TRACO 2026

Influence of Social, Environmental, and genetic factors to tumor biology as Contributor to Cancer Outcome Disparities

Stefan Ambs, Laboratory of Human Carcinogenesis, CCR/NCI
ambss@mail.nih.gov

I have no financial relationships to disclose

NIH NATIONAL CANCER INSTITUTE

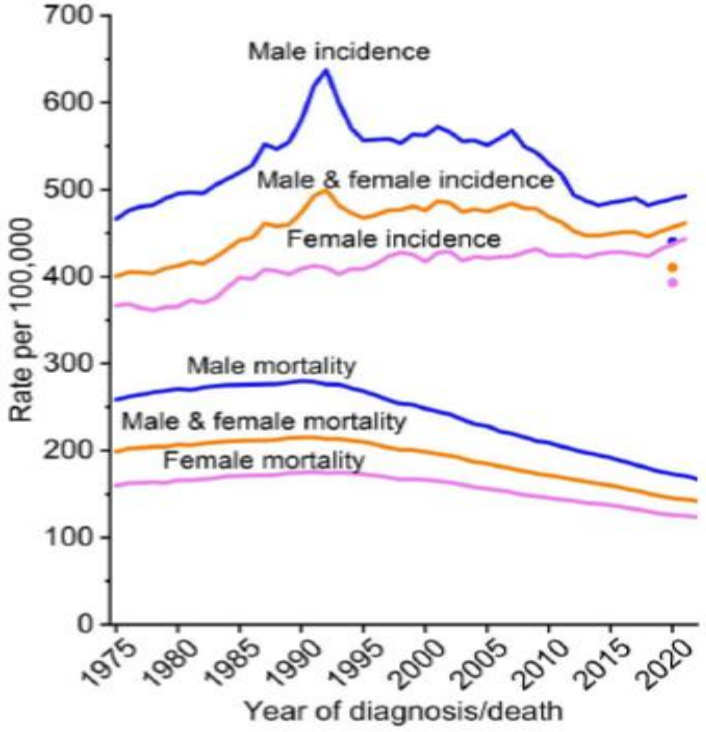
Talking points

Talking Points

- Cancer Health Disparities in US and globally
- Causes of Cancer Health Disparities
  - Society to Cell to Outcome Framework
- Our Research - Examples

US Cancer Incidence

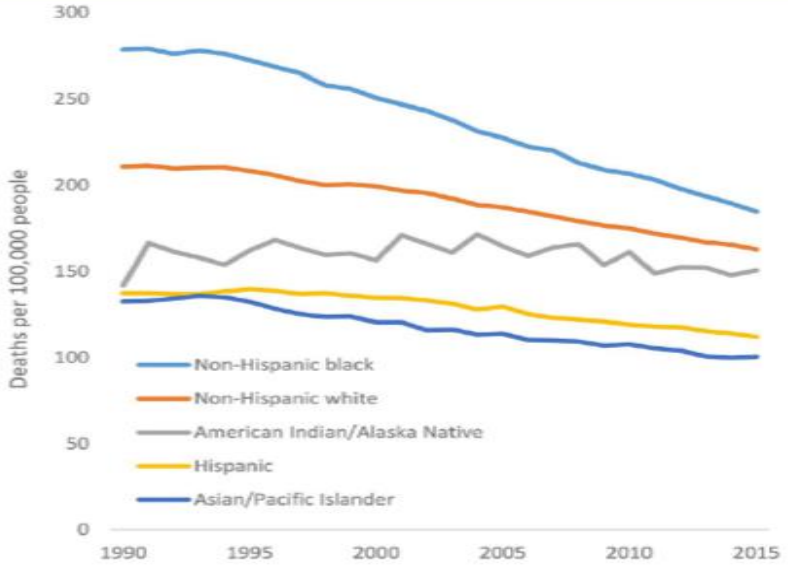
US Cancer Incidence and Mortality Rates



Siegel et al., CA Cancer J Clin. 2025; 75: 10-45

Population group

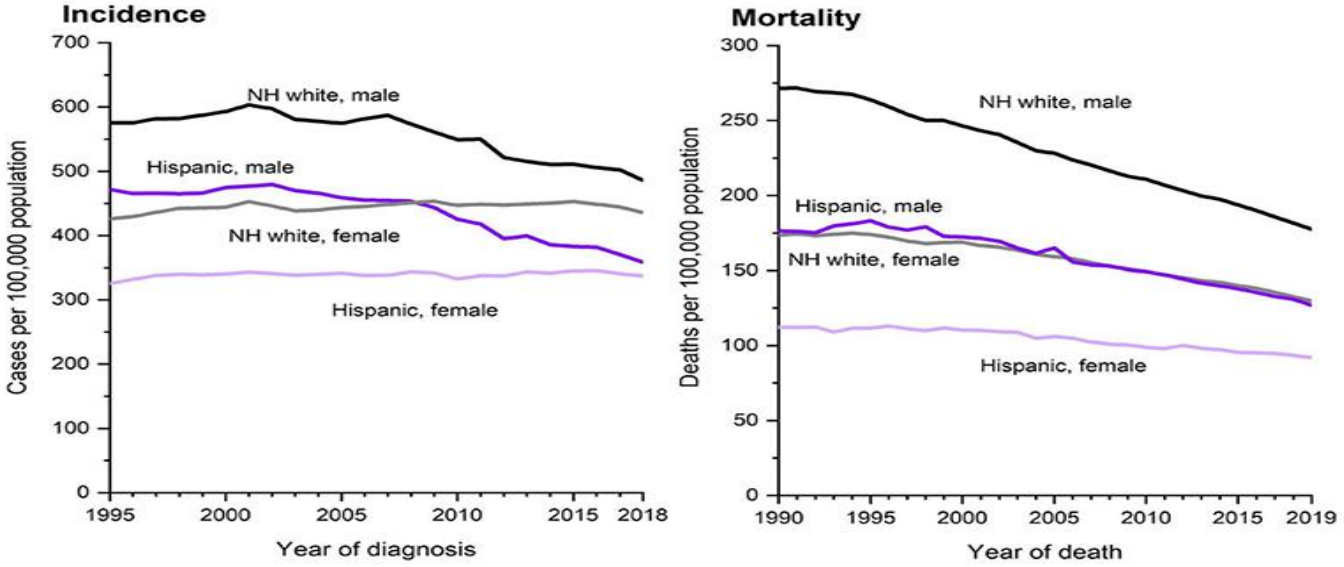
U.S. Cancer Mortality by Population Group (categorization by self-reported race/ethnicity)



Siegel et al., CA Cancer J Clin 2018, 68: 329-39

Population groups

U.S. Cancer Mortality by Population Group (categorization by self-reported race/ethnicity)

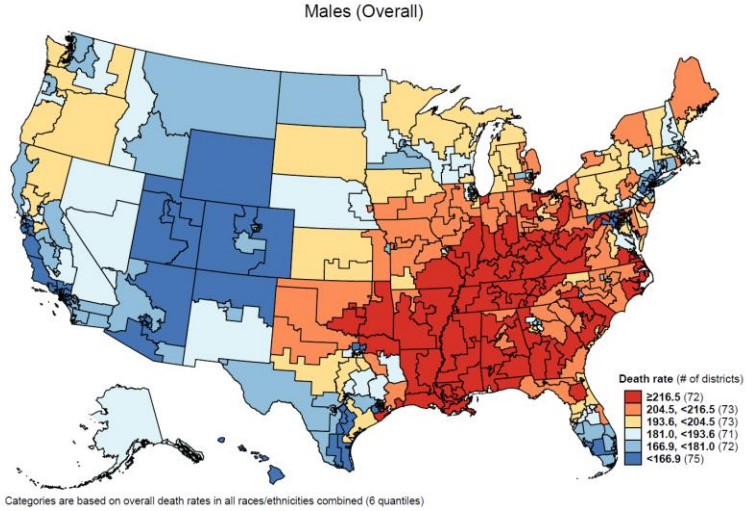


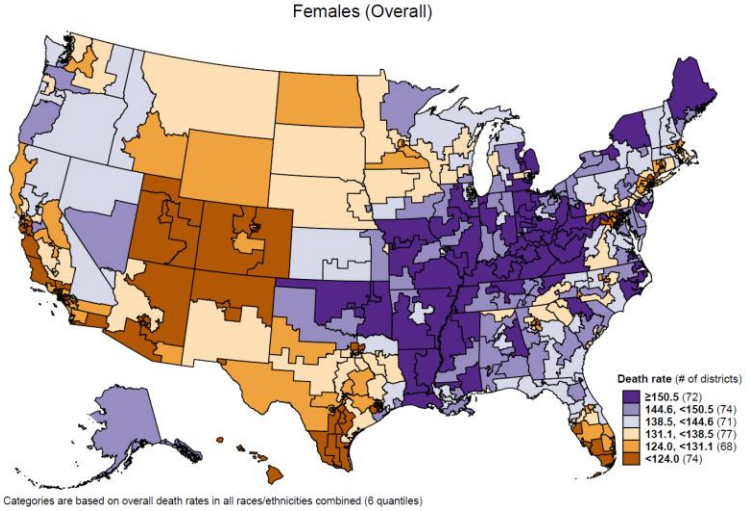
Miller et al., CA CANCER J CLIN 2021;71:466–487

Cancer Death Rates by US Congressional District

Period: 2014-18

AACR American Association for Cancer Research ANNUAL MEETING 2025 CHICAGO
APRIL 25–30 | AACR.ORG/AACR2025 | #AACR25

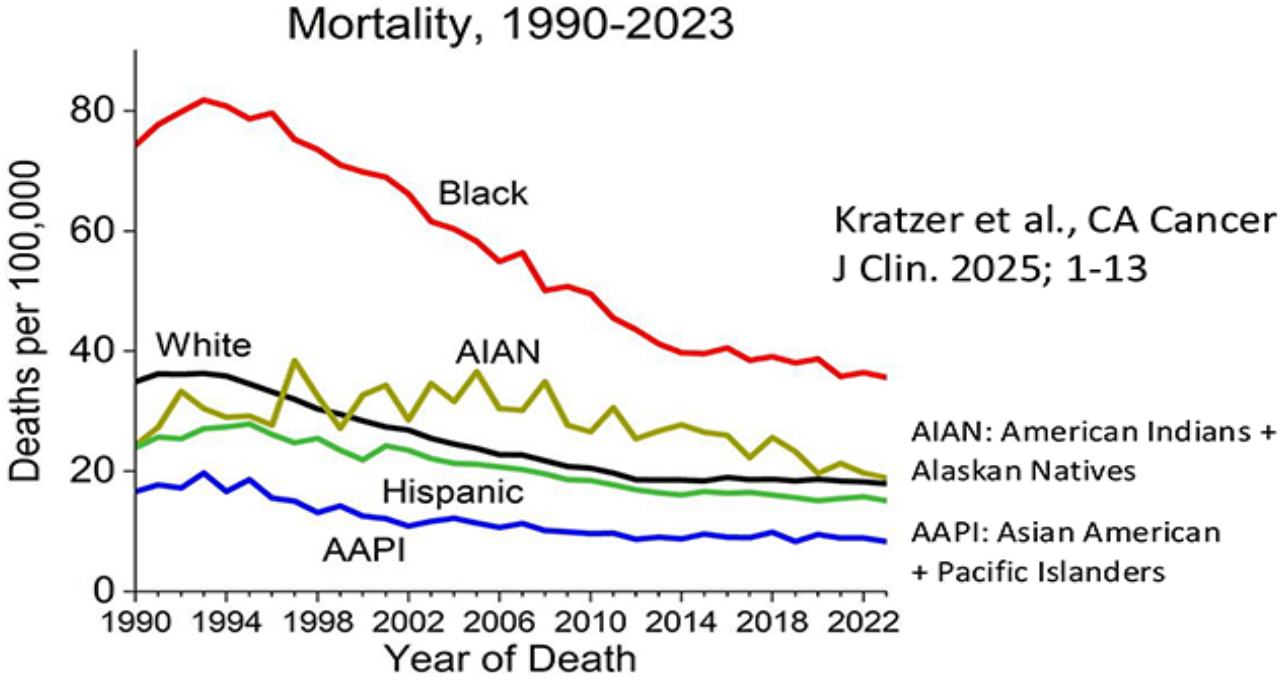




"US Cancer Belt"

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

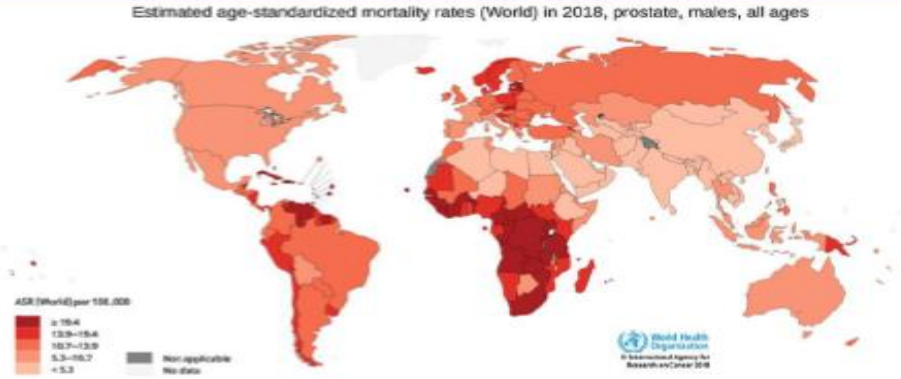
Disparities in Prostate Cancer Mortality Rates among US Population Groups



African Ancestry

Global Burden of Prostate Cancer Among Men of African Ancestry

Global Cancer Statistics 2018



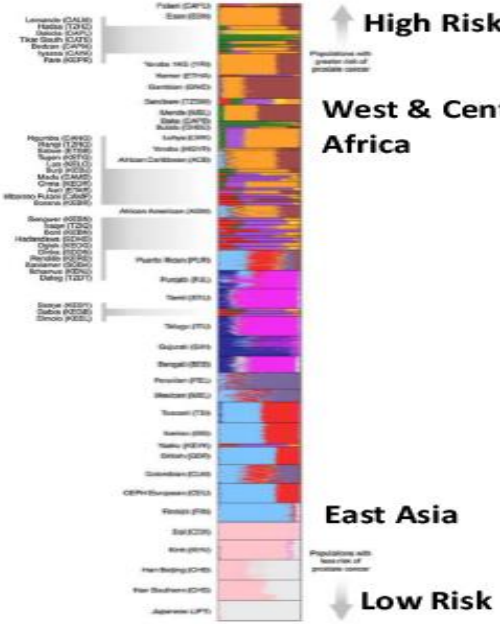
Leading cause of cancer deaths among men (of sub-Saharan African ancestry)



Prostate and breast cancer risk

African Ancestry Confers Risk of Prostate Cancer and Influences Breast Cancer Biology

Quantified genetic ancestry-inferred risk for prostate cancer
Lachance et al. Cancer Res 2018, 78: 2432 – 43



Profiles in Triple-Negative Breast Cancer Underlie Altered Tumor Biology and Clinical Outcome in Women of African Descent

Rachel Martini[1,2], Princesca Delpe[3], Timothy R. Chu[4], Kanika Arora[4], Brittany Lord[1,2], Akanksha Verma[3], Deepa Dedi[3], Balasubramanyam Karanam[5], Isra Elhussin[1,2], Yalei Chen[5], Endale Gebreigzabher[3], Joseph K. Oppong[7,8], Ernest K. Adjei[7,8], Aisha Jibril Suleiman[7,8], Baffour Awuah[7,8], Mahlteme Bekele Muleta[7,8], Engida Abebe[7,8], Ishmael Kyei[7,8], Frances S. Aitpillah[7,8,15], Michael O. Adinku[7,8], Kwasi Ankomah[7,8], Ernest Baawuah Osei-Bonsu[7,8], Dhananjay A. Chitale[1,2], Jessica M. Bensenhaver[1,2], David S. Nathanson[1,2], LaToya Jackson[1], Lindsay F. Petersen[1,2], Erica Proctor[1,2], Brian Stonaker[1], Kofi K. Gyan[1], Lee D. Gibbs[1,2], Zarko Manojlovic[1,2], Rick A. Kittles[20], Jason White[1], Clayton C. Yates[1,2], Upender Manne[1,2,3], Kevin Gardner[21], Nigel Mongan[22,23], Esther Cheng[24], Paula Ginter[24], Syed Hoda[24], Olivier Elemento[2,25], Nicolas Robine[4], Andrea Sboner[2,25], John D. Carpten[1,2], Lisa Newman[1], and Melissa B. Davis[1,2,3,6]

Martini et al., Cancer Discov. 12:2530-2551, 2022

Neighborhood Environment

Neighborhood Environment Modifies the Association of West African Ancestry with Prostate Cancer

Pichardo et al., JAMA Network Open. 2024;7:e2433546



Association of West African Ancestry with a Prostate Cancer Diagnosis

				Neighborhood Deprivation Stratified Models [e]	
	Model 1 [a]	Model 2 [b]	Model 3 [c]	Low Neighborhood Deprivation	High Neighborhood Deprivation
Prostate Cancer Diagnosis Odds ratio [95% CI], (n = 1,633)					
West African ancestry [δ] [g] (coded as continuous variable)	1.63* [1.23, 2.18]	1.50* [1.12, 2.01]	0.76 [0.54, 1.06]	0.35* [0.20, 0.62]	2.00* [1.35, 2.97]
West African ancestry X Neighborhood Deprivation			*P* = 0.017		

Model 1, unadjusted; Model 2, age-adjusted
Model 3, age- and neighborhood deprivation index-adjusted
** P < .05*

Conclusions

Conclusions from this Study

- Neighborhood environments may determine how West African genetic ancestry modulates prostate cancer risk
- Our data indicate that West African genetic ancestry is a greater risk factor for men residing in deprived neighborhoods
- While genetic ancestry-inferred risk has been considered a non-modifiable risk factor, our study argues that genetically-inferred risk is a modifiable risk factor – not a determination
- Improving neighborhood environments may alleviate both the prostate cancer burden directly and the risk inferred by West African genetic ancestry (among men residing in areas with high deprivation)

Cancer Health Disparities

Causes of US Cancer of Health Disparities

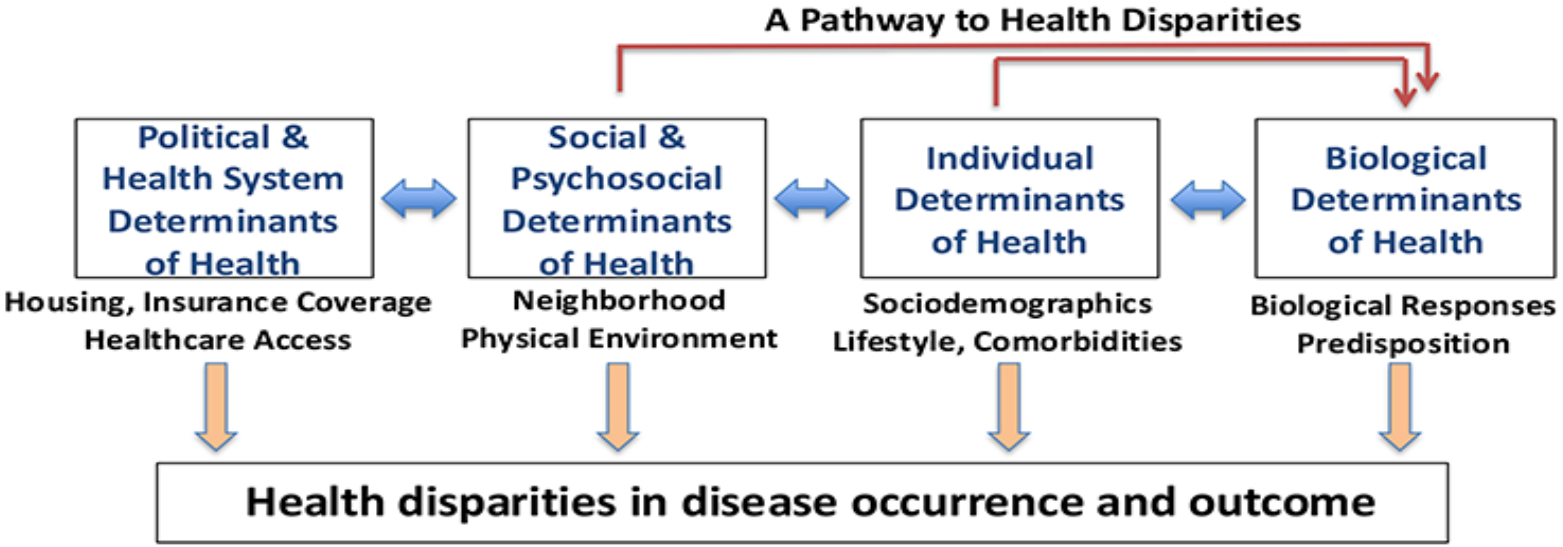
Cancer Health Disparity = Health Care Disparity

- 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, lack of 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

Outcomes

Society to Cell to Outcomes Framework

- **Framework links multilevel exposures to health disparities and biological responses**



Research Opportunities

Society to Cell to Outcomes
What are the Research Opportunities?

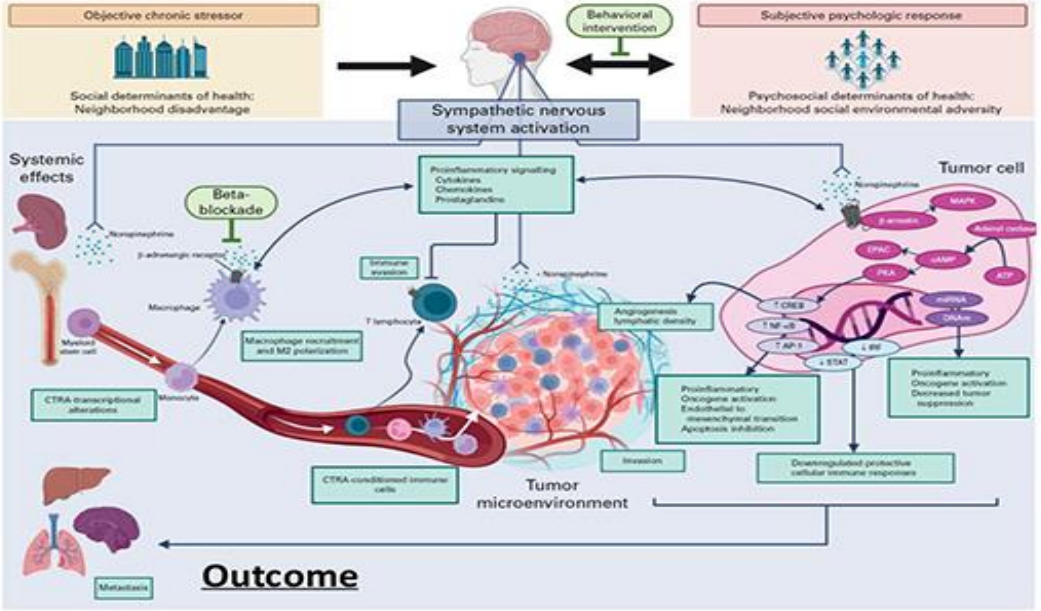
- **Gaining a more complete understanding of cancer disparities**
- **Gaining knowledge how interventions at various levels can promote positive outcomes and reduce disparities**
  - policy, behavioral & pharmacologic interventions
- **"Proof" of causality for exposure-to-outcome associations**
- **Integrative epidemiology: multi-disciplinary approach with integration of population & lab research-based methodologies**
  - much can be learned

Chronic Stress

Impact of Chronic Stress on Tumor Biology
A Society to Cell to Outcomes Pathway

Society as Multilevel Stressor: Neighborhood Disadvantage, Social Isolation, Discrimination etc

Most advanced example: stress signaling



Society

Cell

Goel et al.
JCO, 42: 3618-27, 2024

Stress Study

NCI Breast Cancer Stress Study

Harris, Pichardo, et al. JAMA Network Open, 2025;8:e2459754

- **Study evaluates the impact of chronic stress, inadequate social support, racial discrimination, and neighborhood deprivation on breast tumor biology**
- **Key observations:**







Chronic Stress associated with a high tumor mutational burden

Social Support associated with more favorable, immune-stimulatory changes

Chronic *stress*, exposure to *discrimination*, and *neighborhood deprivation* associated with

- aggressive tumor biology, deleterious immune cell profiles, systemic inflammation, and suppression of the antitumor immune response

Disparity research

Our Health Disparity Research

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 have been the analysis of tumor biology and the investigation of candidate risk factors (society) influencing this biology
  - Chronic stress exposure
  - Comorbidities
  - Systemic chronic inflammation
  - Neighborhood environment
  - Genetic ancestry

Cancer Comorbidities

Large and Persistent Disparities in Cancer Comorbidities

- Co-occurring chronic diseases (co-morbidities) negatively affect cancer survival
- Comorbidities affect poor communities more so than affluent communities
- Impede clinical trial participation
- Patients with comorbidities frequently experience a delayed diagnosis
- Challenge to cancer care: comorbidities complicate the decision-making process after a cancer diagnosis
- Patients with comorbidities are less likely to receive therapies with curative intent
- Comorbid conditions may increase social isolation
- Treatment of comorbidities may impact tumor biology – anti-inflammatory drugs, immune suppressive drug, treatment of diabetes with insulin and metformin are examples

Disparity Research

Our Health Disparity Research

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 have been the analysis of tumor biology and the investigation of candidate risk factors (society) influencing this biology
  - Chronic stress exposure
  - Comorbidities
  - Systemic chronic inflammation
  - Neighborhood environment
  - Genetic ancestry

Prostate Cancers

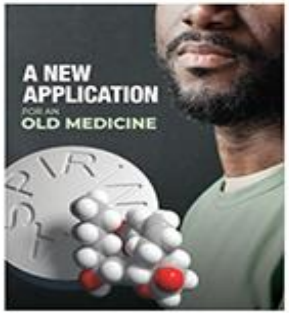
US Prostate Cancer Outcome Disparity and the Excessive Burden Among African American Men - A Research Priority

Inflammation, Comorbidities, and Stress Signaling as Contributors to the US Prostate Cancer Outcome Disparity

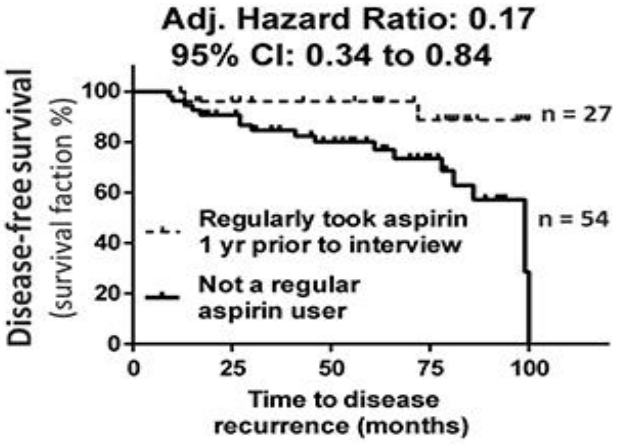
How do these exposures explain the excessive prostate cancer mortality among African American men?

Aspirin Use

Aspirin Use May Prevent Recurrent and Fatal Prostate Cancer in African American Men



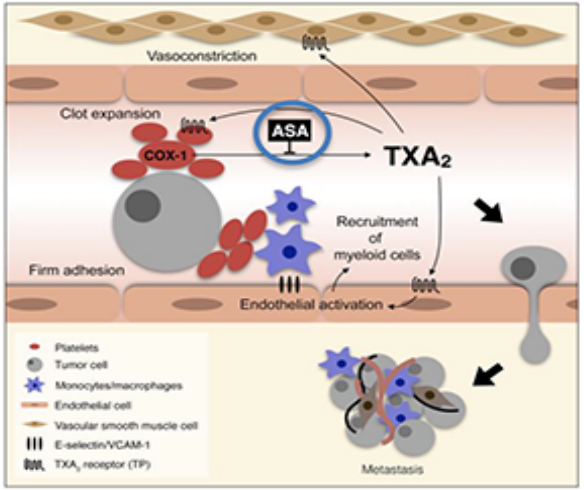
- Aspirin use may protect against a disease recurrence in African American men (NCI-Maryland Prostate Cancer Study)
  - *Smith et al., Cancer Epidemiol. Biomarkers Prev. 2017, 26: 845-53*
- Decreased prostate cancer mortality among African American aspirin users in Southern Community Cohort Study
  - *Tang et al., Cancer Epidemiol. Biomarkers Prev. 2021, 30: 539-44*



Inflammation Signaling

Inflammation-related Thromboxane A2 (TXA2) Signaling Increases Metastasis

Platelet TXA2 enhances metastasis



Lucotti et al., JCI 2019;129:1845-62

TXA2 is a small molecule eicosanoid

One TXA2 mechanism:
Promotes cancer cell adhesion to endothelial cells and movement out of the vasculature (lung cancer)

Another TXA2 mechanism:
Promotes metastasis via suppression of T cell immunity to metastasis (lung and liver cancer metastasis models)

Aspirin prevents metastasis by limiting platelet TXA_2 suppression of T cell immunity

https://doi.org/10.1038/s41586-025-08626-7
Received: 23 February 2023
Accepted: 8 January 2025
Published online: 5 March 2025
Open access
Check for updates

Jie Yang[1,2], Yumi Yamashita-Kanemaru[1], Benjamin I. Morris[1], Annalisa Contursi[3,4], Daniel Trojkovich[1], Jingru Xu[1], Elinca Petrescan[1], Jayne Benson[1], Alexander C. Evans[1], Alberto G. Conti[1], Aws Al-Deka[1], Layla Dahmani[1], Adnan Audic-Belithous[1], Baojie Zhang[1], Hanneke Okkenhaug[1], Sarah K. Whiteside[1], Charlotte J. Imianowski[1], Alexander J. Wesolowski[1], Louise V. Webb[1], Simone Puccio[3], Stefania Tacconelli[3,4], Annalisa Bruno[3,4,5], Sara Di Berardino[3,4], Alessandra De Michelis[3,4], Heidi C. E. Welch[1], I-Shing Yu[6], Shu-Wha Lin[6], Suman Mitra[7,8], Enrico Lugli[7], Louise van der Weyden[9], Klaus Okkenhaug[1], Kourosh Saeb-Parsy[9], Paola Patrignani[3,4], David J. Adams[10] & Rahul Roychoudhuri[1,11]

Yang et al., Nature 2025;640:1052-61

Prostate Cancer Metastasis

High Urinary Thromboxane B2 (TBX2) Associates with Metastatic Prostate Cancer 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).

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

Thromboxane B2

High Urinary Thromboxane B2 (TBX2) Associates with Metastatic Prostate Cancer 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).

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

Thromboxane B2

Thromboxane B2 (TXB2) Associates with Fatal 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*

Inflammation in African American men

Potential Root Causes of Increased Inflammation in African American Men

Neighborhood Deprivation

Observation: Living in a deprived neighborhood correlates with an increased activity score for a proteome-defined systemic inflammation signature



JAMA Network | Open

Original Investigation | Equity, Diversity, and Inclusion

Association of Neighborhood Deprivation With Prostate Cancer and Immune Markers in African American and European American Men

Margaret S. Pichardo, MD, PhD, MPH; Tsion Zewdu Minas, PhD; Catherine M. Pichardo, PhD; Maeve Bailey-Whyte, PhD, MPH; Wei Tang, PhD; Tiffany H. Dorsey, BS; William Wooten, MPH, MS; Brid M. Ryan, PhD, MPH; Christopher A. Loffredo, PhD; Stefan Ambs, PhD, MPH



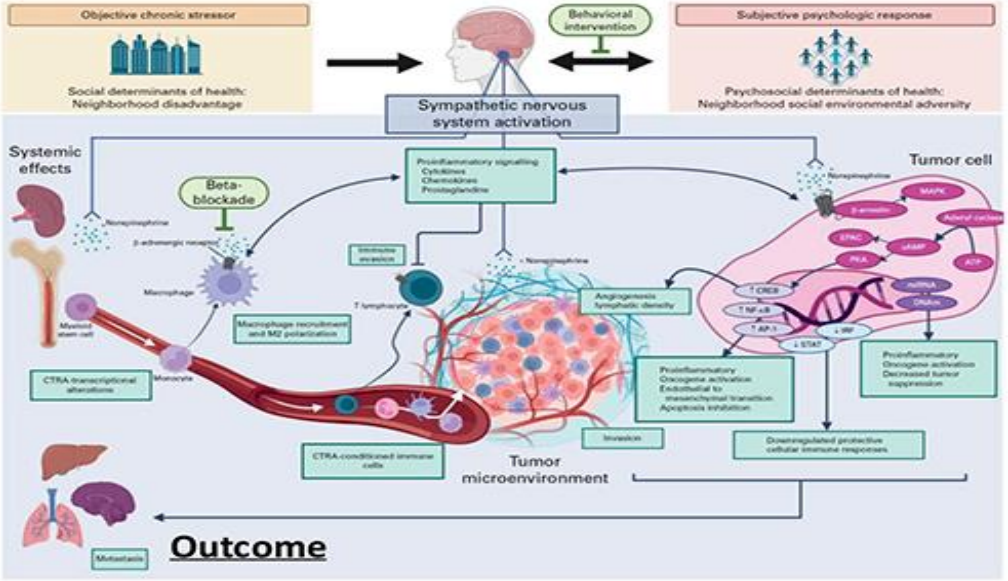
Margaret Pichardo

Chronic Stress

Impact of Chronic Stress on Cancer Patients

Exposure to chronic stress increases markers of systemic inflammation

Society as Multilevel Stressor: Neighborhood Disadvantage, Social Isolation, Discrimination etc



Society

Cell

Goel et al.
JCO, 42: 3618-27, 2024

Urinary metabolites

Allostatic Load & Urinary Metabolites as Stress Exposure Markers and their Interrelationship

Allostatic load

- defined as “wear and tear to our body” due to chronic stress
- captures co-morbidities
- 8/10-item variable

Urinary markers of stress exposure

- Cortisol sulfate (stress hormone)
- adrenaline and noradrenaline (β-adrenergic stress signaling)
- Mass spec measurements







Correlation matrix (n = 405)

allostatic load	0.04	0.01	0.03
	cortisol	0.31	0.35
		adrenaline	0.53
			noradrenaline

Pearson correlation coefficient

Prostate Cancer Mortality

Association of Allostatic Load and Urinary Markers of Stress Exposure with Prostate Cancer Mortality

All-cause mortality	Combined cohort adj. HR (95% CI)	Prostate cancer mortality	Combined cohort adj. HR (95% CI)
Allostatic Load	**1.23 (1.12,1.36)**	Allostatic Load	1.05 (0.87,1.27)
Cortisol	1.04 (0.95,1.15)	Cortisol	**1.54 (1.27,1.88)**
Adrenaline	1.02 (0.94,1.11)	Adrenaline	**1.44 (1.22,1.70)**
Noradrenaline	**1.11 (1.01,1.22)**	Noradrenaline	**1.66 (1.32,2.08)**

cases = 798; **exposure**: continuous scores; **adjustments**: clinical and socioeconomic variables

Lessons Learned

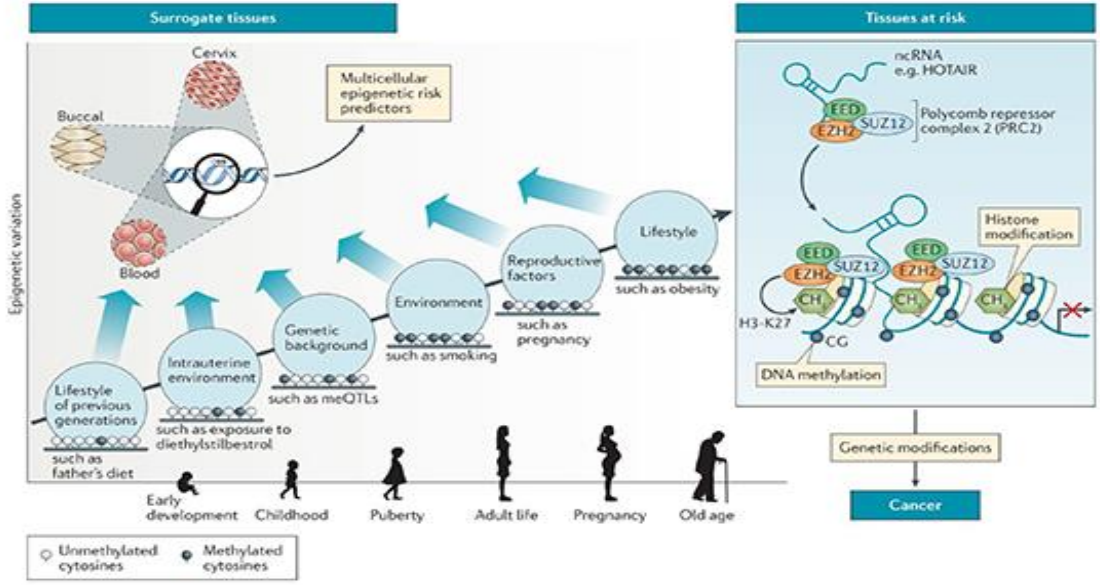
Lessons Learned

- Systemic inflammation may disproportionately affect African American men with prostate cancer and contribute to the survival health disparity for this disease
- Adverse neighborhood factors may lead to an increase in systemic inflammation
- Allostatic load - as a measure of multiple comorbidities – did not correlate with urinary markers of stress exposure
- Allostatic load associated with all-cause but not prostate cancer-specific mortality
- Urinary stress exposure markers associated with disease mortality

Social Epigenomics

Social Epigenomics

Seeks to link social determinants of health to disease causation through investigations of epigenomic modifications and their effects on disease biology



Widschwendter et al., Nature Reviews Clinical Oncology, 15: 292-309, 2019

Social Determinants

Social Determinants of Health and Lifestyle Factors Modify the Epigenome

Examples from the literature

Low early-life social class leaves a biological residue manifested by decreased glucocorticoid and increased proinflammatory signaling

Gregory E. Miller[a,1], Edith Chen[a], Alexandra K. Fok[b,c], Hope Walker[a], Alvin Lim[a], Erin F. Nicholls[a], Steve Cole[d,e,f], and Michael S. Kobor[b,c]

nature neuroscience

Epigenetic regulation of the glucocorticoid receptor in human brain associates with childhood abuse

Patrick O McGowan[1,2], Aya Sasaki[1,2], Ana C D'Alessio[3], Sergiy Dymov[3], Benoit Labonté[1,4], Moshe Szyf[2,3], Gustavo Turecki[1,4] & Michael J Meaney[1,2,5]

Epigenetic differences arise during the lifetime of monozygotic twins

Mario F. Fraga*, Esteban Ballestar*, Maria F. Paz*, Santiago Ropero*, Fernando Setien*, Maria L. Ballestar†, Damia Heine-Suñer‡, Juan C. Cigudosa§, Miguel Urioste§, Javier Benitez§, Manuel Boix-Chornet†, Abel Sanchez-Aguilera†, Charlotte Ling‖, Emma Carlsson‖, Pernille Poulsen**, Allan Vaag**, Zarko Stephan††, Tim D. Spector††, Yue-Zhong Wu‡‡, Christoph Plass‡‡, and Manel Esteller*§§

ARTICLE

Received 27 Feb 2015 | Accepted 16 Nov 2015 | Published 15 Dec 2015 DOI: 10.1038/ncomms10392 OPEN

Hypomethylation of smoking-related genes is associated with future lung cancer in four prospective cohorts

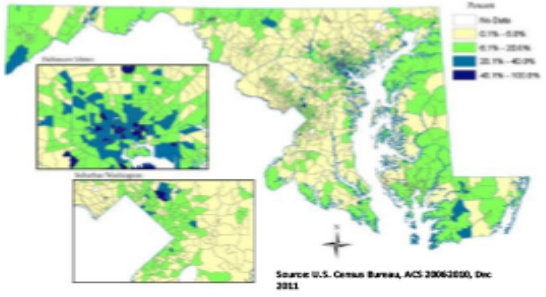
Francesca Fasanelli[1,2,*], Laura Baglietto[3,4,5,6,*], Erica Ponzi[1], Florence Guida[7], Gianluca Campanella[7], Mattias Johansson[8,9], Kjell Grankvist[9], Mikael Johansson[10], Manuela Bianca Assumma[1], Alessio Naccarati[1], Marc Chadeau-Hyam[7], Ugo Ala[11], Christian Faltus[12], Rudolf Kaaks[13,14], Angela Risch[12,14,15], Bianca De Stavola[16], Allison Hodge[5], Graham G. Giles[5,6], Melissa C. Southey[17], Caroline L. Relton[18], Philip C. Haycock[18], Eiliv Lund[19], Silvia Polidoro[1], Torkjel M. Sandanger[19,**], Gianluca Severi[1,3,4,5,6,**] & Paolo Vineis[1,7,**]

Neighborhood Deprivation Index

Neighborhood Deprivation Index

- Neighborhood socioeconomic deprivation was measured using Neighborhood Deprivation Index (NDI; *Messer et al.*, 2006, PMID: 17031568)
- Census-tract level data were drawn from the 2000 Census using participants' addresses

Percent Poverty by Census Tract, Maryland, 2006-2010



- PCA: Extracted a single factor representing the shared variance from deprivation indicators

Variables retained in NDI	
% households in poverty	% female headed households with dependent children
% households on public assistance	% households earning <$30,000/year
% percent households with no car	% males and females unemployed

Work by Catherine Pichardo

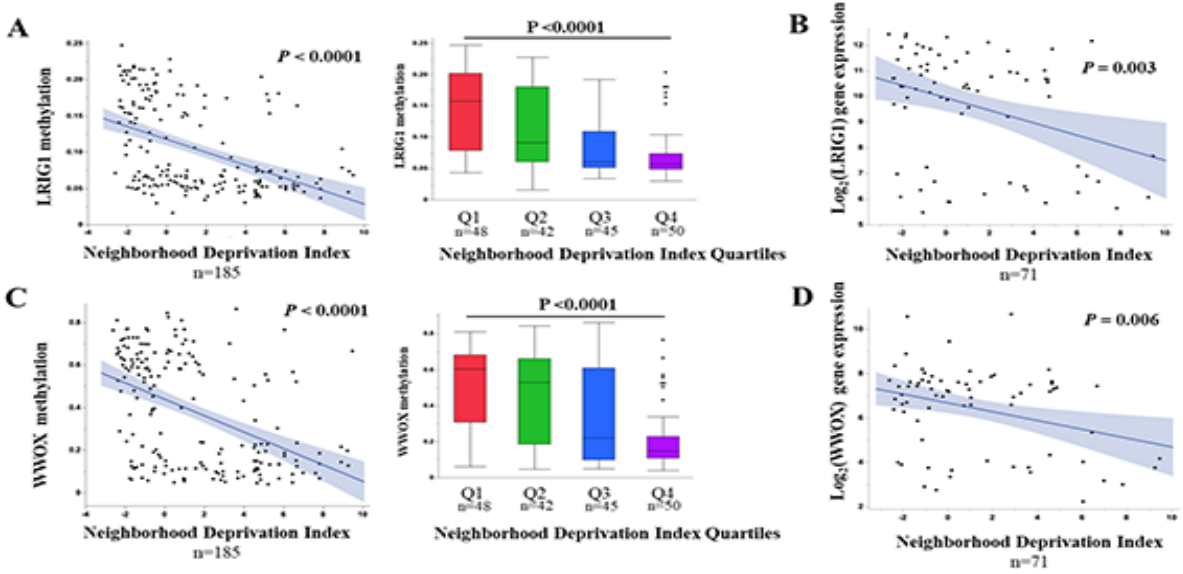
- Lower NDI values = less deprivation, Higher NDI values = greater deprivation

Tumor suppressors

Neighborhood Deprivation Associates with the Silencing of Tumor Suppressors, *LRIG1* and *WWOX*

Jenkins, Rossi, et al; JAMA Network Open. 2023;6:e2341651

Analysis of 185 breast tumors and genome-wide methylation





Brittany Jenkins



Tiffany Dorsey

LRIG1 (locus: cg26131019) and *WWOX* (cg02171206) methylation sites are in the gene body

Lessons Learned and Gaps

- **There are numerous examples showing that social determinants of health & environmental exposures associate with epigenetic alterations in tissues and subsequent disease or disease severity**

- Social Epigenomics covering cancer health disparities is still in its infancy and needs larger observational studies combined with experimental research
- Research studying epigenetic alterations in tissue samples, instead of blood, needs to be extended

NIH NATIONAL CANCER INSTITUTE 35

Collaborators

Collaborators

- Clayton Yates, Johns Hopkins/Tuskegee University
- Shahin Sayed & Francis Makokha (Kenya), Gretchen Gierach, Jonine Figueroa, Rose Yang (all DCEG/NCI), Eytan Ruppin (CCR), and CCR Health Disparities Flex Award team
- Julian Candia, Brid Ryan, and Xin Wei Wang (CCR/NCI)
- Michael Cook, DCEG/NCI, now at Our Future Health UK
- Rick Kittles, Morehouse School of Medicine
- Jay Fowke, Bill Blot, and Wei Zheng, SCCS, Vanderbilt University
- Chris Loffredo, Georgetown University
- Ludmila Prokunina-Olsson, DCEG/NCI
- George Stark and Eric Klein, Cleveland Clinic
- and many thanks to our UMD contractor (PI Dean Mann and team members)