Cancer Health Disparities

TRACO, 2022

Analysis of Tumor Biology and Blood- or Urine-based Biomarkers to Advance Cancer Health Disparity Research

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NIH NATIONAL CANCER INSTITUTE

Definition

Definition of Cancer Health Disparity

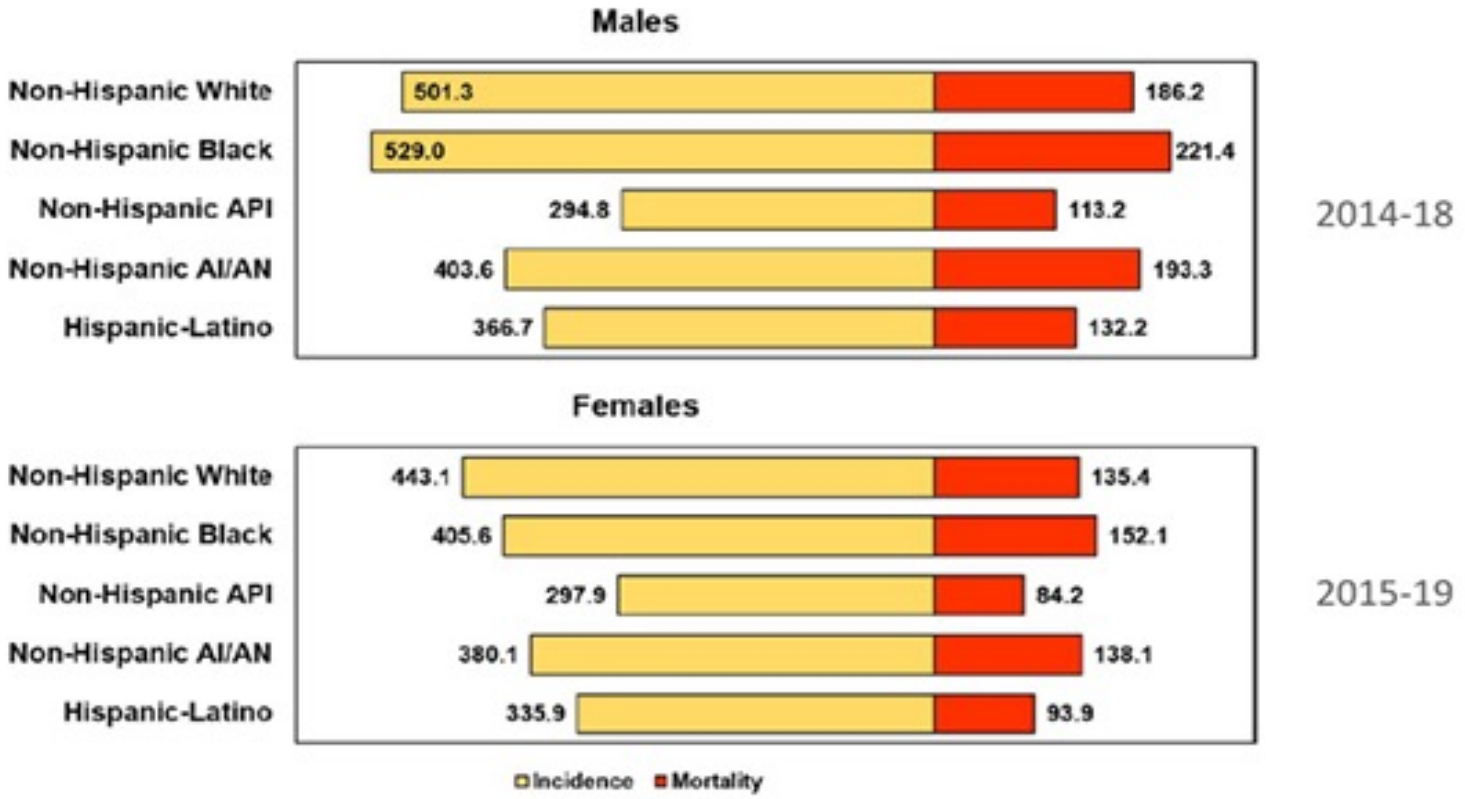
- **Cancer health disparity is an unequal burden of cancer (incidence, mortality, survivorship and quality of life) among population groups**
  - Race/ethnicity
  - Socioeconomic status
  - Geographic location
  - Gender

An important resource to study cancer health disparities is NCI's Surveillance, Epidemiology, End Results Program providing information on cancer statistics

Cancer incidence and death rates

Cancer Incidence and Death Rates by Population Group in the United States (SEER and National Center for Health Statistics data)

Age-standardized



API, Asian American and Pacific Islanders
AI/AN, American Indian and Alaska Natives

Islami et al.
CA Cancer J Clin 2022, 72: 112-143

Cancer death rates

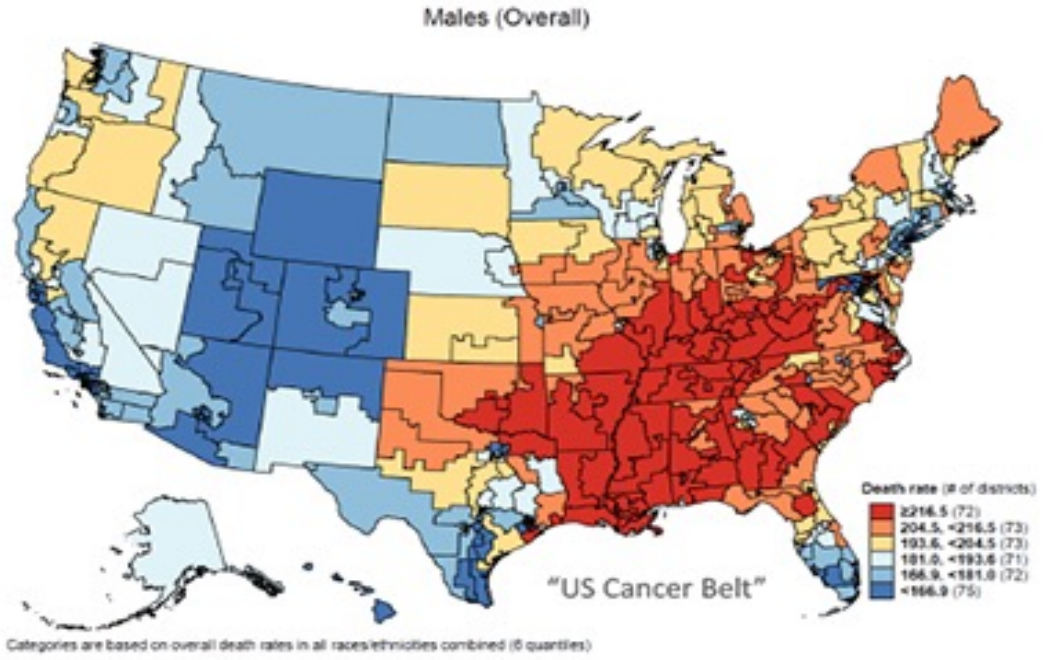
Cancer Death Rates by Population Group and Cancer Site

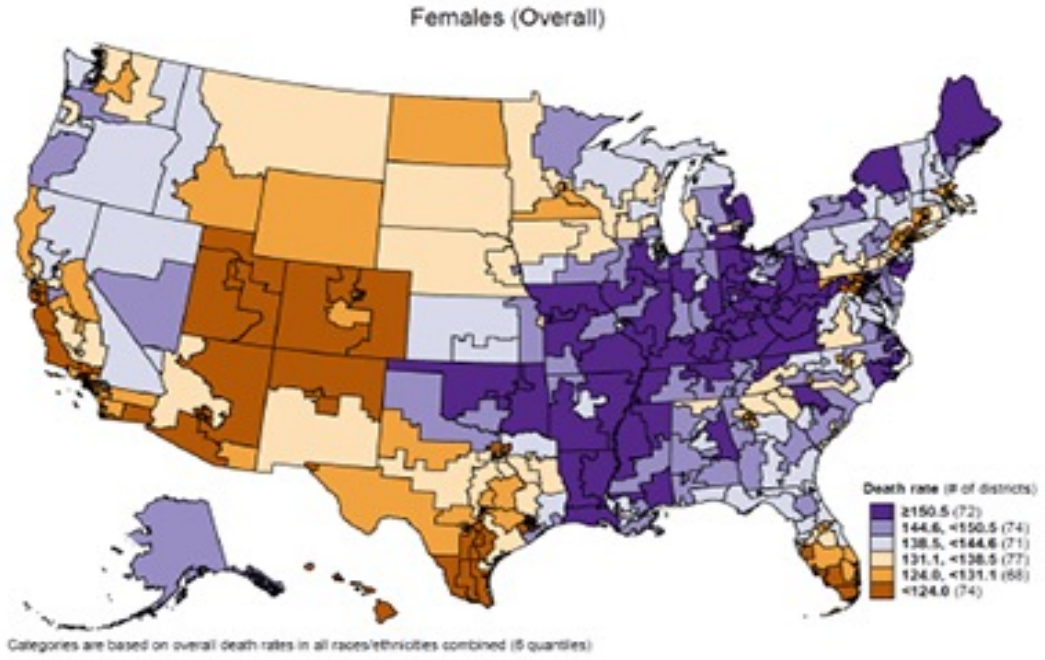
CANCER SITE BY SEX	NH WHITE	RATE RATIO (95% CI) NH BLACK	NH AI/AN	NH API	HISPANIC-LATINO
Death rate: 2015-2019					
All cancers combined					
Males	1	1.19 (1.18-1.20)	1.04 (0.20-1.88)	0.61 (0.60-0.61)	0.71 (0.68-0.71)
Females	1	1.12 (1.12-1.13)	1.02 (0.30-1.74)	0.62 (0.62-0.63)	0.69 (0.67-0.70)
Lung and bronchus					
Males	1	1.15 (1.14-1.16)	0.90 (0.40-1.40)	0.57 (0.56-0.58)	0.47 (0.42-0.48)
Females	1	0.85 (0.84-0.86)	0.91 (0.44-1.38)	0.47 (0.46-0.48)	0.35 (0.29-0.35)
Breast, female	1	1.41 (1.39-1.43)	0.90 (0.50-1.29)	0.59 (0.58-0.60)	0.69 (0.62-0.70)
Prostate	1	2.13 (2.10-2.16)	1.18 (0.66-1.70)	0.48 (0.47-0.50)	0.88 (0.77-0.89)
Colorectum					
Males	1	1.44 (1.42-1.47)	1.35 (0.76-1.94)	0.70 (0.68-0.73)	0.87 (0.76-0.89)
Females	1	1.31 (1.29-1.33)	1.27 (0.77-1.77)	0.70 (0.68-0.72)	0.75 (0.65-0.77)
Liver and IHBD					
Males	1	1.57 (1.54-1.60)	2.02 (1.23-2.81)	1.52 (1.48-1.56)	1.57 (1.39-1.60)
Females	1	1.35 (1.31-1.39)	2.29 (1.66-2.93)	1.46 (1.41-1.52)	1.67 (1.42-1.72)

API, Asian American and Pacific Islanders
AI/AN, American Indian and Alaska Natives

Congressional district death rates

Overall Cancer Death Rates by Congressional District in the US (2014-18)





Islami et al.
CA Cancer J Clin 2022, 72: 112-143

Health disparity causes

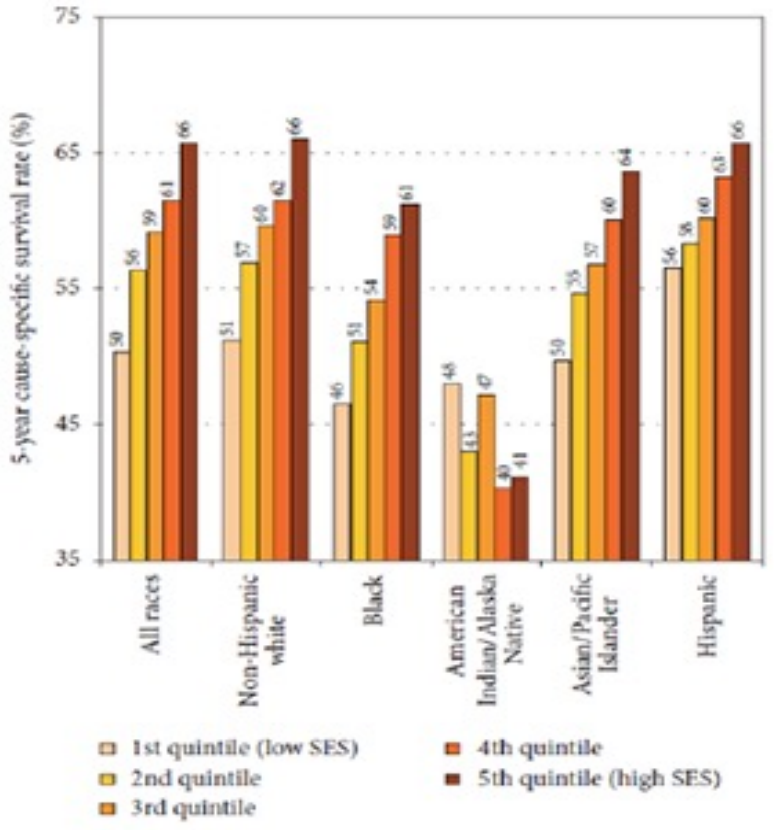
Causes of Cancer of Health Disparities

Cancer Health Disparity = Health Care Disparity

- Income and education influence health insurance coverage and access to appropriate early detection, treatment and palliative care
- Socioeconomic factors influence exposure to cancer risk factors: tobacco use, poor nutrition, physical activity, and obesity
- Poor and minority communities are targeted by tobacco companies and fast food restaurants, and have fewer opportunities for healthy nutrition and physical activity
- Cultural factors influence health behavior, attitudes toward disease, and choice of treatment
- Racial discrimination in health care settings is delaying treatment

Cancer survival by race/ethnicity

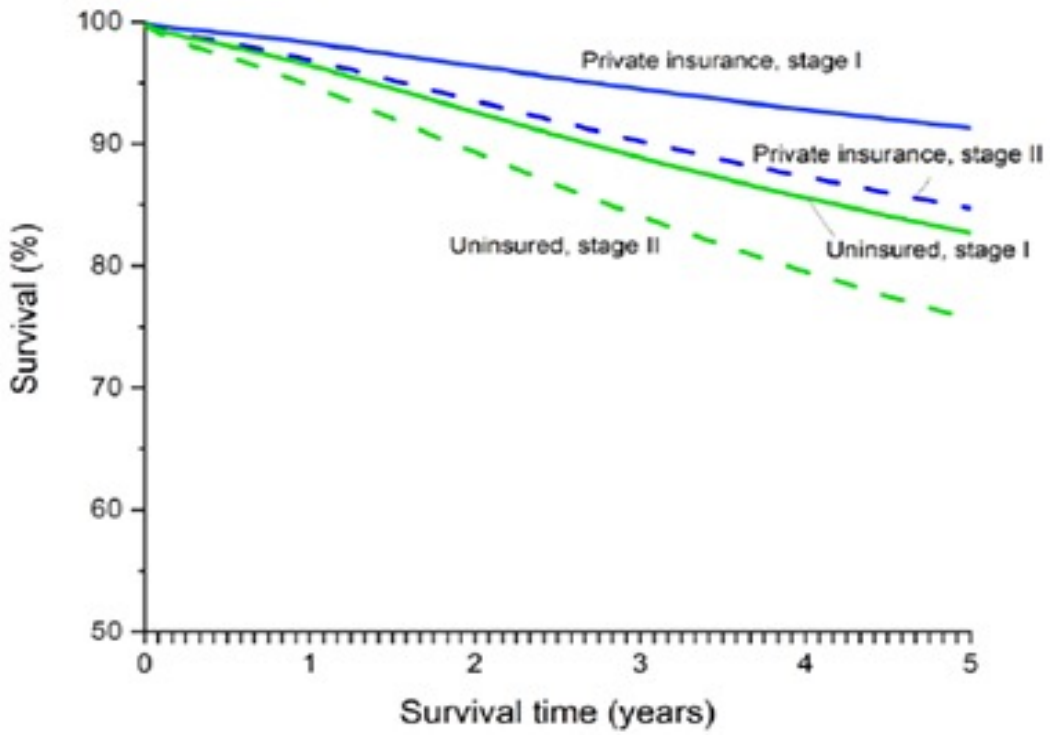
Five-Year Cancer Survival Rate for all Cancer Sites Combined by Sensus Tract Socioeconomic Index and Race/Ethnicity



Singh & Jemal, J Environ & Public Health 2017, ID 2819372

Colon cancer survival by insurance status

Disparities in Colorectal Cancer Survival by Insurance Status

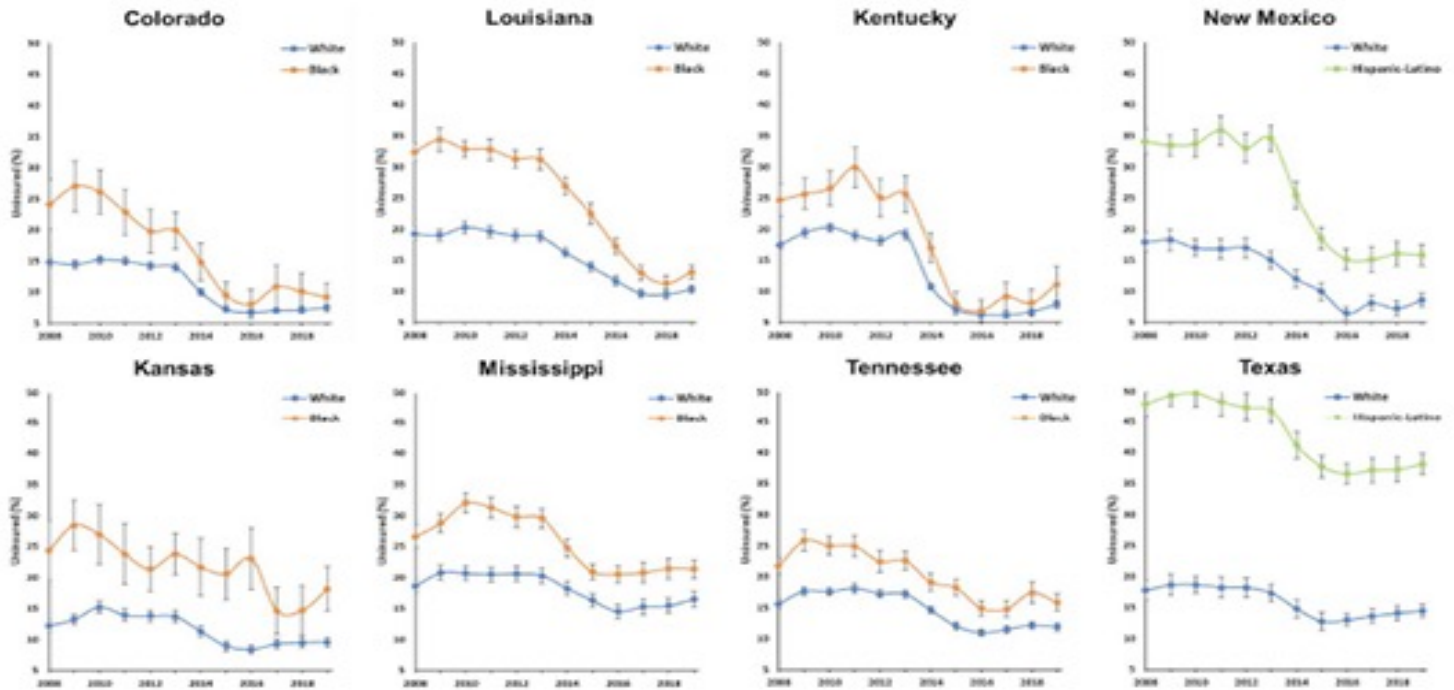


Miller et al., CA Cancer J Clin 2022, 72: 409-436

Cancer survival and Medicaid

Trends in Proportion of Individuals with no Health Insurance in Medicaid Expansion States (top) and Non-Expansion States (2008-2019)

Impact of Affordable Care Act (signed into law in 2010)

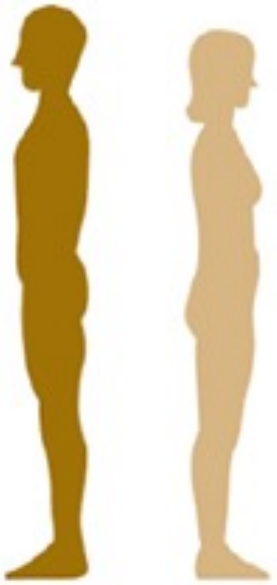


Islami et al.
CA Cancer J Clin 2022;72: 112-143

Cancer survivors

Estimated Number of US Cancer Survivors by Disease Location (for 2022)

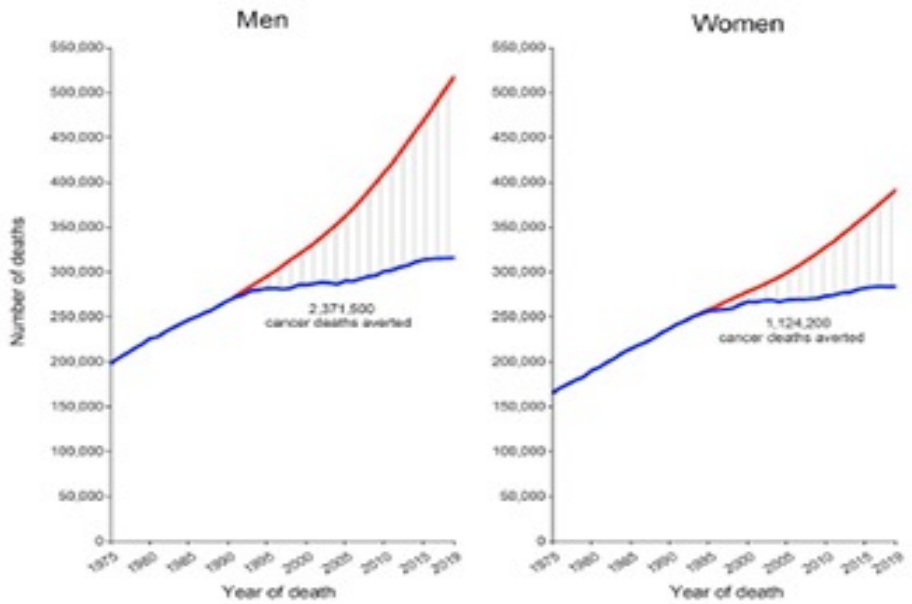
Male		Female	
Prostate	3,523,230	Breast	4,055,770
Melanoma of the skin	760,640	Uterine corpus	891,560
Colon & rectum	726,450	Thyroid	823,800
Urinary bladder	597,880	Melanoma of the skin	713,790
Non-Hodgkin lymphoma	451,370	Colon & rectum	710,670
Kidney & renal pelvis	376,280	Non-Hodgkin lymphoma	394,180
Oral cavity & pharynx	311,200	Lung & bronchus	367,570
Testis	303,040	Uterine cervix	300,240
Leukemia	300,250	Ovary	246,940
Lung & bronchus	287,050	Kidney & renal pelvis	230,960
All sites	**8,321,200**	**All sites**	**9,738,900**



Cancer averted deaths

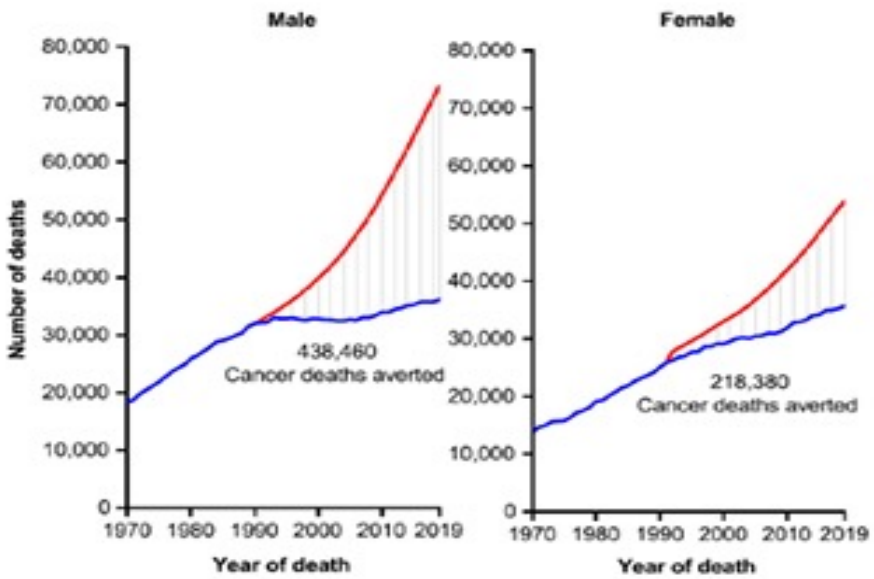
Number of Cancer Deaths Averted for Men and Women in the US

Whole Population



Siegal et al.
CA Cancer J Clin 2022;72: 112-143

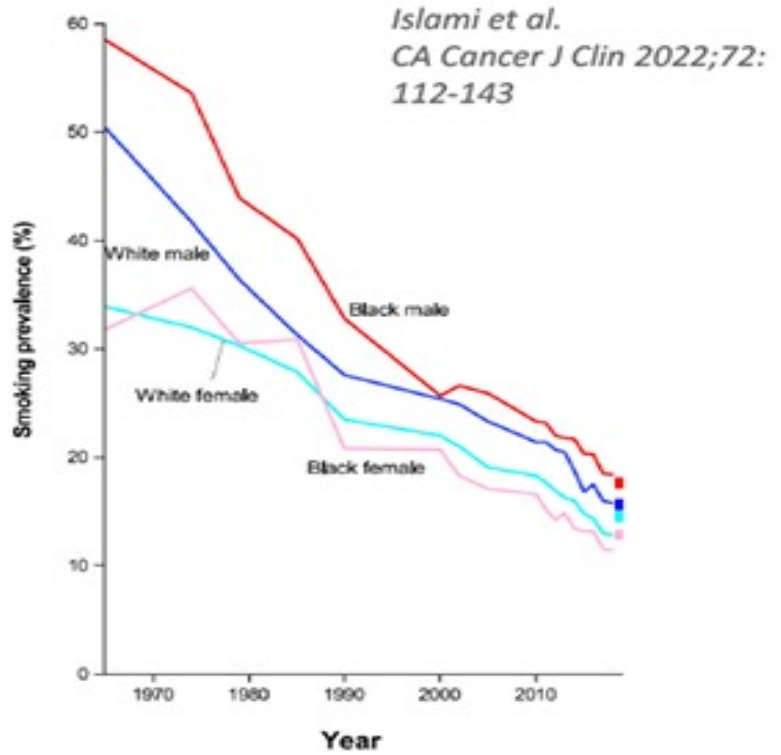
African Americans

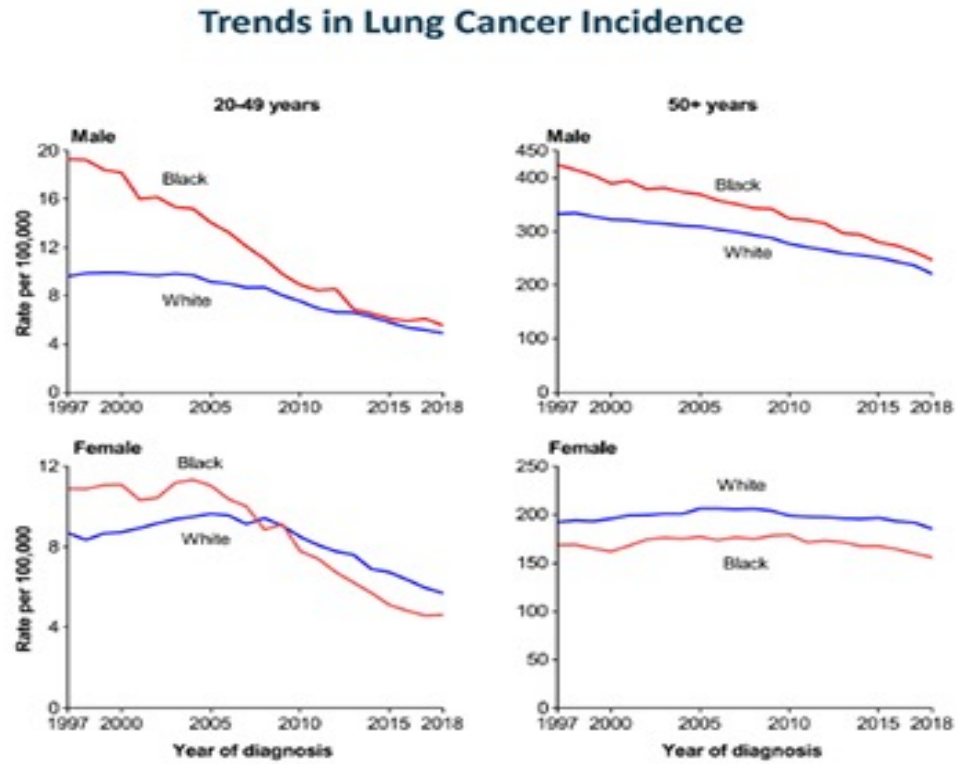


Giaqunito et al.,
CA Cancer J Clin 2022, 72: 202-29

Smoking prevalence

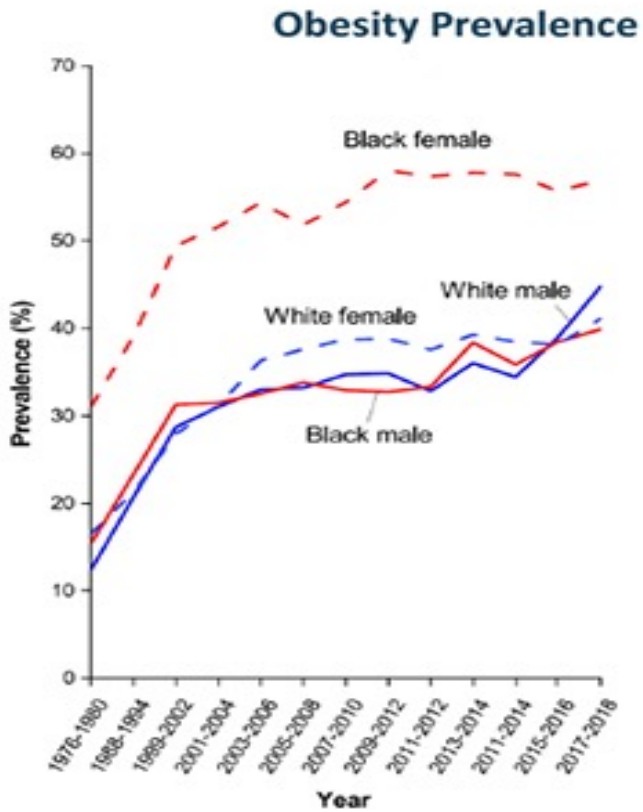
Trends in Adult Smoking Prevalence among US African Americans and European Americans





Obesity

Adult Obesity Prevalence and Participating in Screening among African Americans and European Americans

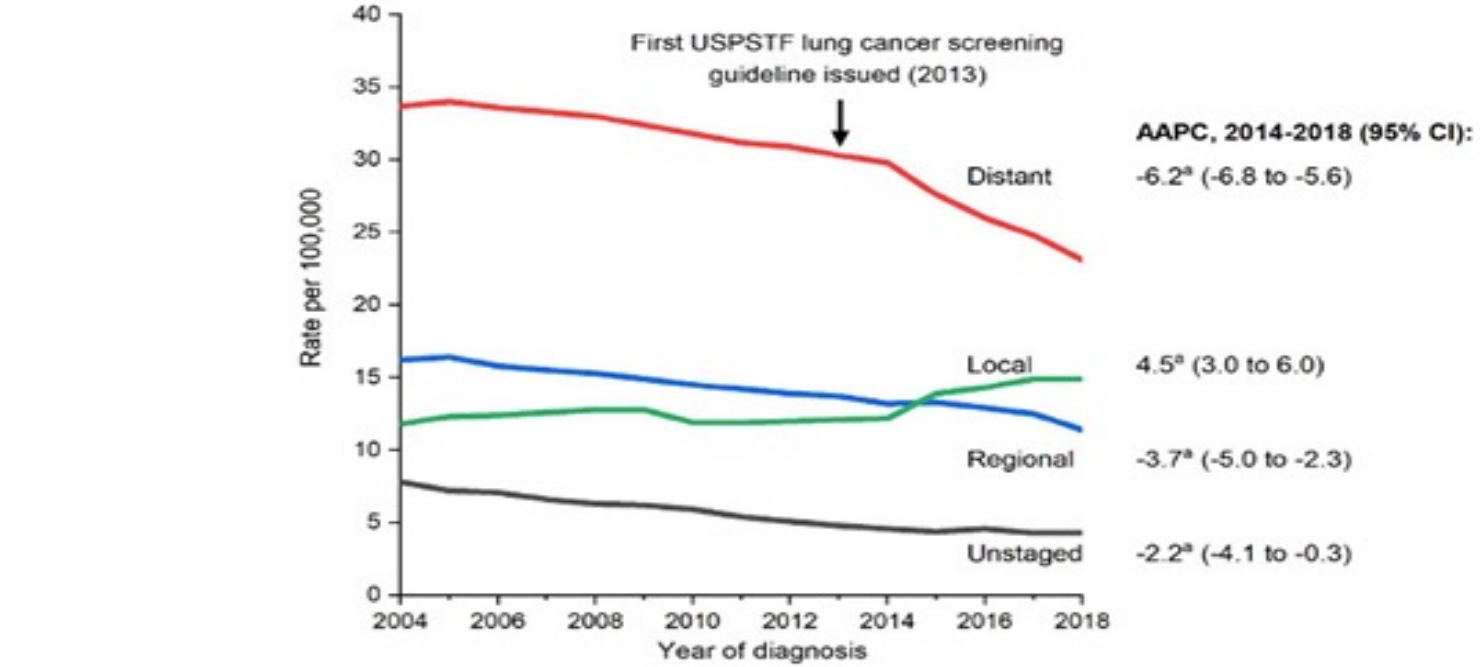


	BLACK	WHITE
HPV vaccination (youth 13-17 years)		
Females		
≥1 dose	72	71
Up-to-date[a]	53	54
Males		
≥1 dose	72	66
Up-to-date[a]	55	49
Breast cancer screening		
Up-to-date (women ≥45 years)[b]	66	64
Mammogram within the past 2 years (women 50-74 years) (USPSTF guidelines)	74	73
Cervical cancer screening (women 25-65 years)		
Up-to-date[c]	88	86
Colorectal cancer screening[d]		
Adults ≥50 years	65	68
Males	64	69
Females	66	66
Adults ≥ 45 years	57	58
Males	58	59
Females	57	57
Prostate-specific antigen test (men ≥50 years)[e]		
Within the past year	33	37

Giaquinto et al., CA Cancer J Clin 2022, 72: 202-29.

Lung cancer

Trends in Lung Cancer Incidence Rates by Stage at Diagnosis and the Potential Impact of Low-Dose Computed Tomography (LDCT)



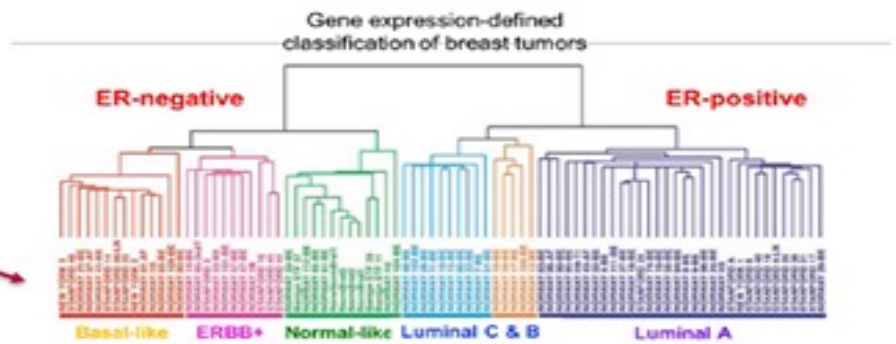
Siegal et al.
CA Cancer J Clin 2022;72: 112-143

Breast cancer

Is Biology Contributing to Cancer Health Disparities? Example: Breast Cancer

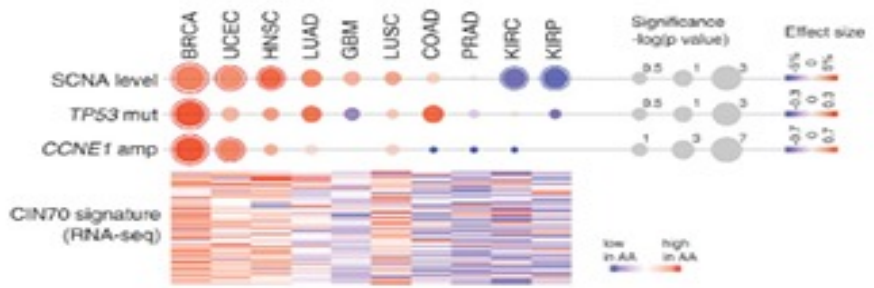
- **Race/ethnic disparity in prevalence of estrogen receptor (ER)-negative and triple-negative breast cancer in the US** *(Carey et al., JAMA 2006, 295: 2492 – 2502)*
- **Breast cancer patients in West Africa commonly present with high grade and triple-negative disease** *(Huo et al., JCO 2009, 27: 4514 – 21)*

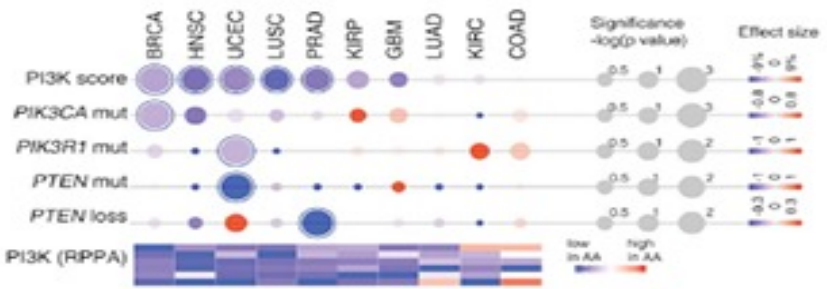
Most common among women of African descent



Genomic alterations

Differences in the Prevalence of Genomic Alterations in Tumors between Patients of African and European Ancestry





SNCA: somatic copy-number alterations
CIN70: 70 genes chromosomal instability signature

BRCA: breast cancer
UCEC: endometrial cancer
HNSC: head & neck cancer
LUSC & LUAD: lung cancer
GBM: glioblastoma
COAD: colon cancer
KIRC: kidney cancer, clear cell
KIRP: kidney cancer, papillary cell

Yuan et al. Cancer Cell, 2018, 34: 549-560

Recombination deficiency

CCR Publication

ARTICLES
https://doi.org/10.1038/s43018-019-0009-7
nature cancer

Higher prevalence of homologous recombination deficiency in tumors from African Americans versus European Americans

Sanju Sinha[1,2,3,5], Khadijah A. Mitchell[1,5], Adriana Zingone[1], Elise Bowman[1], Neelam Sinha[2,4], Alejandro A. Schäffer[2], Joo Sang Lee[2], Eytan Ruppin[2] and Brid M. Ryan[1*]

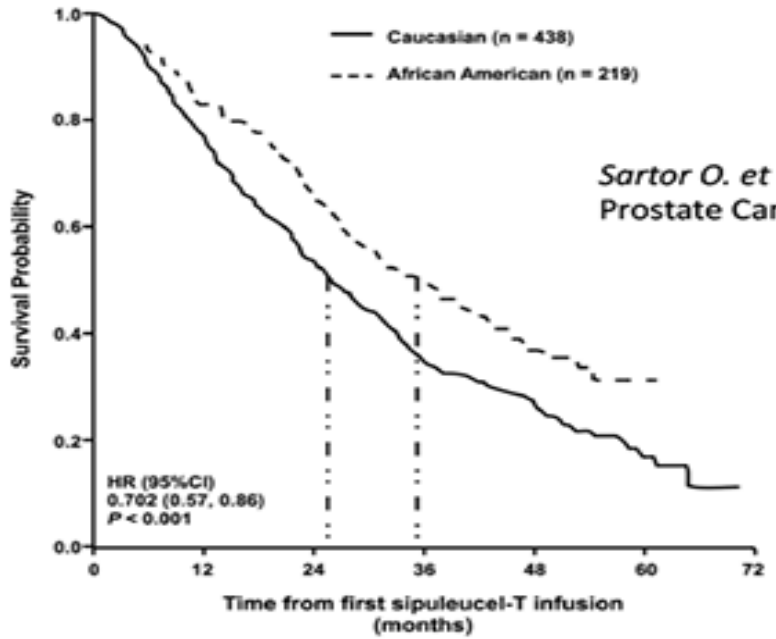
To improve our understanding of longstanding disparities in incidence and mortality in lung cancer across ancestry, we performed a systematic comparative analysis of molecular features in tumors from African Americans (AAs) and European Americans (EAs). We find that lung squamous cell carcinoma tumors from AAs exhibit higher genomic instability—the proportion of non-diploid genome—aggressive molecular features such as chromothripsis and higher homologous recombination deficiency (HRD). In The Cancer Genome Atlas, we demonstrate that high genomic instability, HRD and chromothripsis among tumors from AAs is found across many cancer types. The prevalence of germline HRD (that is, the total number of pathogenic variants in homologous recombination genes) is higher in tumors from AAs, suggesting that the somatic differences observed have genetic ancestry origins. We also identify AA-specific copy-number-based arm-, focal- and gene-level recurrent features in lung cancer, including higher frequencies of *PTEN* deletion and *KRAS* amplification. These results highlight the importance of including under-represented populations in genomics research.

Better survival with Sipuleucel T

Better Survival of African-American than European-American Men with Metastatic Prostate Cancer when Treated with the Sipuleucel T Cancer Vaccine

Outcome from Proceed trial/registry: 1902 patients [221 African-American (AA)] with metastatic castration-resistant prostate cancer received ≥ 1 Sipuleucel infusions with long-term follow up.

Adaptive immunotherapy:
Activated dendritic cells that recognize the prostate cancer antigen, prostatic acid phosphatase, are reinfused into patients.



Sartor O. et al.,
Prostate Cancer Prostatic Dis. 2020, 23:517-526

NSCLC

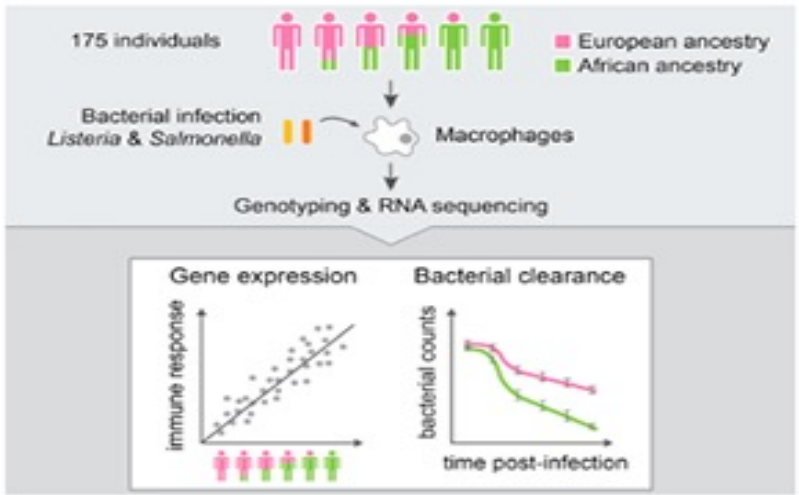
Race/Ethnicity-Related Differences in Survival Among Advanced-Stage Non-Small Lung Cancer Patients who Received Immunotherapy

Gupta et al.
J Immunotherapy 2022, 45: 132-137

Genetic ancestry

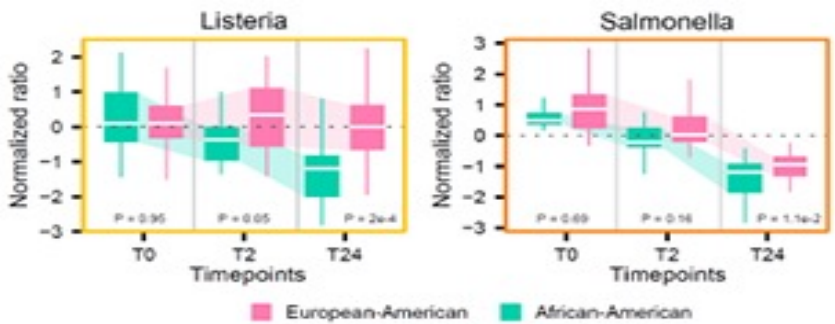
Genetic Ancestry and Natural Selection are Drivers of Population Differences in the Immune Response to Pathogens

Nédélec et al. (Barreiro lab), Cell 2016, 167: 657-69



CD14-positive blood monocytes were differentiated into macrophages

- ~ 10% of macrophage-expressed genes show ancestry-associated differences in the gene regulatory response to infection
- African ancestry predicts a stronger inflammatory response and reduced intracellular bacterial growth
  - Large proportion of response genes is under genetic control



Research priority

Research Priority

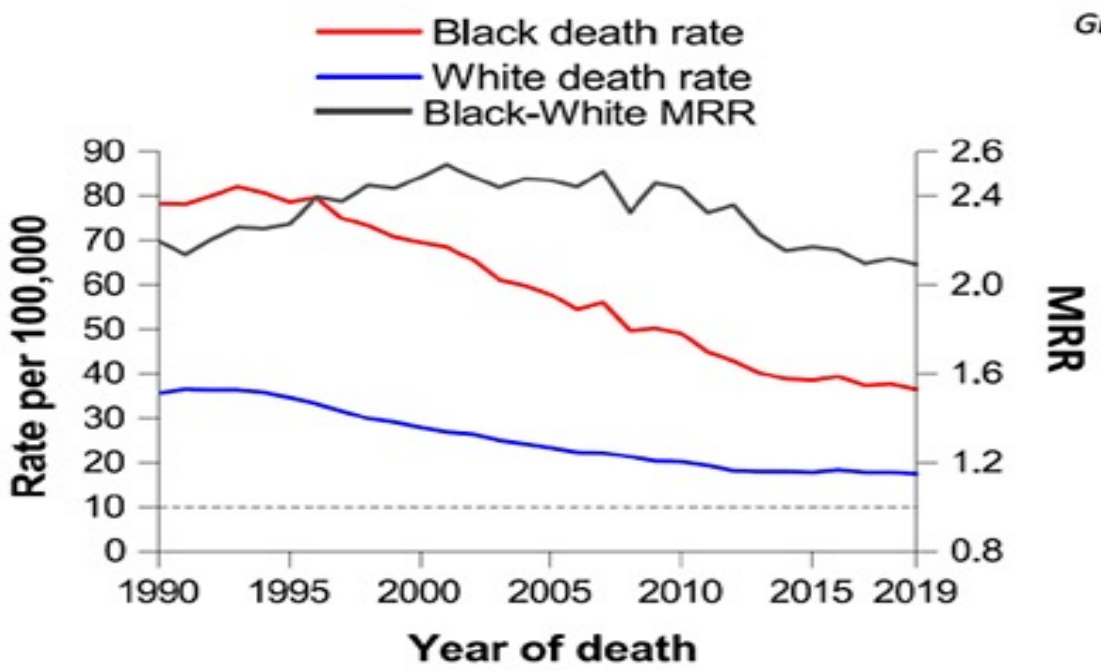
We seek an increased understanding of the causes for the survival health disparity in prostate and breast cancer between African American and European American men and women

- Key approaches are the analysis of tumor biology and the investigation of candidate risk factors

Mortality disparity

Mortality Health Disparity for Prostate Cancer in the United States

African-American (or black/AA) versus European-American (or white)

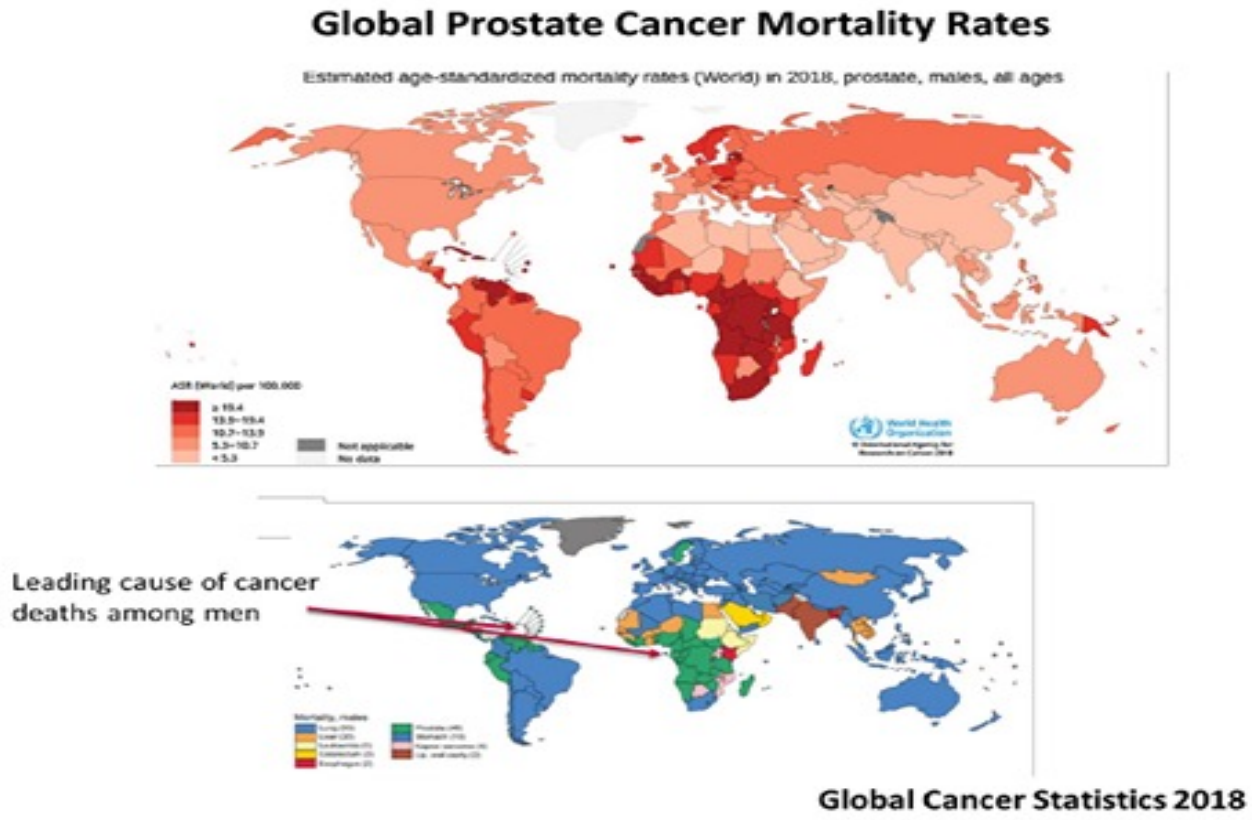


Giaquinto et al, CA Cancer J Clin 2022

MRR = Mortality Rate Ratio
2-fold excess risk among AA

Prostate cancer

Global Burden of Prostate Cancer

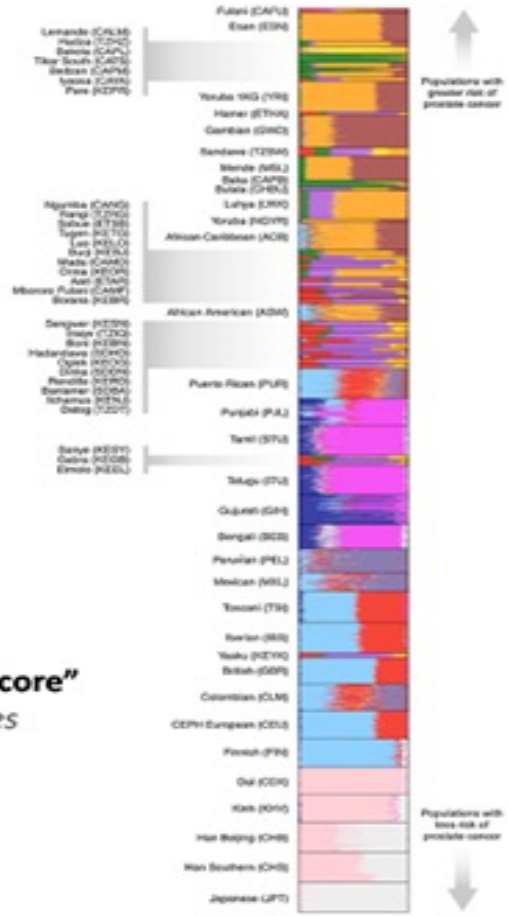


Genetic ancestry

Ranking of Prostate Cancer Risk by Genetic Ancestry

- **Admixture mapping identifies 8q24 as a locus of increased risk for African-American (AA) men to develop prostate cancer** *(Freedman et al., PNAS 2006, 103: 14068 – 73)*
  - Risk alleles are more common among AA men, conferring the highest population attributable risk among men of African ancestry (*Nat Genet 2007, 39: 638 – 44 & 954 – 6*)

→ West African ancestry confers an increased risk of prostate cancer

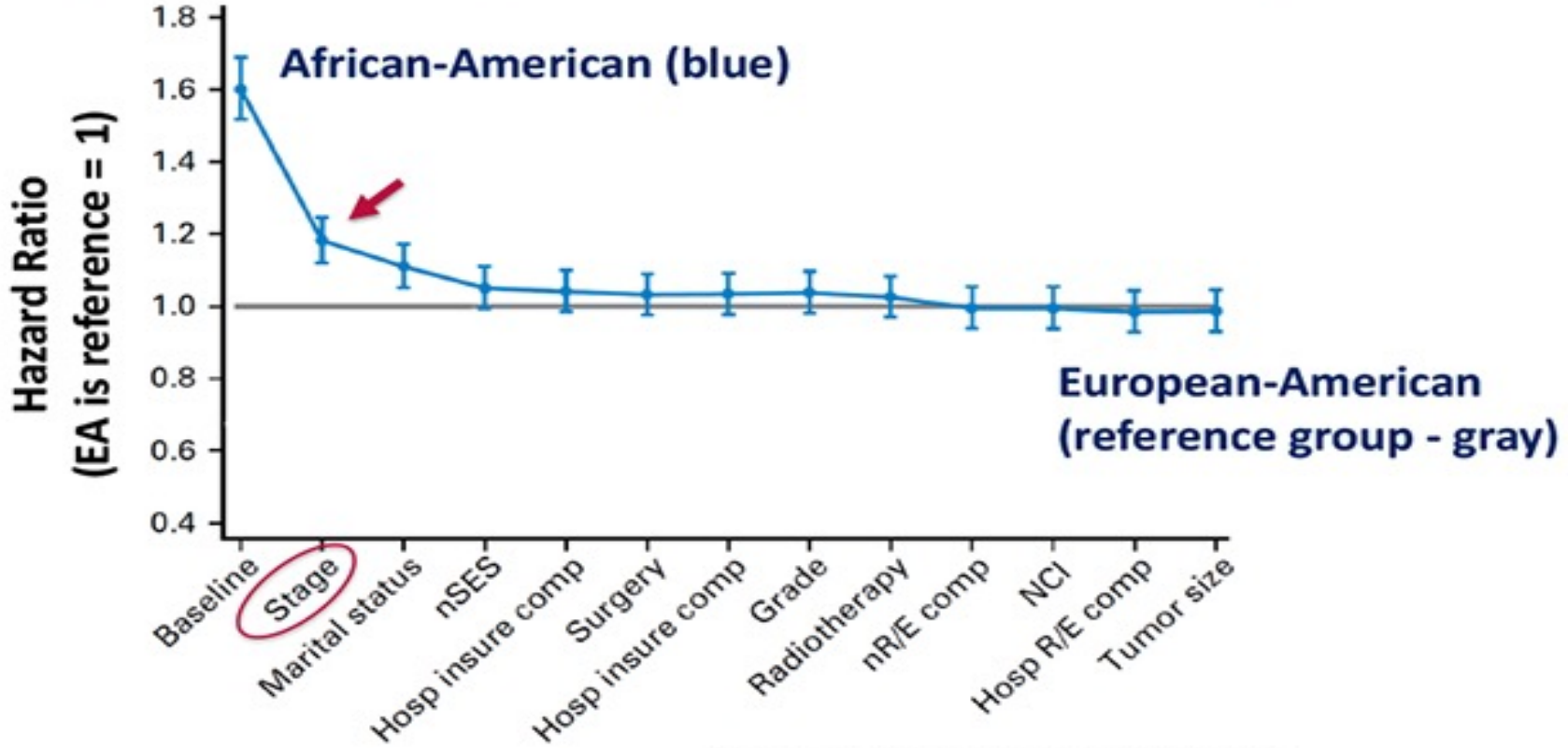


"Genetic Ancestry Risk Score"
Lachance et al. Cancer Res 2018, 78: 2432 – 43

Causes of disparity

Causes of the Prostate Cancer Survival Health Disparity

Advanced stage disease among African-American men is a key driver



Ellis et al. (S. Gomez), JCO 2018, 36: 25-33
California Cancer Registry data

Advanced stage disease

What is the Cause of the Prominent Role of Advanced Stage Disease in the Survival Health Disparity?

- Access to health care leading to a delayed diagnosis
- Aggressive tumor biology in African-American men

Interferon signature

A Prevalent Immune-Inflammation and Interferon Signature in Prostate Tumors of African-American Men

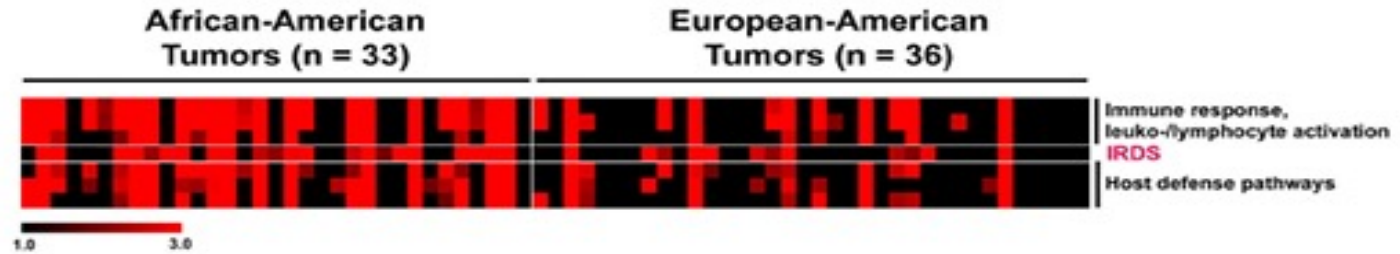
Inflammation Signature reported by us: *Wallace….Ambs, Cancer Res 2008, 68: 927– 36*

Up-regulated in African-Americans

- *IFNγ, INDO, PTPN22, STAT1*
- *CCL4, CCL5, CCL8, CCL19, CXCL9, CXCL11, CXCR4, CCR7*
- *IL-15 & 16*
- *ISG15, ISG20, IFI16, IFI27, IFI44 & 44L, IFIT1, IFIT3, IFITM(1/2/3), IRF1 & 8*
- *MX1 & 2, OAS1 & 2, OASL*
- *TAP1 & 2*

Many are viral infection response genes

"Viral Mimicry" Signature

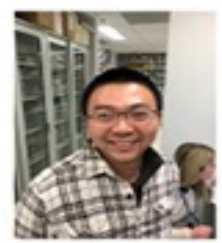


Interferon Signature(s)	AA	EA	Permutated *P* value*	FDR (%)*
Interferon-related DNA damage resistance signature (IRDS)	22/33 (67%)	12/36 (33%)	1.6×10^{-4}	3.7

Ming Yi, ABCC-NCI, using Pathway-level Comparative Analysis

IRDS signature
- *Weichselbaum et al., PNAS 2008, 105: 18490-5*

Wei Tang

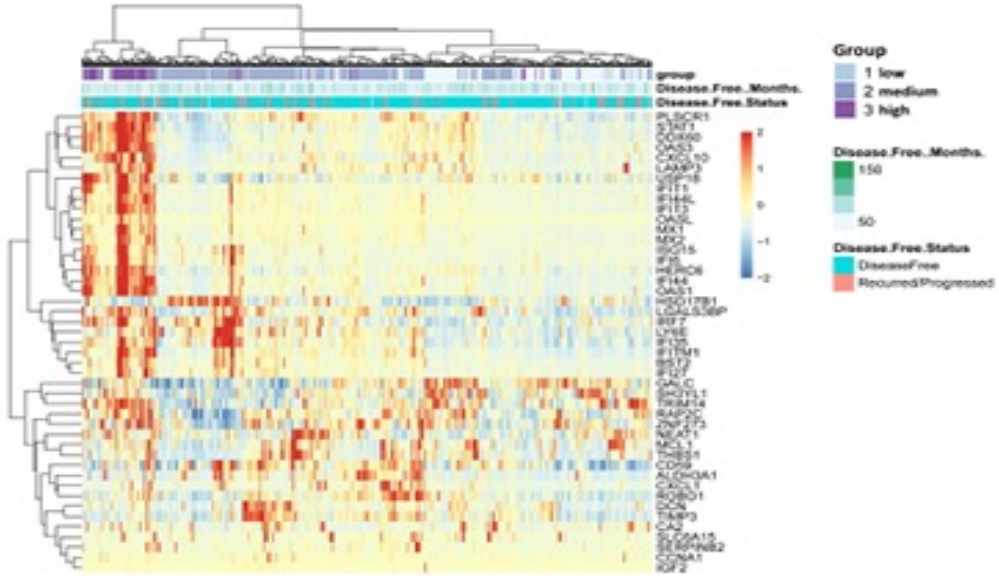


Tang et al., Clin Cancer Res. 24, 5471-81, 2018

Interferon and disease recurrence

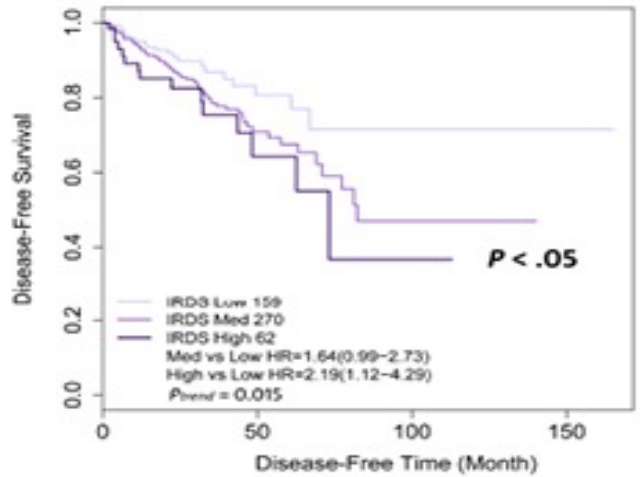
Interferon Signature (IRDS) is Associated with Early Disease Recurrence in the TCGA Prostate Cancer Cohort

Expression of 45 IRDS genes identifies prostate tumors with low (159), medium (270), and high (62) expression of this signature. TCGA cohort (n = 491): mainly European-American men



The Cancer Genome Atlas (TCGA) dataset

High IRDS expression in prostate tumors is associated with decreased disease-free survival



Tang et al., Clin Cancer Res. 24, 5471-81, 2018

Clinical implication

Clinical Implication of the Interferon Signature

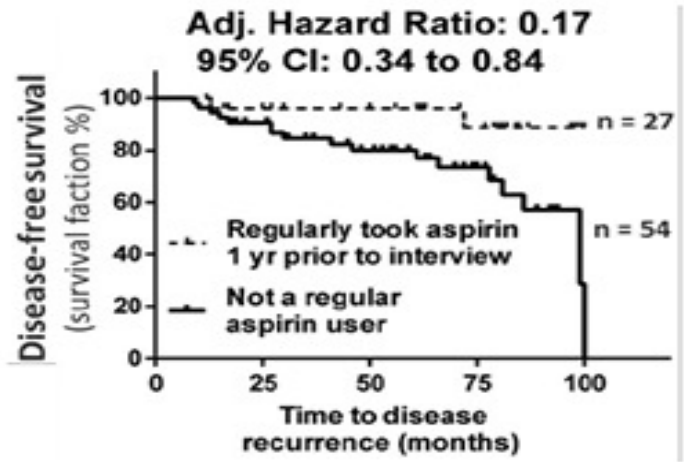
- **Tumors with an interferon-stimulated gene (ISG) signature are highly susceptible to inhibition of adenosine deaminase acting on RNA (ADAR1) (*Gannon et al., Nature Communications 2018, 9: e5450; Liu et al., Nature Medicine 2019, 25: 95-102*)**

ADAR1 function: RNA A-to-I editing by ADAR1 has been proposed to prevent cytoplasmic RNA sensors of the innate immune system, such as MDA5 and PKR, from erroneously recognizing endogenous dsRNA as foreign. ADAR1 loss: leads to an aberrant interferon response.

Aspirin

Aspirin Use May Prevent Advanced Disease and Disease Recurrence in African-American Men

- **Increased disease-free survival among African-American aspirin users in NCI-Maryland Prostate Cancer Study**
  - *Smith et al., Cancer Epidemiol. Biomarkers Prev. 2017, 26: 845-53*
- **Decreased prostate cancer mortality among African-American aspirin users in Southern Community Cohort Study**
  - *Tang et al., Cancer Epidemiol. Biomarkers Prev. 2021, 30: 539-544*



Precision medicine

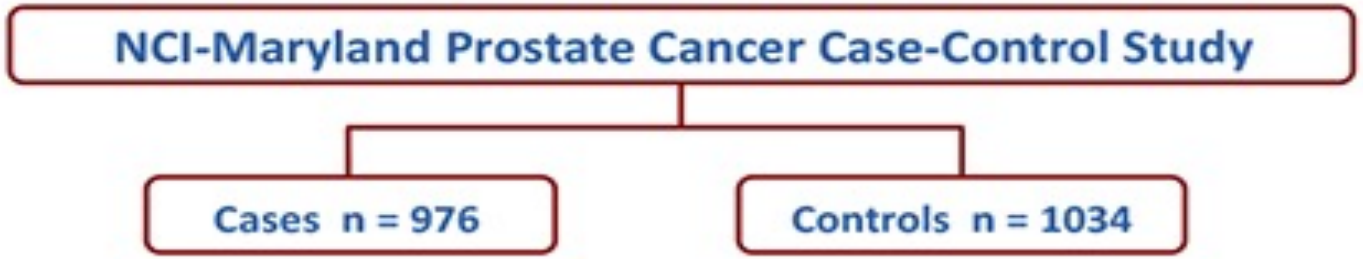
A Precision Medicine Study of How Inflammation May Underlie the Excessive Burden of Prostate Cancer in Men of African Ancestry

DoD Impact Award W81XWH-18-1-0588: Collaborative study with Clayton Yates (Tuskegee University), Michael Cook (DCEG/NCI) and the Prostate Cancer Transatlantic Consortium (CaPTC)

Hypothesis: Systemic low-grade inflammation is a prostate cancer risk factor in men of African descent, and correlates with West African ancestry and exposures, a distinct tumor biology, and aggressive disease.

Prostate cancer

Resource for the Prostate Cancer Studies

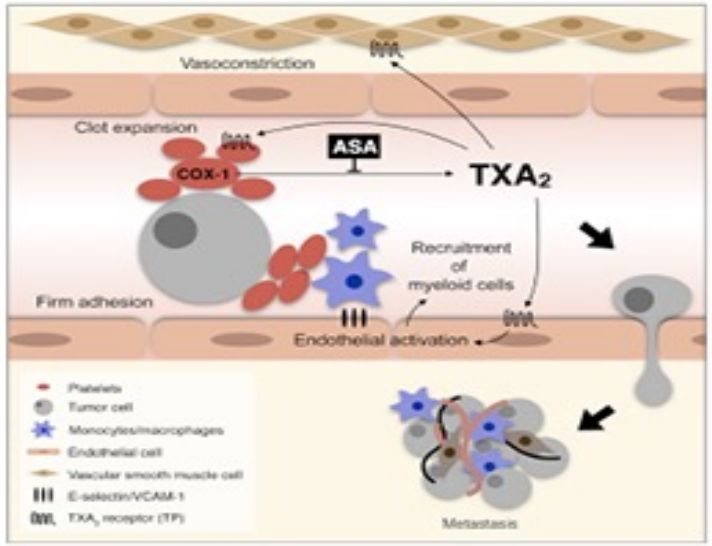


- **Comparable numbers of African-Americans and European-Americans**
  - Ancestral origin: self-reported and determined with ancestry-informative markers
- **Population-based controls**
- **Survey data, blood, urine, and fresh-frozen tumor specimens**
  - Survival follow up (disease-free, disease-specific, overall)
- **Completed National Comprehensive Cancer Network Risk Score classification for all cases**
- **Established a Neighborhood Deprivation Index for all men by linking their address to census track demographic, economic and population data** (followed *Messer et al. 2006* guidelines)

Thromboxane A2 signaling

Hypothesis: Inflammation-related Thromboxane A2 (TXA2) Signaling is Increased in African-American Patients and is a Risk Factor by Increasing Metastasis

TXA2 enhances metastasis



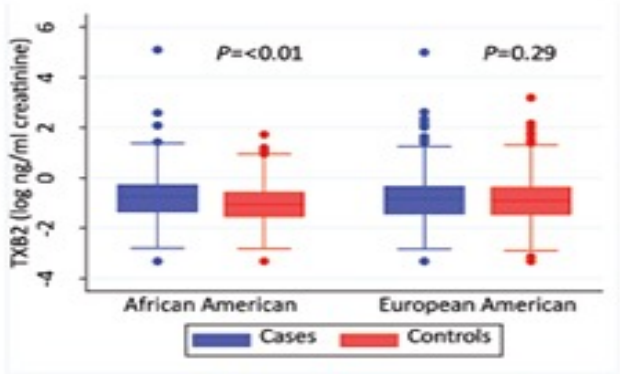
Lucotti et al., JCI 2019;129:1845-1862

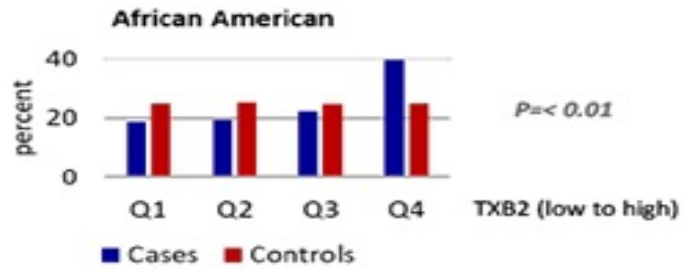
Maeve Bailey-Whyte

Measured the stable TXA2 metabolite, 11-dehydro-thromboxane B2 (TXB2), in urine samples
(collaboration with Ginger Milne, Vanderbilt U)

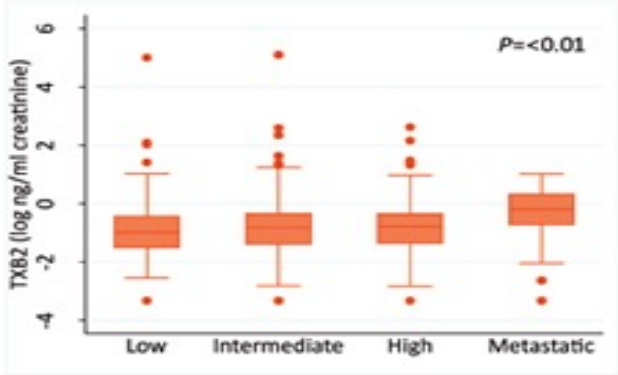
Urinary TXB2 levels

Urinary Thromboxane B2 (TXB2) Levels in African American and European American Men and Their Association with Prostate Cancer and Metastasis





Urinary TXB2 is high in men with metastatic prostate cancer



NCCN Risk Score Classification

Kiely…Ambs, JNCI, 114: djab129, *2022*

TBX2 and metastasis

High Urinary Thromboxane B2 (TBX2) Associates with Metastatic Disease in the NCI-Maryland Study

Association of high urinary TXB2 with National Comprehensive Cancer Network Risk Score for metastatic prostate cancer

NCCN Risk Score	OR (95% CI)	*P* value
Low	Ref	
Intermediate	1.49 (0.98-2.26)	0.06
High/Very High	1.34 (0.80-2.26)	0.27
Regional/Metastatic	**2.60 (1.08-6.28)**	**0.03**

High TXB2: > median

*Unconditional logistic regression adjusted for age at study entry, BMI (kg/m2), diabetes (no/yes), aspirin (no/yes), education (high school or less, some college, college, professional school), family history of prostate cancer (first-degree relatives, yes/no), self-reported race, smoking history (never, former, current), treatment (0=none, 1=surgery, 2=radiation, 3=hormone, 4=combination).

TBX2 and lethal disease

Thromboxane B2 (TXB2) associates with lethal disease in African-American men

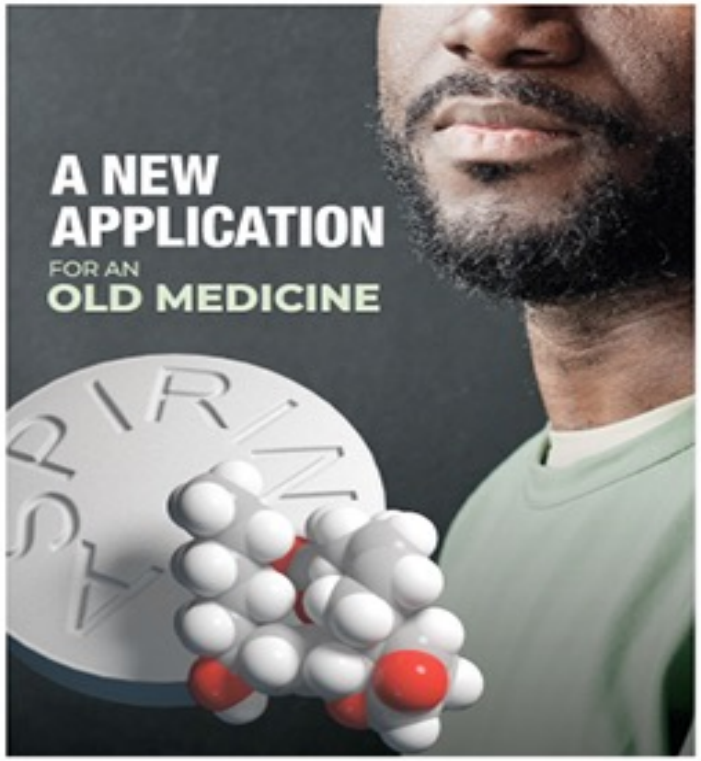
Association of urinary TXB2 with prostate cancer-specific survival		
	African-American	**European-American**
TXB2 level	HR (95% CI)	HR (95% CI)
≤ Median	Ref.	Ref.
> Median	**4.74 (1.62 -13.9)**	1.12 (0.34 -3.66)
Continuous data	**1.59 (1.07 -2.36)**	1.35 (0.90 -2.01)

Kiely…Ambs, JNCI, 114: djab129, *2022*

Conclusion

Conclusion

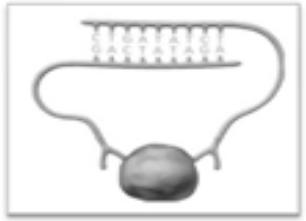
- Platelet-derived, pro-metastatic thromboxane A2 may enhance lethal prostate cancer in African American men
  - driver: systemic inflammation?



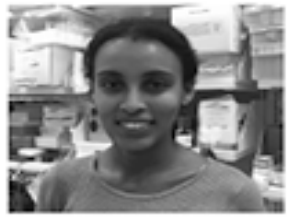
Immune markers

Analysis of Immune-Oncological Markers in Blood Samples from Ghanaian, African-American, and European-American Men

Olink technology: Excellent data for 82 of the 92 markers



Tsion Minas

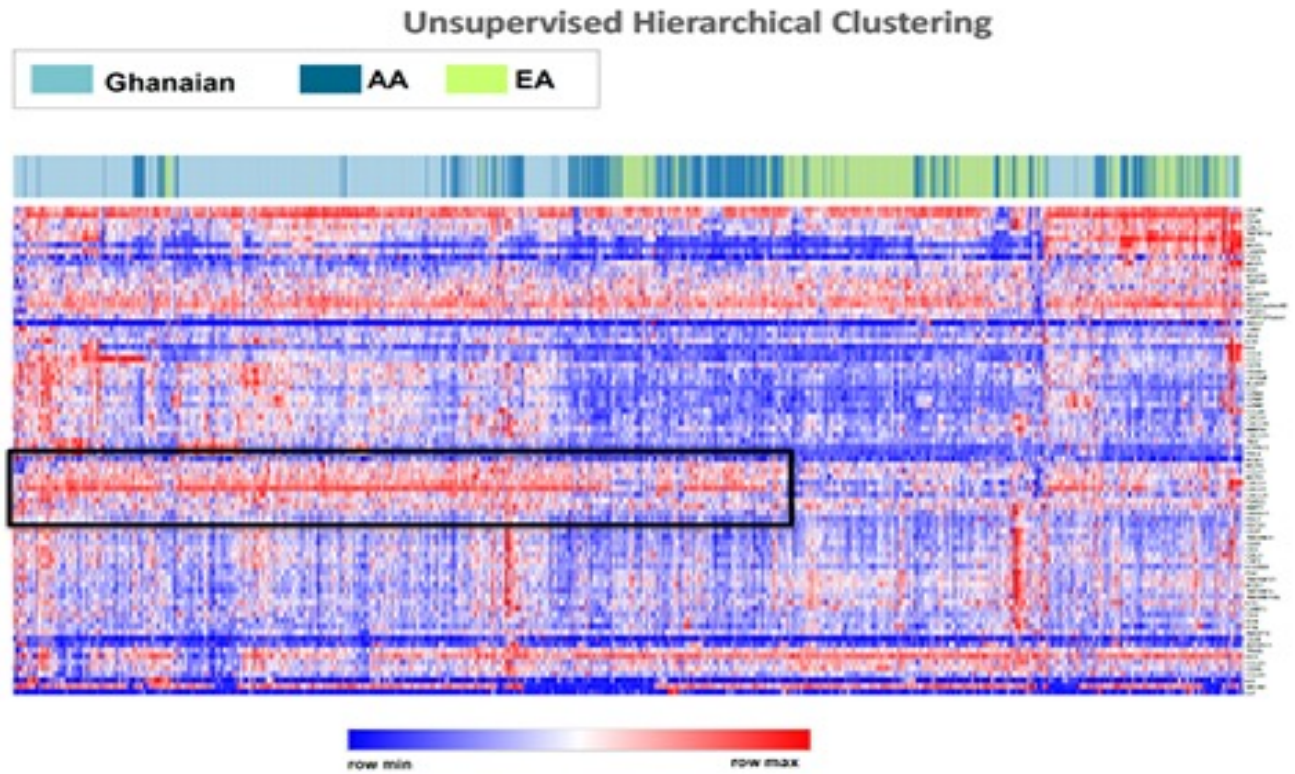


Study	NCI-MD				Ghana Prostate Study	
Race	EA		AA		Af (Ghana)	
N	879		768		1143	
	Case	Control	Case	Control	Case	Control
N	425	454	394	374	489	654
Age, mean (SD)	65.5 (8.1)	67.2 (8.3)	63.1 (7.9)	64.5 (7.8)	69.3 (10.0)	59.8 (7.1)
BMI, mean (SD)	28.0 (4.3)	27.8 (4.7)	28.0 (5.2)	29.6 (5.4)	25.6 (5.1)	24.3 (4.4)
Gleason>=8, n (%)	73 (17%)	-	67 (17%)	-	158 (32%)	-

Markers and population groups

Levels of the 82 Immune-Oncology Markers Associate with Population Groups

Ghanaian men grouped with AA rather than EA men



Healthy Volunteers

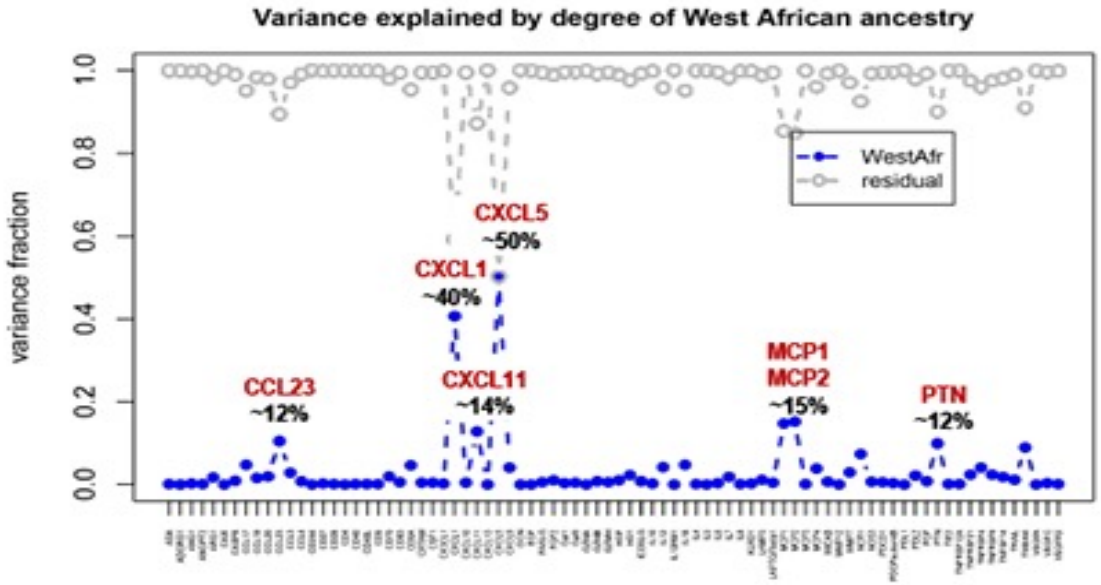
- Ghanaian **(n=654)**
- African American (AA) **(n=374)**
- European American (EA) **(n=454)**

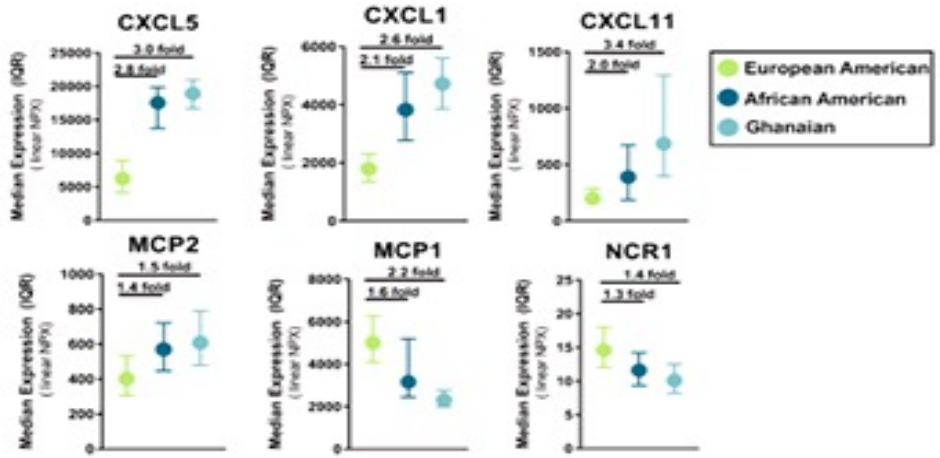
Chemokines

Levels of some Chemokines Strongly Correlate with Degree of West African Ancestry

NCI-Maryland Cohort: healthy male volunteers

African American (n=374) and European American (n=454)

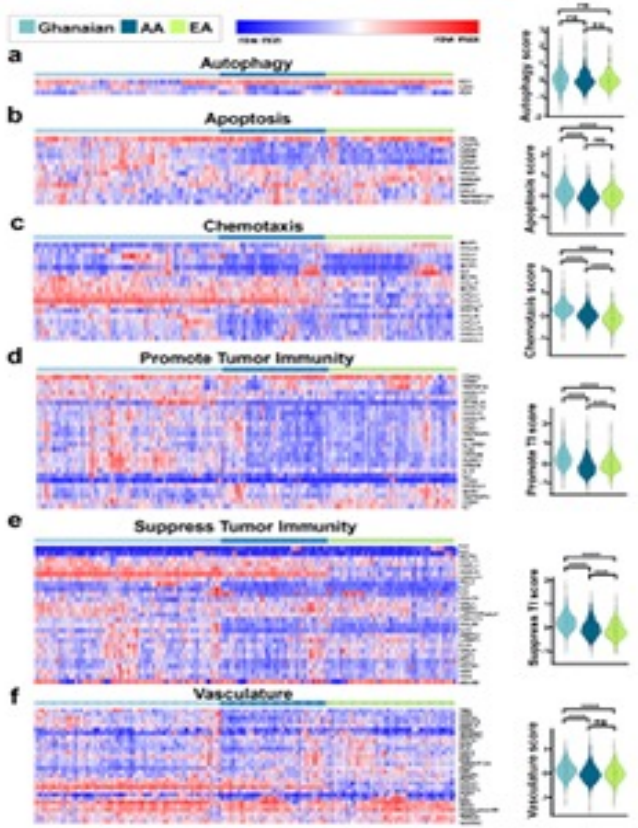


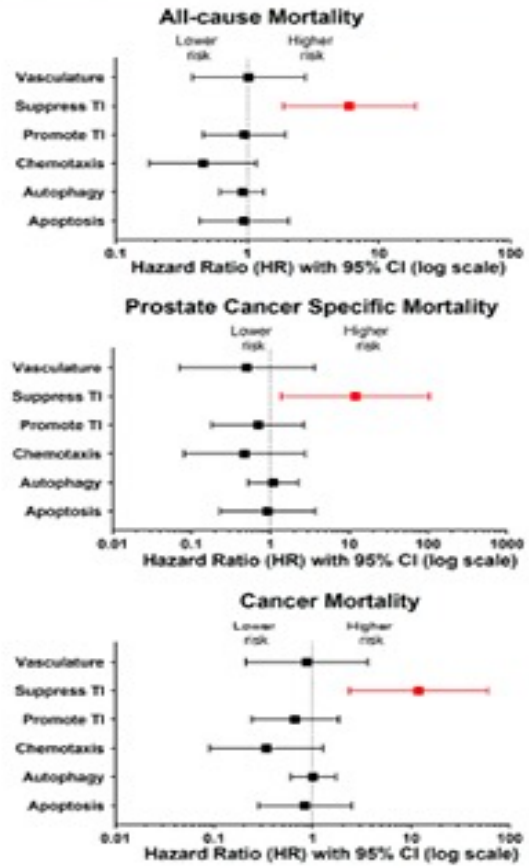


45 out of the 82 markers show some association with degree of West African ancestry;
association remained significant for 42 after stringent Bonferroni multicomparison adjustment

Tumor immunity suppression

Suppression of Tumor Immunity is Associated with Decreased Survival among Men with Prostate Cancer





Immunity score

High Suppression of Tumor Immunity Score Associates with Metastatic Prostate Cancer

Suppression of Tumor Immunity associates with National Comprehensive Cancer Network Risk Score for prostate cancer aggressiveness

NCCN Risk Score	Total OR (95% CI)*	AA OR (95% CI)*	EA OR (95% CI)*
Low	Ref	Ref	Ref
Intermediate	1.04 (0.68-1.59)	0.89 (0.46-1.70)	1.18 (0.65, 2.13)
High/Very High	1.47 (0.87-2.48)	1.33 (0.59-2.98)	1.72 (0.83, 3.54)
Regional/Metastatic	**3.79 (1.59-9.04)**	**5.90 (1.43-24.34)**	3.16 (0.95, 10.50)
***P* value for Trend**	**0.004**	**0.019**	**0.040**

Note: Bolded data indicate significant associations in the logistic regression analysis.

*Logistic regression adjusted for age at study entry, BMI (kg/m2), diabetes (no/yes), aspirin (no/yes), education (high school or less, some college, college, professional school), family history of prostate cancer (first-degree relatives, yes/no), self-reported race (not included in the stratified analysis), income (less than $10k, $10-30K, $30-60K, $60-90k, greater than $90k), smoking history (never, former, current), treatment (0=none, 1=surgery, 2=radiation, 3=hormone, 4=combination).

High suppression of tumor immunity is defined by the median score in the NCI-Maryland control population (≤ median vs. > median)

Summary

Summary

- **Our findings support the hypothesis that tumor-associated and systemic inflammation is a prostate cancer risk factor among men of African descent and promotes a distinct immune environment and disease progression**
  - **Immune environment in the circulation may increase the odds of metastasis**
  - **Signature may have both an ancestral and environmental cause (possible gene-environment interaction involving a virus, *Minas…Ambs, Commun Biol, 1: 191, 2018*)**
  - **but may lead to a favorable response to immune therapies**

- **Regular aspirin use may prevent lethal prostate cancer in African-American men**

Immune-inflammation signature

Future Studies – Origin and Impact of Immune-Inflammation Signature

- **Investigate the social and ancestral basis of prostate cancer inflammation** (82 immune-inflammation markers and arachidonic acid metabolites)
  - Neighborhood deprivation index
  - Quantitative trait locus analysis

- **Characterize the tumor biology of men with African ancestry using genomics and multiplex immunohistochemistry with spatial analysis**
  - Prostate tumors from African men – Nigeria, Kenya, South Africa

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Collaborators

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