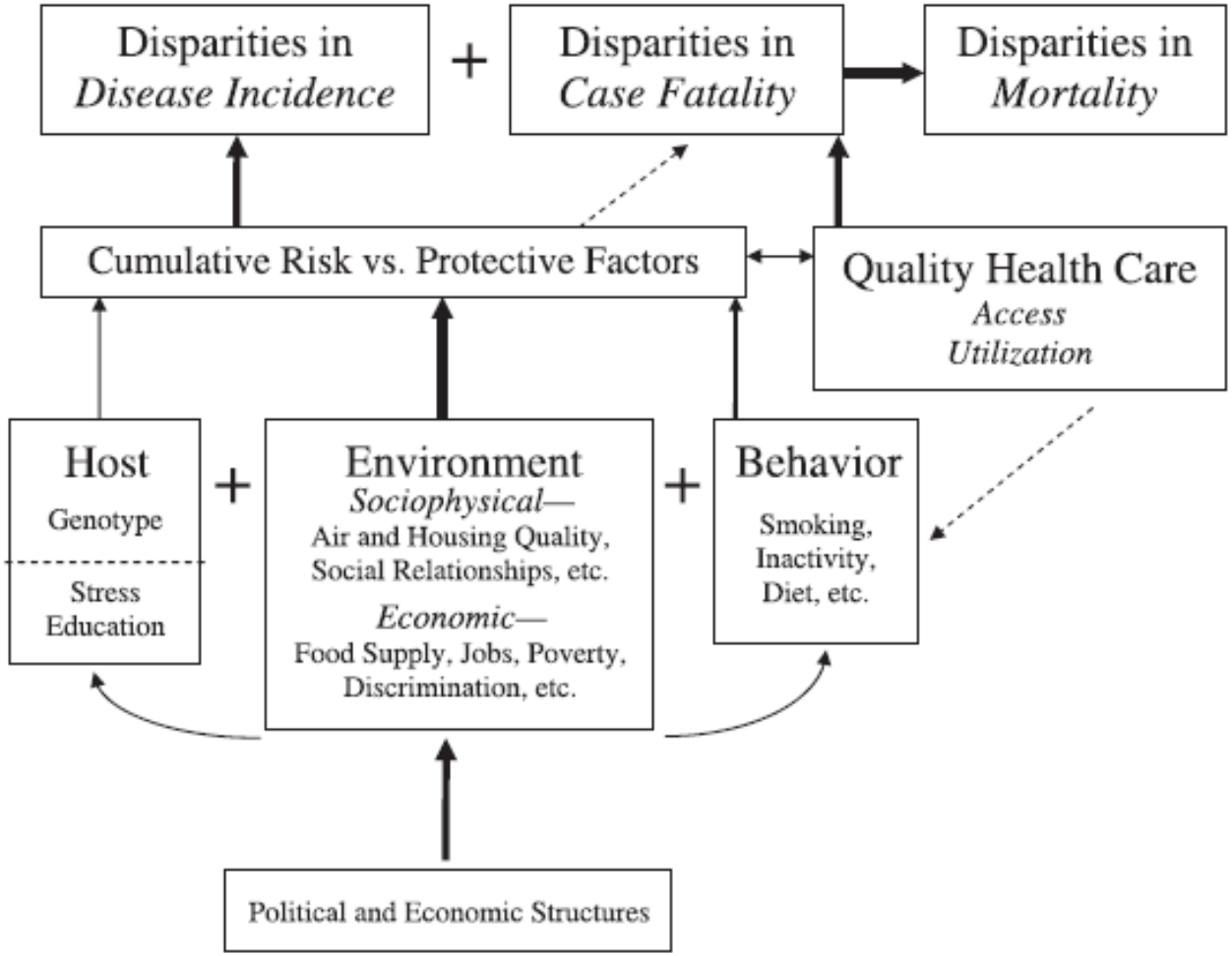


Figure 1. Key determinants of health disparities.

James, SA Epidemiologic Reviews 31(1):1-6

Questions?