

Cancer health disparities



The Causes and Consequences of Cancer Health Disparities

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• Disparities in cancer incidence

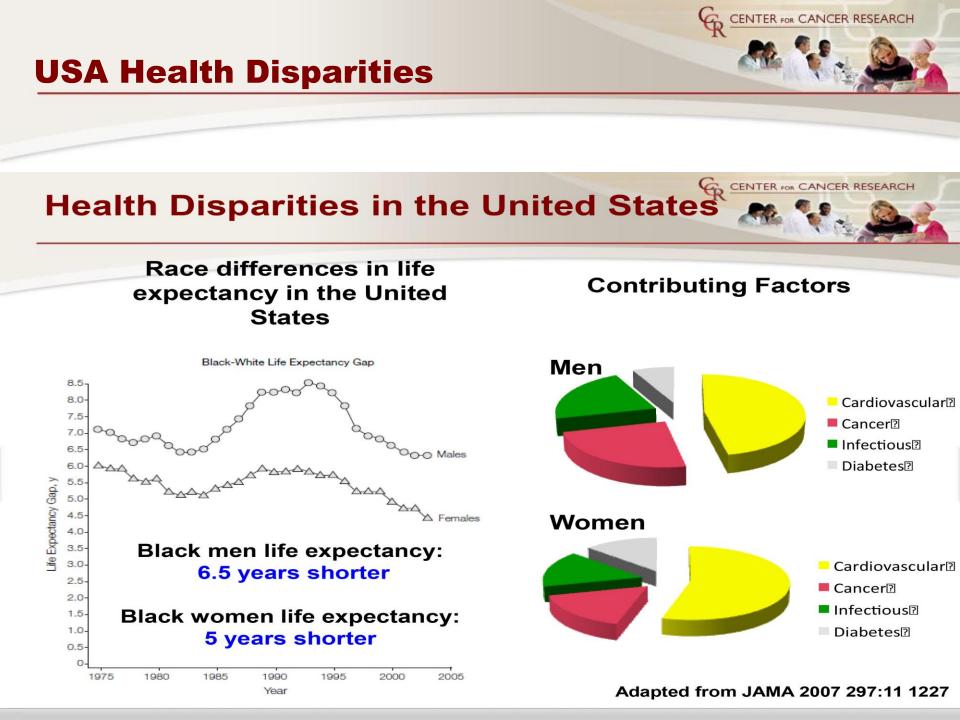
Disparities in cancer outcomes



 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



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."

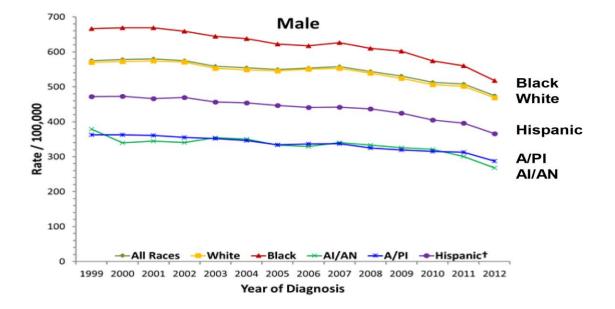


Excess Burden of Cancer in the African-American Community

"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"

Incidence rates

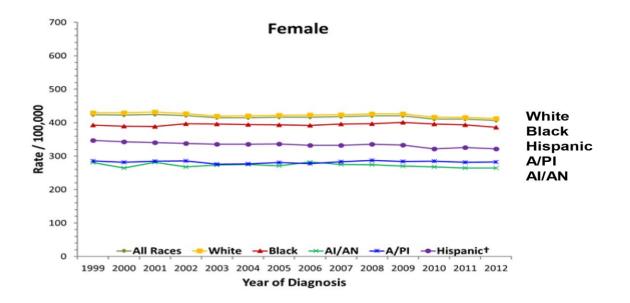




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Incidence rates





Breast cancer incidence

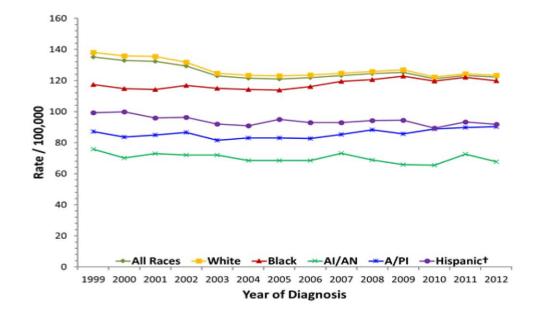
Whites compared with Blacks

Breast cancer incidence is higher in



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Female Breast Cancer Incidence Rates* by Race and Ethnicity, U.S., 1999–2012



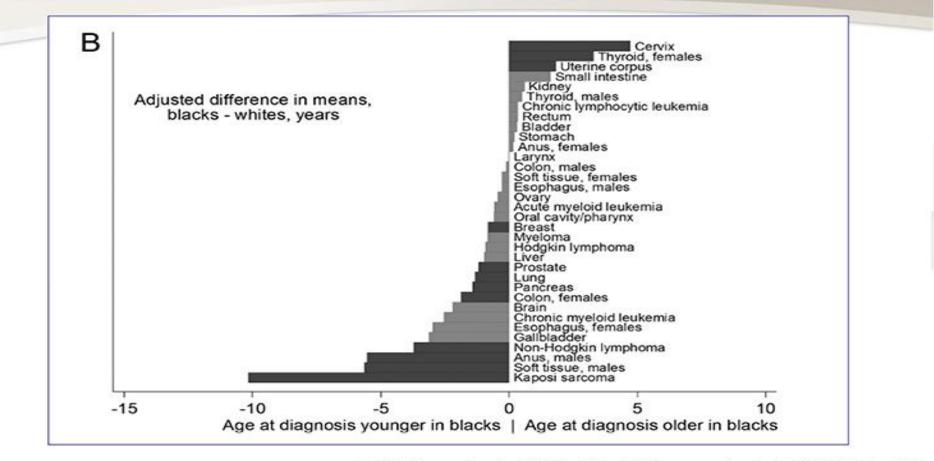
Diagnosis age

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6





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

Diagnosis age



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

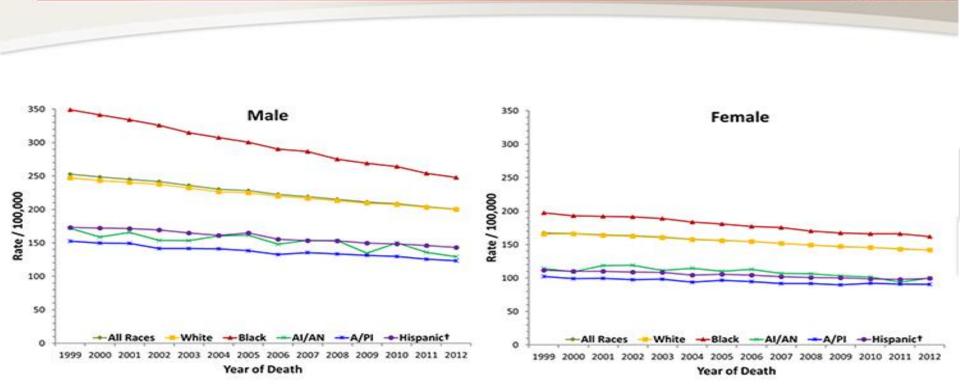
Robbins et al., JNCI J Natl Cancer Inst (2015) 107 (3)

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Mortlity rates

Sex, U.S., 1999-2012

Mortality Rates by Race/Ethnicity and



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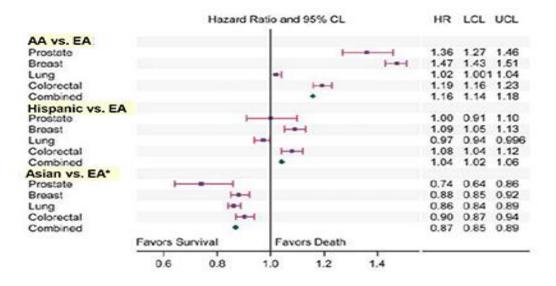
AA = African-American; EA = European-American

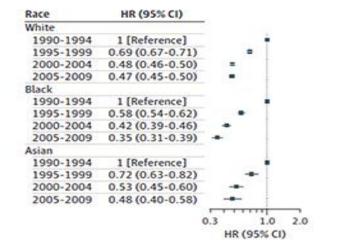
Aizer et al., Cancer 2014, 120: 1532-9 Zeng et al., Jama Oncology 2015 1: 88-96

Survival Health Disparities by Cancer Site

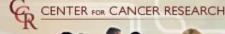
African Americans have the highest rate of cancer specific mortality Racial differences are not reducing over time Breast cancer—might even be getting worse

Survival health disparities between population groups









Prostate cancer

Cancer site

Key determinants

Key determinants of disparities

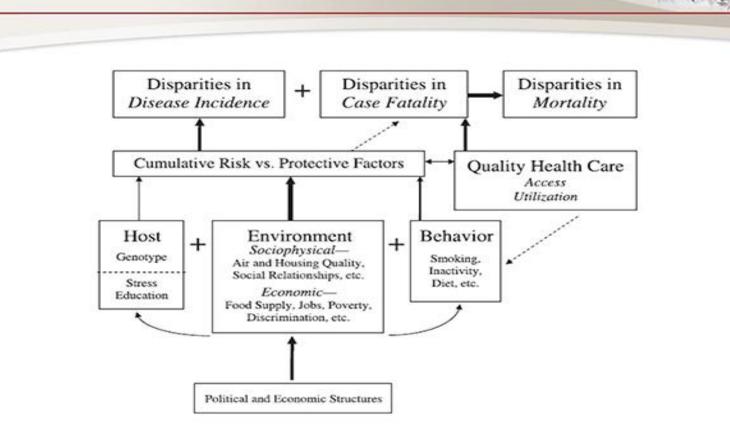


Figure 1. Key determinants of health disparities.

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Some of the reasons for disparities in incidence

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Genetic? Differential susceptibility?

Tobacco use

Nutrition & Physical Activity

Infection (Hepatitis B, HPV)

Some of the reasons for disparities in mortality

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Lack of early-detection

Lack of timely and aggressive treatment

Access to care

Genetics?



Disparity geography

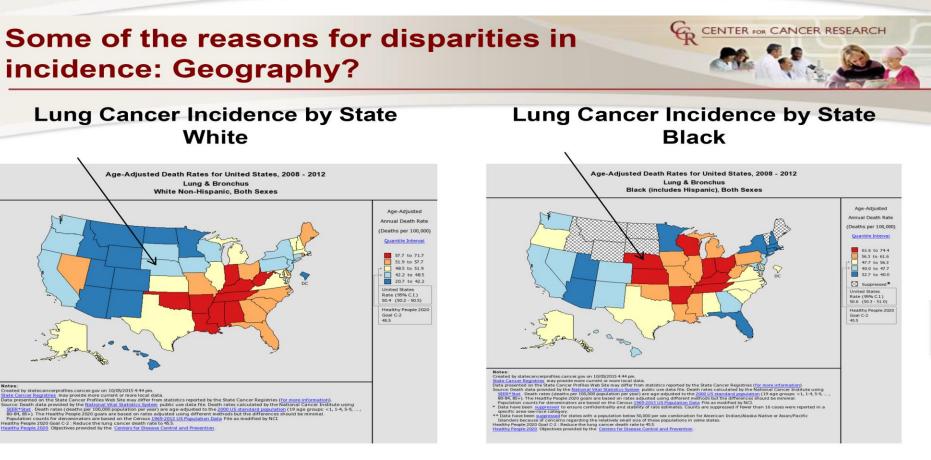
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Some of the reasons for disparities in incidence: Geography?

Incidence Rates by State Highest The number of people who get cancer is called cancer incidence. In the United States, the rate of getting cancer varies from state to state. Kentucky All Cancers Combined Rhode Island Incidence Rates* by State, 2012 † Delaware Interval Louisiana Data not availablet New Jersey 3714 to 4313 MT ND. 431.4 to 448.4 OR 50 448.5 to 463.0 WY 463.1 to 515.1 NE NV UT CO. CA KS: MO Lowest NC AZ OK. New Mexico NM Arizoma TX. Wyoming Alaska CDC Virginia

Geography disparity



- Regional differences in smoking prevalence may contribute to disparities in lung cancer incidence
- Residential migration; Racism; Advertising; Cultural influences; Community structure; Social stress

http://statecancerprofiles.cancer.gov





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
- Areas with the highest percentage of African Americans have the highest exposure to cancer-associated pollutants (Environ Health Perspect. 2005 113(6): 693–699)

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- Exposure to second-hand tobacco smoke
- Can a deleterious neighborhood-effect early in life affect health outcomes through physiological adaptations to the environment?
 - Similar to the "Barker hypothesis" of the developmental origins of adult diseases including heart disease and diabetes.
 - Mechanism of adaptation may include epigenetic modification of gene expression

Geography



Rural populations are more likely Unequal burden of pollution

- Forego medical care and prescriptions due to cost
- Report fair/poor heath and health-related unemployment
- Experience psychosocial distress
- Can a deleterious neighborhood-effect early in life affect health outcomes through physiological adaptations to the environment?
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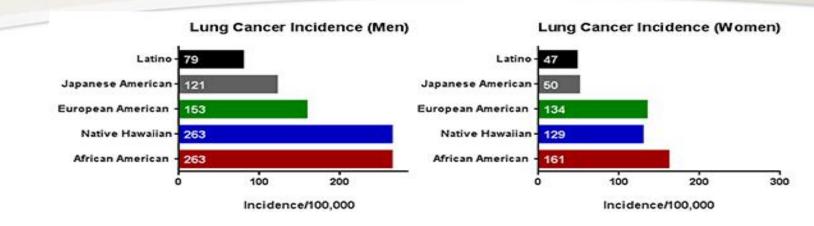
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Tobacco use

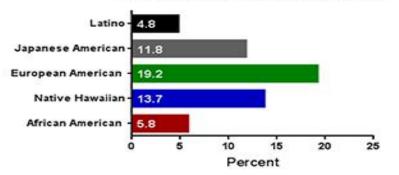


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Lung cancer incidence is highest in African Americans despite having the second to lowest prevalence of high intensity smoking

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





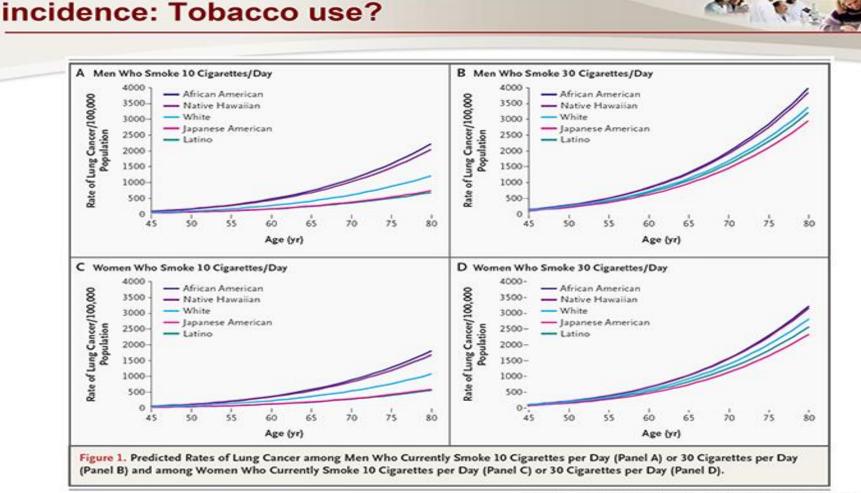
 Initiate smoking later (average age at onset, 17.4 years for blacks versus 14.7 years for whites; p < .05)

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- Smoke fewer cigarettes (14.1 versus 18.4 cigarettes per day)
- Prevalence as adults similar (Black men, 23.9%; black women, 19.2%; white men, 24.5%; white women, 19.8%)
- Disparities observed in never smokers
- Menthol cigarettes not associated with increased risk of lung cancer relative to non-menthol cigarettes

Tobacco use

Some of the reasons for disparities in



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

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Some of the reasons for disparities in incidence

Geography

Genetic? Differential susceptibility?

> Tobacco use

Nutrition & Physical Activity

Viruses (Hepatitis B, HPV)

Extrinsic factors



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Some of the reasons for disparities in incidence: **Extrinsic Factors**

- Metformin is one of the most prescribed medications in the United States
- Recent study of VA records finds that metformin use is associated with reduced risk of prostate cancer in Hispanic men only
- Use of metformin and finasteride was associated with a greater prostate cancer incidence reduction in Hispanics and AA compared with NHW

Table 3. HR (95% CI) of prostate cancer incidence associated with metformin use by race/ethnicity: comparison between unadjustment and adjustment of generalizability weights that calibrate between race/ethnic groups

	NHW	AA	Hispanics
Metformin	0.91 (0.82-1.01)	1.10 (0.94-1.27)	0.63 (0.49-0.80)
		0.92° (0.82-1.04)	0.50 ^{a,b} (0.47-0.52)
Metformin + Statin	0.58 (0.49-0.69)	0.70 (0.58-0.86)	0.40 (0.30-0.53)
		0.59 ^a (0.48-0.72)	0.32 ^{a,b} (0.28-0.35)
Metformin + Finasteride	0.48 (0.37-0.63)	0.61 (0.44-0.77)	0.58 (0.37-0.99)
		0.25 ^{a,b} (0.16-0.39)	0.25 ^{a,b} (0.20-0.30)

Abbreviations: AA, African American; NHW, non Hispanic white.

^aGeneralizability weights were used to calibrate posttreatment clinical characteristics between comparison groups. ^bSignificantly different from NHW based on 95% CI of HR.

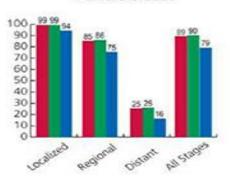


Some of the reasons for disparities in cancer mortality: Lack of early detection?

Lack of early detection

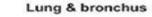
Some of the reasons for disparities in cancer mortality: Lack of early detection?



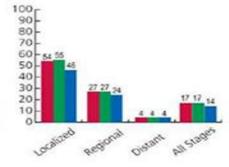


Female breast

Liver & intrahepatic bile duct

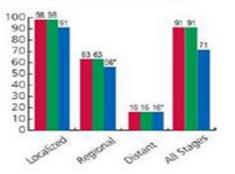


Colorectum

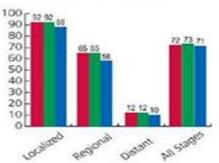


Esophagus

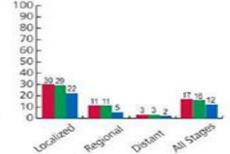
Melanoma of the skin

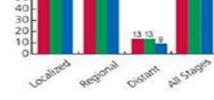


CA CANCER J CLIN 2015;65:5-29



Kidney & renal pelvis





100,

90

80

70

60

50

90 90 87



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





- Possibly for some cancers
- Breast cancer mammography use similar in equal access to care setting (Cancer 2013 Oct 1;119(19):3531-8)

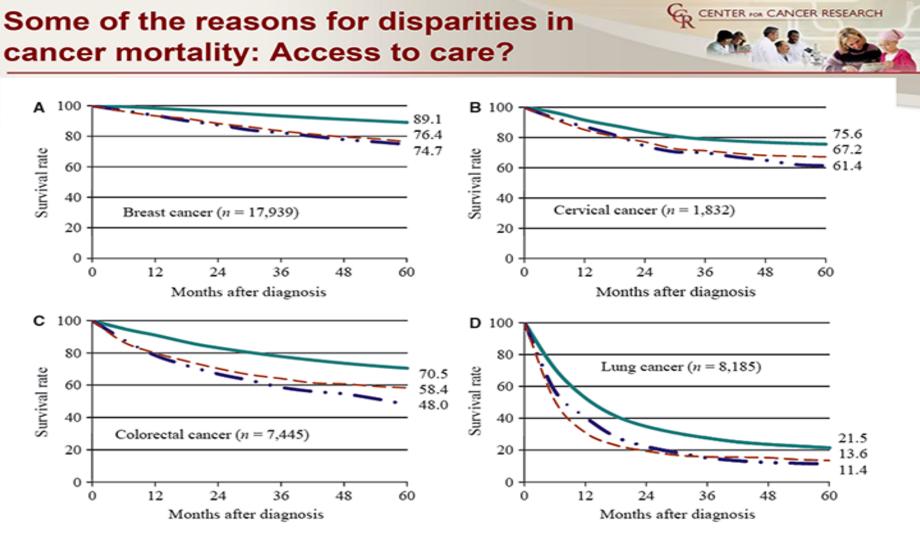
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- Colorectal cancer screening is lower among African Americans even in an equal access to care setting (Cancer. 2013; 4(3): 270–280)
- Uptake of screening for other cancers, such as HPV, may also be lower in minority populations
- But the differences exist even in cancers where there is no validated screening modality (lung, esophagus, etc)



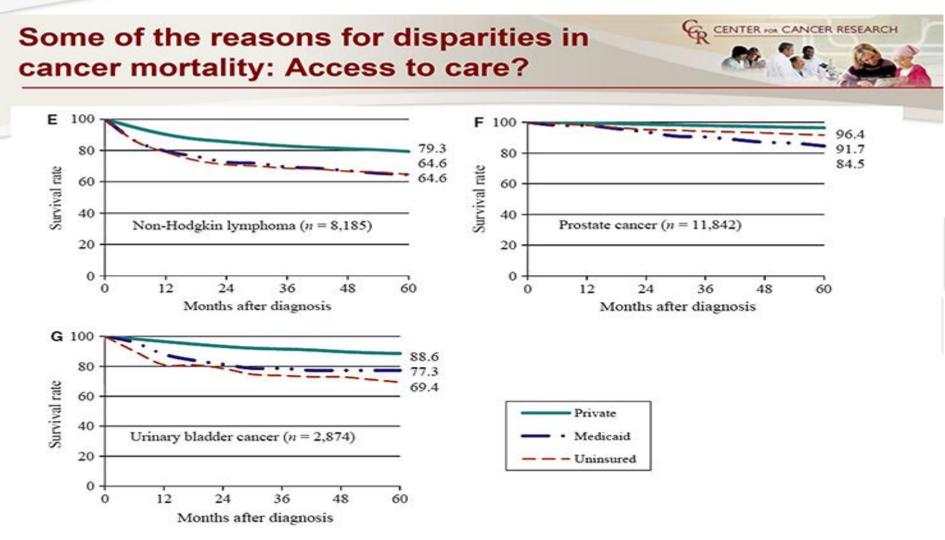
Some of the reasons for disparities in cancer mortality: Access to care?

Access to care



Cancer Medicine 2013; 2(3): 403–411

Access to care

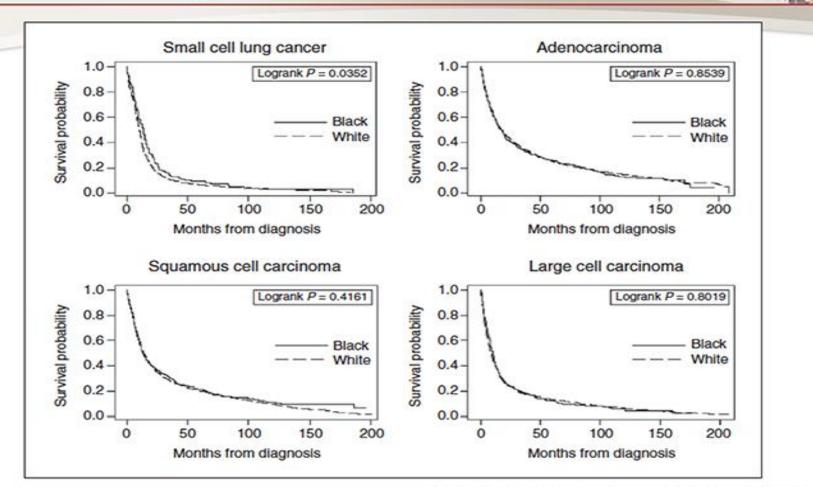


Cancer Medicine 2013; 2(3): 403-411

Lung cancer access to care

cancer mortality: Access to care?

Some of the reasons for disparities in



Cancer Epidemiol Biomarkers Prev; 21(10) 2012

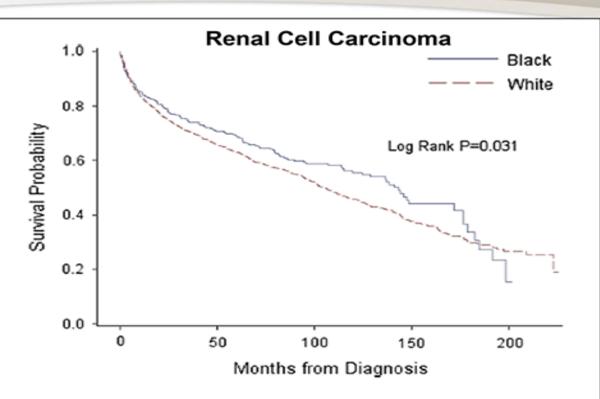
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Renal cell carcinoma access to care



US Department of Defense Cancer Registry Military Health System (MHS)

"The lack of racial difference in survival among RCC patients in the MHS may be related to equal access to health care. Improved access could reduce the survival disparity among RCC patients in the general population".



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Fig. 1 Kaplan–Meier survival curves comparing Black and White clear cell RCC patients diagnosed from 1988 to 2004 in the US Department of Defense Cancer Registry

Cancer Causes Control 2015 26(7):1019-26

Myeloma access to care

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

Multiple myeloma

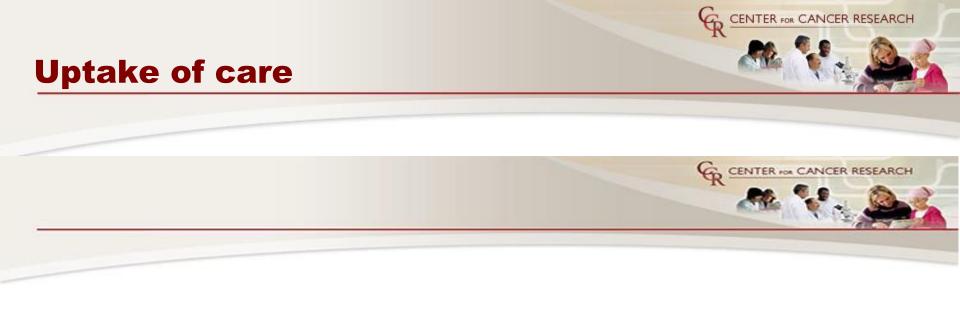
Increased incidence among African Americans but adverse disparities in outcome not observed African Americans may have a more indolent form of MM

100 Disease-Specific Survival (%) Blacks - Whites - 95% CI 75 50 p < 0.00125 0 0 2 10 8 6 Years After Diagnosis

AA patients with myeloma have better survival than EA patients

Waxman et al. Blood 2010

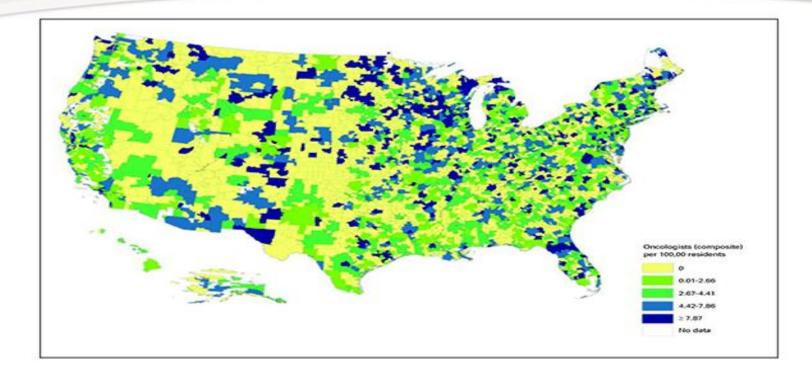
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Some of the reasons for disparities in cancer mortality: Access and uptake of care?

Oncologist density





Chun Chieh Lin et al. JCO doi:10.1200/JCO.2015.61.1558

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Access and uptake of care

mortality: Access and uptake of care?

Some of the reasons for disparities in cancer

Figure 9

Disparities in Treatment

14.0%

Surgery

61.5%

- 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)



28.6%

ALA – Too Many Cases Too Many Deaths 2010

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46.9%

Chemotherapy

Access and uptake of care

Some of the reasons for disparities in cancer

mortality: Access and uptake of care?

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

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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*	95% CP	
Surgery, all subjects	0.75	0.37-1.53	
Chemotherapy, all subjects	0.79	0.59-1.04	
Tumor stage			
1	2.52	0.64-9.98	
II	0.98	0.61-1.60	
111	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	

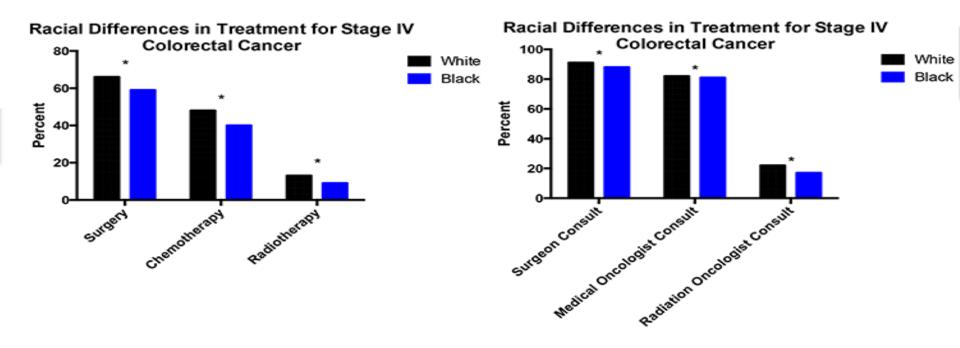
N = 2560.

*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.

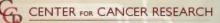
Access and uptake of care

Some of the reasons for disparities in cancer center the CANCER RESEARCH mortality: Access and uptake of 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



Some of the reasons for disparities

- in cancer mortality: Access and
- uptake of care?
- **Potential factors that influence**
- access and uptake of care:
- Personal beliefs
- •Fear
- •Culture
- Patient-doctor relationship
- Patient bias
- Provider bias
- Patient-doctor communication
- Co-morbid conditions

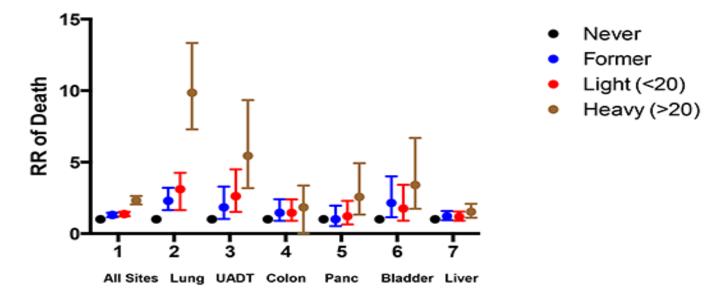
Smoking cessation





- African Americans are at risk for continued smoking and thus poor cessation outcomes
- Lung, pancreatic, bladder, and liver cancer patients at risk of poorer outcomes

Relative Risk of Death and Smoking after Diagnosis



Smoking cessation



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Some of the reasons for disparities in cancer mortality: Smoking cessation?

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.
- Blacks 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 mortality



Factors that contribute to racial differences in outcomes:

- Access to screening
 - Less engagement might lead to a later stage of diagnosis
- Access to care
 - Reduced access reduces availability of potentially life saving therapeutic interventions

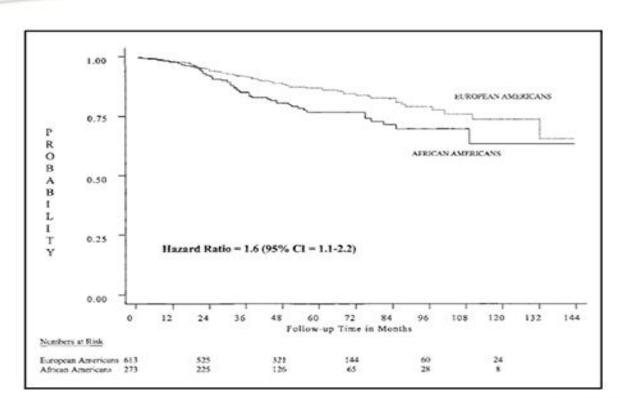
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- Uptake of care
 - Reduced uptake of therapeutic options reduces availability of potentially life saving therapeutic interventions
- >Smoking
 - Continued smoking is associated with adverse outcomes

But..... There are some cancers where, even in an equal access to care setting, disparities in survival persist

Disparities persist



For some cancers, disparities persist even

in equal access to care settings

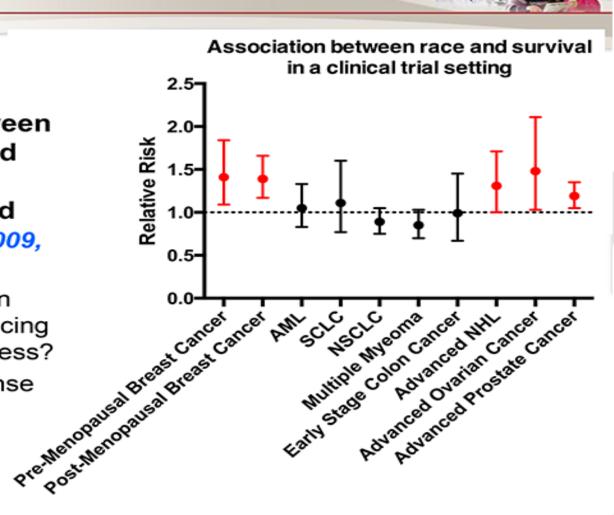
Cancer 1998, 82: 1310 - 1318; Cancer 2003, 98: 894 - 899 JNCI 91:17, 1999 JNCI Monographs, No. 35, 2005

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Biology

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?



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While data suggest that access to quality care is a factor in cancer disparities, other factors also play a major role, including tumor biology and genetics

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Intrinsic differences in tumor biology influencing disease aggressiveness?

Differences in response to therapy?

Biology

Is biology a contributing factor?

- Differences in
 - Genetics
 - Somatic mutations
 - Molecular subtype and gene expression
 - · Gene expression and methylations profiles
 - Systems biology
 - Inflammation
 - Cell biology

Differences in gene expression, molecular subtypes and molecular signatures will reveal differences in tumor biology between African American and European American patients

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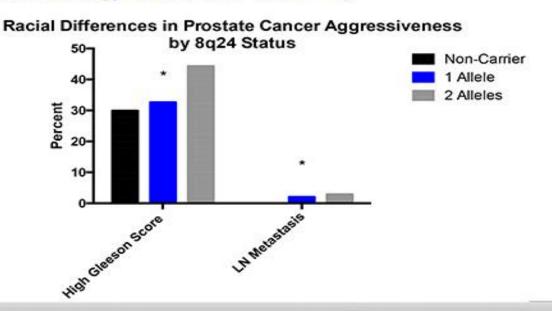
Genetics



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Biological determinants of cancer health disparities in outcome: 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)





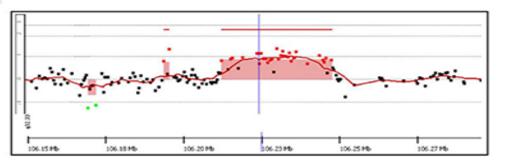


Duplication event at 14q32.33 encompasses IGHG3 in African American prostate tumors (familial, suggesting inherited predisposition)

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Contribute to the high prevalence and mortality of prostate cancer in African American men?

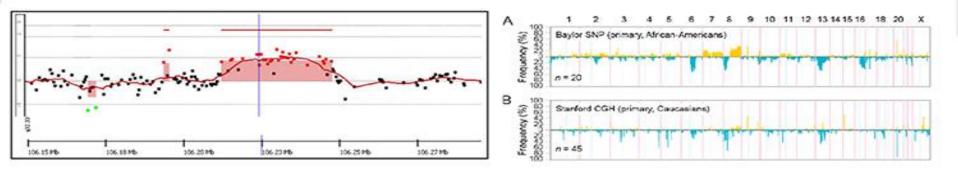


Prostate 2013 73(6):614-23

Genetics



- Duplication event at 14q32.33 encompasses IGHG3 in African American prostate tumors (familial, suggesting inherited predisposition)
- Contribute to the high prevalence and mortality of prostate cancer in African American men?
- Differences exist in the regions amplified and lost in European American and African American prostate cancers



Prostate 2013 73(6):614-23

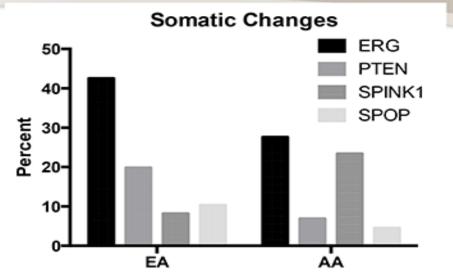
Neoplasia 2009 11(3):305-12.

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Somatic mutations

Biological determinants of cancer health disparities in outcome: Somatic mutations

 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)



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- 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

Biological determinants of cancer health disparities in outcome: Molecular subtype

Population differences in molecular subtypes and disease grade

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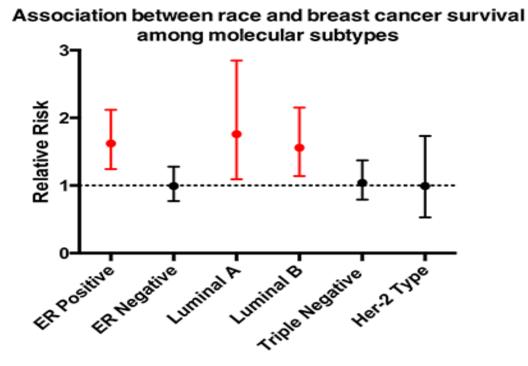
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 Race/ethnic disparity in prevalence of basal-like/triple-negative breast tumors (JAMA 2006, 295: 2492 – 2502; J Clin Oncol 2009, 27: 4514 – 21)

Tumor Status	All Cases	No (%)			
		African American*		Non-African American†	
		Premenopausal (n = 97)	Postmenopausal (n = 99)	Premenopausal (n = 164)	Postmenopausal (n = 136)
Basal-like	100	38 (39)	14 (14)	26 (16)	22 (16)
HER2+/ER-	33	9 (9)	7 (7)	9 (6)	8 (6)
Luminal A	255	35 (36)	58 (59)	83 (51)	79 (58)
Luminal B	77	9 (9)	16 (16)	30 (18)	22 (16)
Unclassified	31	6 (6)	4 (4)	16 (10)	5 (4)

Molecular subtype

Biological determinants of cancer health disparities in outcome: Molecular subtype

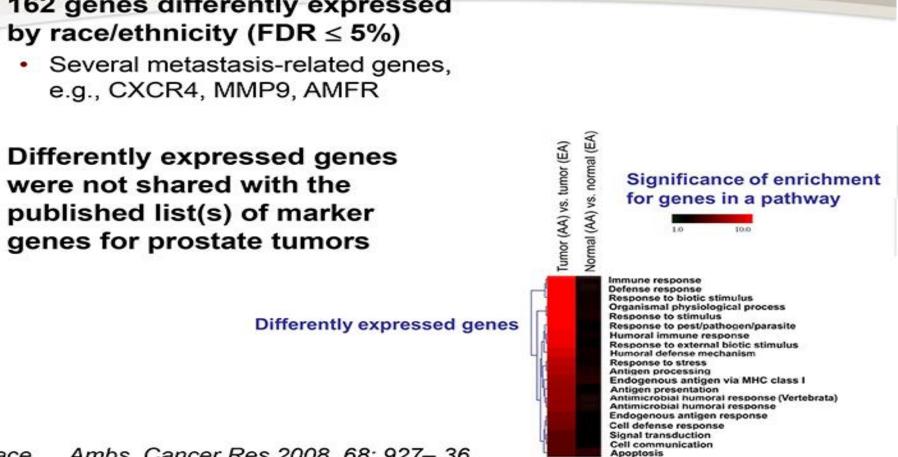


However: Breast cancer survival disparity in US is irrespective of some tumor subtypes (JNCI 2009, 101: 993-1000)

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Wallace Ambs. Cancer Res 2008. 68: 927-36



Biological determinants of cancer health disparities in outcome: Cell biology

162 genes differently expressed

Cell Biology





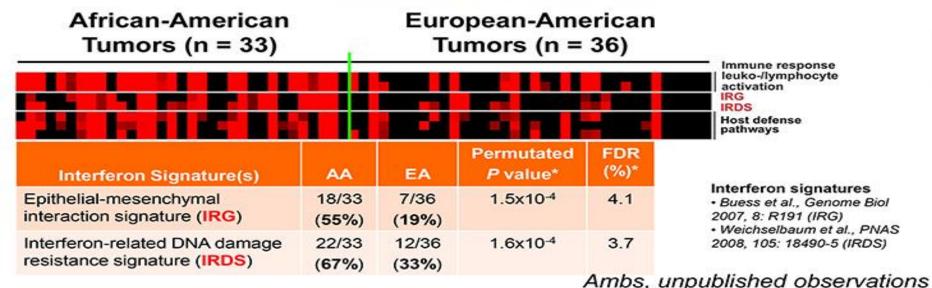
Biological determinants of cancer health disparities in outcome: Cell biology

 Interferon signature predicts survival and poor outcomes (PNAS 2008, 105: 18490 – 95; Genome Biol 2007, 8: R191)

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 IRDS is a predictive marker for resistance to chemotherapy and radiation and poor survival. Key signature genes mediate experimental resistance to therapy (*PNAS 2008, 105: 18490 – 95*)







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Biological determinants of cancer health disparities in outcome: Inflammation

- Increase in some autoimmune/infectious diseases: Lupus and TB (AJPH 2001 91:8 1251-53)
- Increased IL-6 (Am J Hum Genet 2007;80(4):716-26)
- Different allele frequencies (Cytokine 2009;46(2):236-44)
- Cytokine profiles between serum from AA and EA patients are different, some of which are associated with poor outcomes (*Pine.... Ryan..... Harris,* CEBP 2015)
- Inflammation in non-cancerous prostate biopsies is more prevalent among African American than European American men (JNCI 1998, 90: 756 – 60)
- African Americans more likely to have some co-morbidities, such as COPD

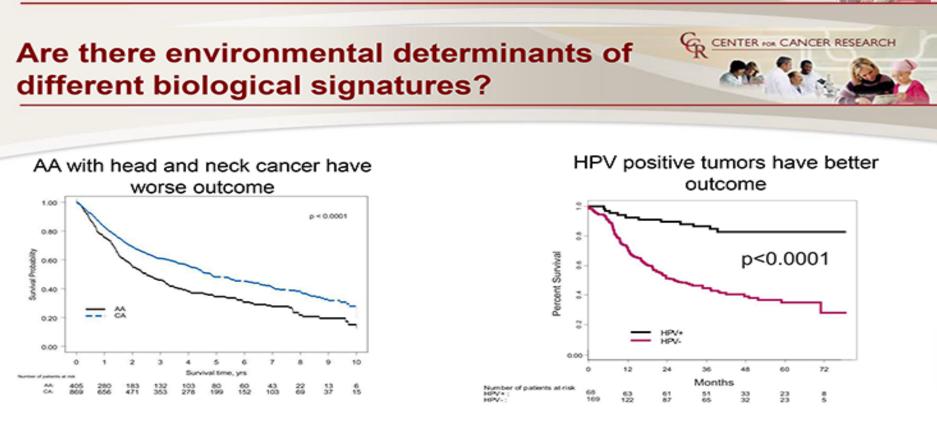
Environmental determinants



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Are there environmental determinants of different biological signatures?

- Viral infections
- Germline differences e.g. SNPs by ancestry
- Stress, different inherent responses to stress
- Reactivation of endogenous retroviruses e.g. HERV-K
- Acquired genetic alterations in tumor
- Toxins
- Air pollution
- Carcinogens
- Don't know yet if and how each of these exposures contribute to biological determinants of cancer health disparities



Zandberg, Head Neck 38: 564, 2016

Environmental determinants

Posner, Annals Oncology 22: 1071, 2011

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Prevalence of HPV is higher in EA patients, Cullen et al discovered this as one of the key factors leading to improved outcomes in EA patients





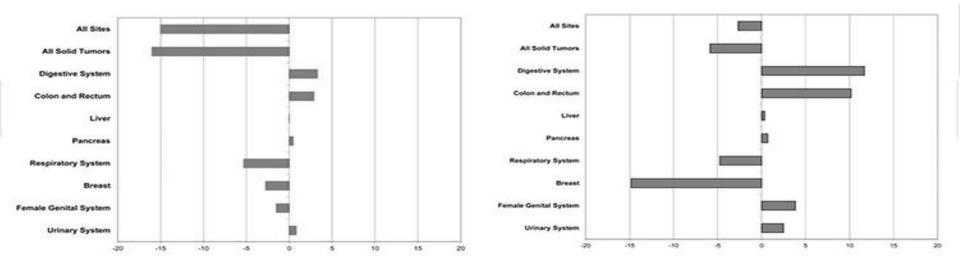
African Americans also have a higher risk of second cancers



African American

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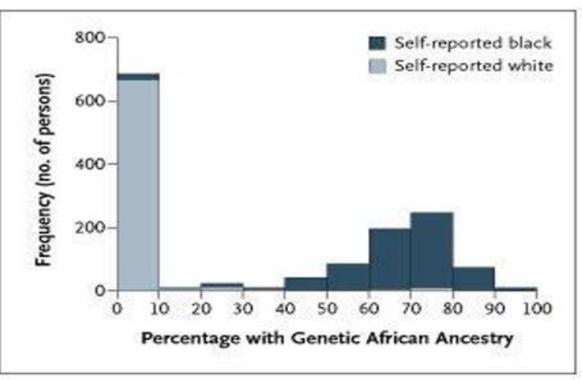
Int J Gynecol Cancer. 2011 21(2): 309-315



Perspectives-Ancestry Informative Markers

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

Frequency Histogram Showing the Percentage of African Ancestry in a Population Living in Cleveland.

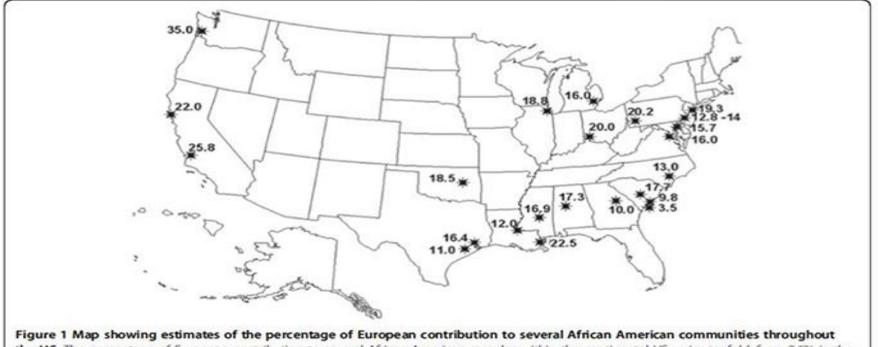


Sinha M et al. N Engl J Med 2006;354:421-422.

Ancestry markers



The percentage of European contribution to several African American communities varies 10-fold



the US. The percentage of European contribution to several African American samples within the continental US varies tenfold, from 3.5% in the isolated Gullah-speaking Sea Islanders from South Carolina to 35% in Seattle. Reproduced from Parra [15].

Human Genomics (2015) 9:1





Increased proportion of Native American ancestry is associated with increased risk of childhood acute lympoblastic leukemic

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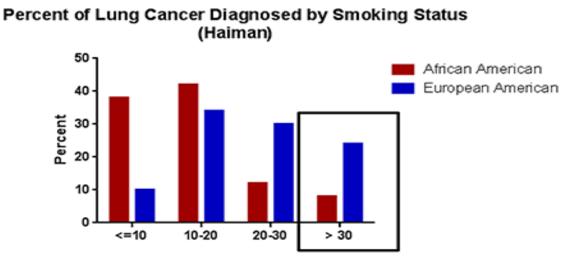
- Screening implications
- Also related to treatment—Children with more than 10% Native American ancestry need an additional round of chemotherapy to respond to the treatment (Yang et al., Nature Genetics 2011 43(3); 237-241)
- Ancestry informative markers provide a greater granularity to studying race

Perspectives screening



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Cancer Health Disparities: Additional Perspectives-Screening



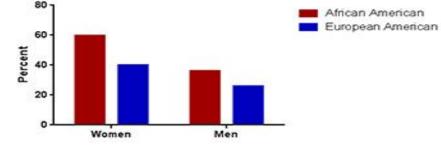
Cigarettes Smoked Per Day

Lung cancer screening guidelines:

Age Smoking history Evidence to support the idea that AA are more susceptible to lung cancer at low doses of cigarettes

Implications for lung cancer screening and potential to widen disparities

CENTER FOR CANCER RESEARCH **Perspectives screening** CENTER HOA CANCER RESEARCH **Cancer Health Disparities: Additional** Perspectives-Screening Percent of Lung Cancer Diagnoses Missed by Current Screening Guidelines (NCI-MD)

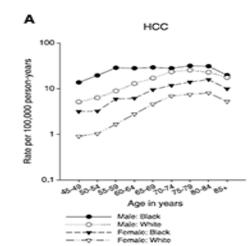


Unintended consequence: Widening of disparities

New Treatments

Some of the reasons for disparities in Center to CANCER RESEARCH mortality: Access to care and new treatments?

- We are aware of biological differences between tumors from different ethnic groups
- Key question: will these differences translate to different responses to targeted therapy?
- Key issue: to avoid increasing disparities we need to ensure equal access to new targeted drugs

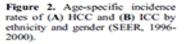


Remain vigilant re the use of new drugs in the clinic?

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Can we expect similar responses across ethnic groups?

CEBP 2006 15(6):1198-203 J Natl Cancer Inst. 2014 18;106(12)



Some of the reasons for disparities in incidence

✓ Geography

Highly possible to play a role but more research needed

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Is it related to pollution, toxin exposure and air quality?

✓ Genetic? Differential susceptibility?

- 8q24 may explain up to 60% of prostate cancer differences
- More research needed on other cancers

✓Tobacco use

Use alone does not explain all disparities

Some of the reasons for disparities in mortality

Lack of early-detection

- Possibly for some cancers, but not all
- Still need to work on programs and strategies to ensure that all populations are aware of, and have the opportunity, to avail of screening
- What are the reasons driving lower use of screening in equal access to care settings/all settings?

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Access to care

- Insurance
- For some cancers, insurance is the reason for differences in outcomes, for others it isn't

Lack of timely and aggressive treatment

 Access to care can drive this, but research also needed on societal, cultural and demographic reasons leading to reduced utility of treatment modalities

Some of the reasons for disparities in mortality

Genetics

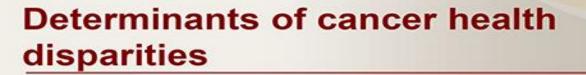
- 8q24 related to prostate cancer aggressiveness
- Are differences in CNV that are also evident in normal tissue
- Somatic mutation profiles of some cancer are different as are the molecular subtypes

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Biology

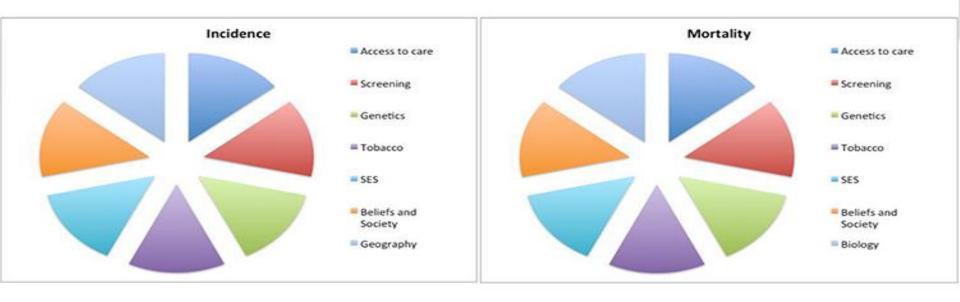
- Gene expression
- Methylation
- Less efficient G2M checkpoint
- Inflammation differences

Determinants



A multidisciplinary problem that requires a multidisciplinary approach

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Determinants of cancer health disparities



•A multidisciplinary problem that requires a multidisciplinary approach including Prevention, Early Detection, Diagnosis, Treatment and Mortality